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Journal of Bioanthropology

Belupoint

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Polazišna točka edukacije svih zdravstvenih radnika - najbolji izvor stručnih informacija iz područja medicine, farmacije i nutricionizma u skladu sa najnovijim smjernicama, studijama, trendovima u liječenju (i samoliječenju).

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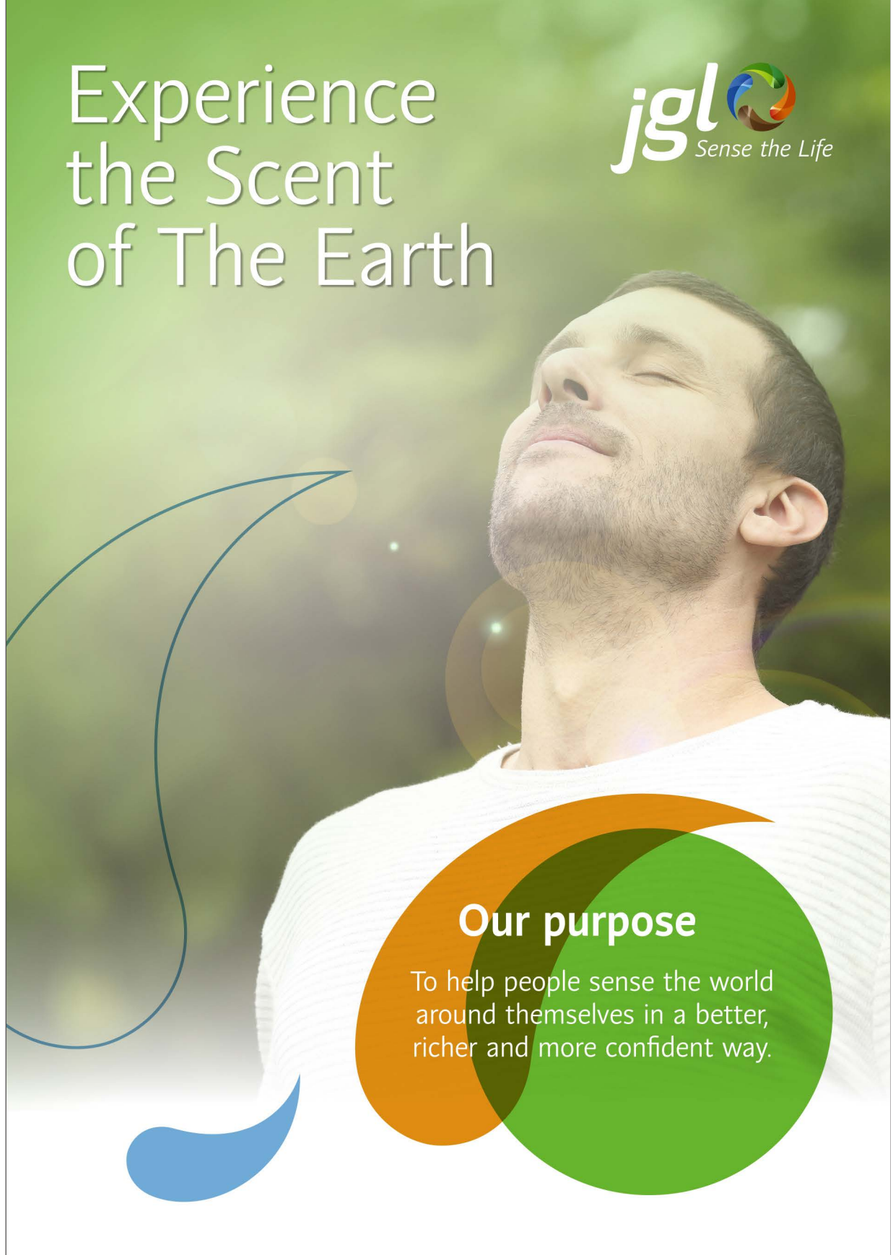

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For issue vol.4, no. 1 in 2024 we were privileged for the opportunity to announce excellent scientific lectures to be presented at the ISABS Conference on Applied Genetics and Mayo Clinic Lectures in Translational Medicine.

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PROGRAM AND ABSTRACTS

The Thirteenth ISABS Conference on Applied Genetics and Mayo Clinic Lectures in Translational Medicine

June 17-20, 2024, Split, Croatia

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Zagreb, 2024

PROGRAM AND ABSTRACTS

THE THIRTEENTH ISABS CONFERENCE ON APPLIED GENETICS AND MAYO CLINIC LECTURES IN TRANSLATIONAL MEDICINE

JUNE 17-20, 2024
Radisson Blu Resort & Spa 5*
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13th ISABS Conference

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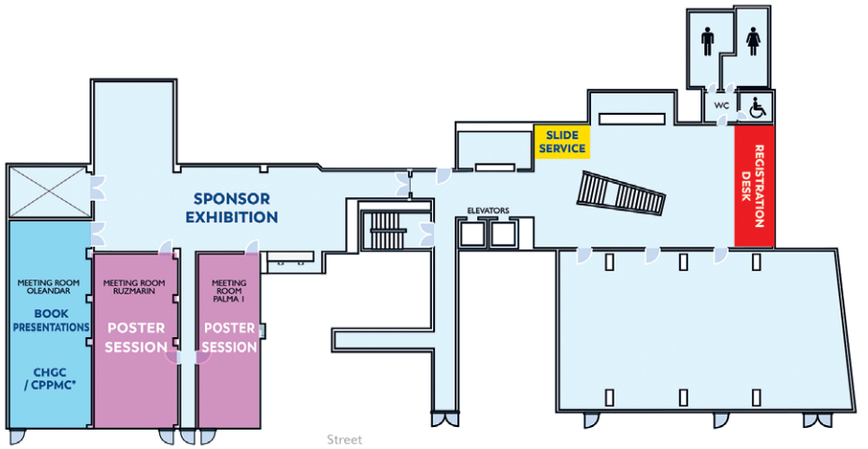

* (9th Croatian Human Genetics Conference & 2nd Croatian Personalized and Precision Medicine Conference)

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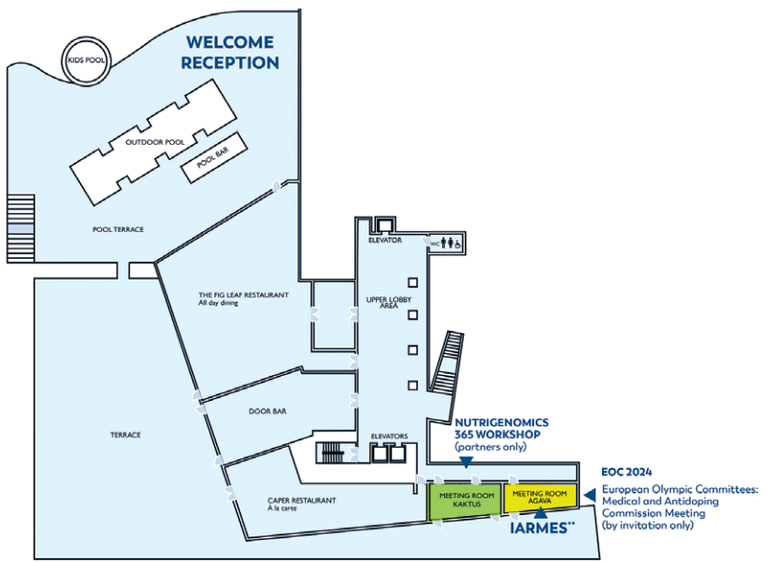

** The First Conference of the International Regenerative Medicine Experts Society (by invitation only)

13th ISABS Conference on Applied Genetics and Mayo Clinic Lectures in Translational Medicine

	SUNDAY, JUNE 16	MONDAY, JUNE 17	TUESDAY, JUNE 18	WEDNESDAY, JUNE 19	THURSDAY, JUNE 20
CONFERENCE ROOM Lower Ground Floor		**9:00 - 12:15** Opening session **14:00 - 15:00** Nobel Laureate Session 1 Richard Roberts **15:00 - 18:15** Moses Samuel Schanfield Memorial Symposium	**8:30 - 12:00** Oral Session 1 **14:00 - 15:00** Nobel Laureate Session 2 Gregg Semenza **15:00 - 17:35** Oral Session 2	**8:30 - 11:40** Oral Session 3 **14:00 - 15:00** Nobel Laureate Session 3 Svante Pääbo **15:00 - 18:15** Oral Session 4 **20:00** ISABS Lecture	**8:30 - 11:15** Oral Session 5 **14:00 - 15:00** Nobel Laureate Session 4 Aaron Ciechanover **15:00 - 16:00** Closing session
OLEANDER Lower Ground Floor	**12:00 - 16:35** **CHGC/CPPMC** (9th Croatian Human Genetics Conference & 2nd Croatian Personalized and Precision Medicine Conference)		**13:00 - 14:00** **BOOKS PRESENTATION** Henry A. Erlich: Genetic Reconstruction of the Past: DNA Analysis in Forensics and Human Evolution (Oxford University Press, 2023) Dragan Primorac, Wolfgang Höppner, and Lidija Bach-Rojecky (editors): Pharmacogenomics in Clinical Practice (Springer, 2023)	**13:00 - 14:00** **BOOKS PRESENTATION** Xiaping Jiang (with Anthony Roberts and Henry C. Lee): Gunshot in Croatia (Dixie W. Publishing, 2023) Dragan Primorac and Moses Schanfield (editors): Forensic DNA Applications: An Interdisciplinary Perspective, 2nd Edition (Rutledge, 2023)	
RUŽMARIN Lower Ground Floor PALMA 1 Lower Ground Floor		**12:30 - 14:00** **POSTER PRESENTATION**	**12:00 - 13:00** **POSTER PRESENTATION**	**12:00 - 13:00** **POSTER PRESENTATION**	
AGAVA First Floor		**16:30 - 18:30** **IARMES** (The First Conference of The International Regenerative Medicine Experts Society dicine Experts Society - by invitation only)		**11:30 - 13:30** **EOC 2024** (European Olympic Committees: Medical and Antidoping Commission Meeting - by invitation only)	
KAKTUS First Floor		**15:00 - 16:00** **Nutrigenomics 365 Workshop** - by invitation only			

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WELCOME TO THE THIRTEENTH ISABS CONFERENCE ON APPLIED GENETICS AND MAYO CLINIC LECTURES IN TRANSLATIONAL MEDICINE!

Dear Colleague,

We invite you to join us at the 13th ISABS Conference on Applied Genetics and Mayo Clinic Lectures in Translational Medicine, Split, Croatia, June 17 – 20, 2024. The conference is the next in a series of biennial events organized by the International Society for Applied Biological Sciences (ISABS), a society dedicated to promoting applied molecular biology (www.isabs.hr).

Since initiating the series in 1997, we have strived to focus and broaden the scope of the conferences. The focus has been on applying cutting-edge analytical methodology in forensic science. In 2003, programs in forensic medicine and in cellular and molecular medicine ran in parallel with the introductory and closing sessions held jointly. The Cellular and Molecular Medicine program was co-organized with the Mayo Clinic, Rochester, Minnesota, USA. Since 2007, we have broadened the area of interest by the introduction of molecular anthropology that, in large part, shares the methodology with forensic genetics. In 2009, we introduced selected topics from individualized medicine, another applied discipline based on the advances in mapping the human genome. In 2011, we included the most recent and most interesting topics in molecular medicine. In 2013 we included genetics applied to the crossing of forensic science, anthropology, and translational medicine. Mayo Clinic again, same as in the past ten years, joined our efforts. It provided a critical link to the cutting-edge clinical applications of genetics. The overall effort culminated in the incorporation of individualized medicine as the third cornerstone, together with forensic and anthropological genetics. We feel this integration of the three areas, united by technology and applicative intent, provides an unprecedented opportunity for further progress in every respect. In the clinical part of the conference, topics covered the latest achievements in regenerative medicine, gene and cell therapy, individualized medicine, new molecular procedures and methodology for early detection of cancer, the clinical importance of circulating tumor cells and immune therapy in cancer treatments. In 2015 we introduced up-to-date results in genomics of individualized medicine, a program in anthropology genetics concerning ancient and modern human genome history, and human genetic history of the continents and forensic genetics program with special emphasis on new knowledge in Next Generation Sequencing (NGS) in forensics, DNA investigative intelligence, and advancements in forensic DNA routine. At the jubilee 10th ISABS conference in Split in 2017, the Nobel Spirit session took place for the first time. This jubilee conference marked a breakthrough towards regenerative medicine and microbiome analysis in forensics, anthropology and medicine and in 2019 we continued with the same "Nobel Spirit" achievements.

We are pleased that the program in 2024 will be more interesting than ever and it will include the following topics: Whole Genome Sequencing for Implementation of Precision Medicine, Gene and Cellular Therapy, Immunotherapy, Pharmacogenomics, Tissue Engineering, Artificial Intelligence in Clinical Medicine, Dendritic Cell Vaccination, Forensic Genetic Genealogy, etc. This year, the fourth "Nobel Spirit" will provide a forum for the four Nobel laureates to stimulate public discussion on the role of science in solving global health issues, acute regional problems such as brain drain, demographic decline, and cultural and social change.

Together with several conference regulars, this 2024 year will bring many new and exciting names, including Nobel Prize laureates Aaron Ciechanover, Sir Richard John Roberts, Svante Pääbo and Gregg L. Semenza. ISABS Lecture "Science, scientists, and scientific publications: the quest for reproducible and useful research." will be held by John Ioannidis (Stanford University, Stanford, CA, USA).

As before, the conference is structured to allow close interaction of the international faculty and attendees. We continue to have traditional Young Investigator Awards and High School Student Future Scientist Awards. Together with formal presentations, there will be meet-the-professor sessions, a gala dinner, and other social occasions meant to enhance opportunities for scientific intercourse, but also to introduce the participants to the town of Split, a destination famous for unspoiled nature and cultural, historic and sporting attractions. We invite you to Split and its Diocletian's Palace, seventeen centuries old, yet swarming with contemporary life. Discover and enjoy the beauties of Croatia, the mild climate, the crystal clear and warm sea, beautiful beaches, virgin nature, and the rich history and cultural heritage. And, above all, enjoy Croatia's warm and friendly people.

We look forward to seeing you in Split!

Dragan Primorac
Stanimir Vuk-Pavlović
Program/Conference Directors

ABOUT SPLIT

There's no place like Split!

Whenever we hear of something dire happening near or far away – be it hurricanes, storms, quakes, floods, volcanoes – we cannot help but recall Diocletian and praise him for his great wisdom in choosing such a fine place for this city of ours. Were you to take the globe, turn it around, spin it like a whirligig, visit every place from the North Pole to the South, from Japan to the Americas, you would see there is nothing so perfectly positioned as this. Ideal in everything. We've got it all, all at hand and all close. We've got the sea and the islands in front, to shield us from the perilous waves and give us somewhere to build our summer houses and take excursions. It is not only the sea that we hold dear, but our river as well. River Jadro is not one of those great rivers that run wild and unpredictable, but rather one that gives us clean water to mix with our wine and wash our eyes of sleep. A place where it is oh so nice, when there is a fiesta in small city close to Split, Solin, to sit on the grass and fling lamb bones into the river after delicious meal. In the heart of the Split we have a mountain, and not just any mountain but a most beautiful specimen with the finest peak imaginable. And on this Marjan mountain, woods whose darkness holds secrets of young loves forged, hidden away from inquisitive eyes. And though we have the sea and the hills and the river and the woods, none of them are a menace to us, making us feel well sheltered instead. As for the climate, we simply can't complain. We are the sunniest city in all of Europe. And yet we are in no want of rain, because we have plenty. Every two or three years a smidgeon of snow falls for our young ones to see. When the summer becomes too hot to bear, the landward breeze keeps us cool. The wind bura blows to clear the air. We are in no danger of earthquakes for we do not have soil of elastic marl that stretches like rubber, and they can do no more than sway us a little. Had we entrusted engineers with drawing such an ideal place on the map, we would not have got this for they would have forgotten or missed something. After all, it is not in vain That they say: "There's no place like Split!" And still we complain how expensive everything in Split is! We ought to be happy and keep quiet, for even with no money jingling in our pockets, we are all just by living here -millionaires!

Miljenko Smoje
Croatian journalist, novelist, and travel writer
Split, October 7th 1964

13TH ISABS CONFERENCE, JUNE 17-20, 2024, SPLIT, CROATIA

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Aaron Ciechanover (Nobel Prize in Chemistry 2004; Technion – Israel Institute of Technology, Haifa, Israel)
Sir Richard J. Roberts (Nobel Prize in medicine in Physiology and Medicine 1993.
Northeastern University, Boston, MA, USA & New England Biolabs, Ipswich, MA, USA)
Božo Pavičin (Ministry of Science and Education of the Republic of Croatia)
Dubravka Brezak Stamać (Education and Teacher Training Agency of the Republic of Croatia)
Manolis Kelis (Massachusetts Institute of Technology, The Broad Institute, Cambridge, MA, USA)
Tamas Ordog (Mayo Clinic, Rochester, MN, USA)
Mitchell Holland (Pennsylvania State University, State College, PA, USA)
Henry Erlich (Children's Hospital Oakland Research Institute, Oakland, CA, USA)
Damir Marjanović (Institute for Anthropological Research, Zagreb, Croatia and International Burch University, Sarajevo, Bosnia and Herzegovina)
Henry Lee (Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven and Henry C. Lee Institute of Forensic Science, West Haven, CT, USA)
Petar Projić (International Center for Applied Biological Sciences, Zagreb, Croatia)

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Alemka Markotić (Clinic of Infectious Diseases "Dr. Fran Mihaljevic", Zagreb, Croatia)
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Josip Crnjac (University Department of Forensic Sciences, University of Split, Split, Croatia)

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Petar Projić (International Center for Applied Biological Sciences, Zagreb, Croatia)

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Vilim Molnar (St. Catherine Specialty Hospital, Zagreb, Croatia)

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Đurđica Kovačić (Medical School, University of Zagreb, Zagreb, Croatia)
Jelena Kovačić (Medical School, University of Zagreb, Zagreb, Croatia)
Jana Mešić (Medical School, University of Rijeka, Rijeka, Croatia and St. Catherine Specialty Hospital, Zagreb, Croatia)
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Kristijan Vrdoljak (Medical School, University of Zagreb, Zagreb, Croatia)

High School Students Committee

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Luka Bulić (University of Zagreb, Medical School, Zagreb, Croatia)
Josip Crnjac (University Department of Forensic Sciences, University of Split, Split, Croatia)
Ivana Erceg Ivkošić (St. Catherine Specialty Hospital and Faculty of Dental Medicine and Health Osijek, Croatia)
Ante Ivkošić (Clinical Hospital "Sveti Duh"; Zagreb, Croatia)
Damir Marjanović (Institute for Anthropological Research, Zagreb, Croatia and International Burch University, Sarajevo, Bosnia and Herzegovina),
Natalija Novokmet (Institute for Anthropological Research, Zagreb, Croatia)
Petar Projić (International Center for Applied Biological Sciences, Zagreb, Croatia)
Vedrana Škaro (Greyledge Europe Ltd, Zagreb, Croatia)
Inga Urlić (Faculty of Science, University of Zagreb, Zagreb, Croatia)

AWARDS

Honorary Membership Award

Honorary membership award has been awarded to **Dr. Henry C. Lee in recognition of his outstanding work in the profession of the forensic sciences and continuous support to ISABS.** Dr. Lee is currently the director of Forensic Research and Training Center at the Henry C. Lee Institute of Forensic Science and a Distinguished Chair Professor in Forensic Science at the University of New Haven. Lee was the Chief Emeritus of the Connecticut State Police from 2000 to 2010 and was the Commissioner of Public Safety for the State of Connecticut from 1998 to 2000 and has served as that state's Chief Criminalist and Director of the State Police Forensic laboratory from 1978 to 2000. Lee has lectured widely, written hundreds of articles published in professional journals, and authored or co-authored more than 40 books on forensic science, crime scene investigation and crime scene reconstruction. He has acted as an advisor or consultant to many law enforcement agencies. He hosted a show on the truTV network, formerly Court TV, titled Trace Evidence: The Case Files of Dr. Henry Lee, which highlighted his work on well-known cases. Lee has also appeared widely on television. He has been a guest on the Taiwanese talk show KangXi Lai Le.

Moses Schanfield Young Investigator Award (MSYIA)

Knowing the importance of including young researchers as active participants of the conference, ISABS encourages PhD and graduate students working toward a degree in the fields related to the conference program themes as well as postdoctoral researchers to join the conference and apply for the Young Investigator Award (YIA). Therefore, for each ISABS conference, YIA are presented for outstanding research presented by investigators who are less than thirty-five years old. The Scientific Advisory Committee of the conference selects finalists from nominees who submit abstracts. Besides the attractive prize, each award recipient is given the opportunity for a Oral communication. The author of each selected abstract receives the Moses Schanfieled Young Investigator Award Certificate as well.

The ISABS Future Scientist Award

A joint project of the International Society of Applied Biological Sciences (ISABS), the Ministry of Science and Education of the Republic of Croatia, and the Croatian Education and Teacher Training Agency. The Scientific Committee of the International Society for Applied Biological Sciences (ISABS) in collaboration with the Croatian Education and Teacher Training Agency and the Croatian Ministry of Science and Education awards the best Croatian high school students' essays with The ISABS Future Scientist Award. The essays must be in the field fields of human biology, genetics and chemistry, and infectious disease diseases (such as COVID-19). ISABS will also reward all teachers-mentors of the winning students.

Recipients of the 2024 Moses Schanfield Young Investigator Award

Floor Claessens, Denmark (Forensic Genetics)
Ivana Domljanović, Switzerland (Molecular Diagnostics)
Martina Glavan, USA (Personalized Medicine)
Vilim Molnar, Croatia (Personalized Medicine)
Illona Uzieliene, Lithuania (Molecular Diagnostics)

Recipients of the 2024 High School Student Future Scientist Award

Dorotea Alaburić, II. Gymnasium, Zagreb, Croatia
Klara Gnjidić, XV. Gymnasium, Zagreb, Croatia
Tončica Grubišić & Vita Medić, III. Gymnasium, Split, Croatia
Sara Polašek, School of Natural Sciences Vladimir Prelog, Zagreb, Croatia
Domagoj Praljak, XV. Gymnasium, Zagreb, Croatia
Jan Vlahinić, Andrija Mohorovičić Gymnasium, Rijeka, Croatia

Recipients of the 2022 Young Investigator Award

Elena Essel, Germany (Anthropological Genetics)
Karlo Miškec, Croatia (Epigenetics)
Amira Nabil, Egypt (Molecular Diagnostics)
Vid Matišić, Croatia (Pharmacogenomics)
Rachelle Turiello, USA (Forensic Genetics)

Recipients of the 2022 High School Student Future Scientist Award

Filip Bulat, VII. Gymnasium, Zagreb, Croatia
Ante Čolak, II. Gymnasium, Zagreb, Croatia
Mei Đulabić Chalfe, V. Gymnasium, Zagreb, Croatia
Robertina Filković, V. Gymnasium, Zagreb, Croatia
Lucija Glavičić Marović, XV. Gymnasium, Zagreb, Croatia
Đurđica Kovačić, III. Gymnasium, Split, Croatia
Nika Adriana Marijanović, Classical Gymnasium, Zagreb, Croatia
Frane Marušić, Jure Kaštelan High School, Omiš, Croatia
Nika Miličević, V. Gymnasium, Zagreb, Croatia
Goran Narančić, XV. Gymnasium, Zagreb, Croatia
Rea Pešušić, Vladimir Prelog Science School, Zagreb, Croatia

Recipients of the 2019 Young Investigator Award

Viktoria Dotz, The Netherlands (Personalized Medicine)
Benjamin Planterose Jiménez, The Netherlands (Forensic Genetics)
Elena Zavala, Germany (Anthropological Genetics)

Recipients of the 2019 High School Student Future Scientist Award

Božo Bradarić Lisić, Vladimir Prelog Science School, Zagreb, Croatia
Matea Bürger, VII. Gymnasium, Zagreb, Croatia
Sara Caktaš, XV. Gymnasium, Zagreb, Croatia
Angela Kalpić, Medical School Split, Split, Croatia
Rea Pešušić, Vladimir Prelog Science School, Zagreb, Croatia
Petar Škrobo, M.A. Reljković Gymnasium, Vinkovci, Croatia

Recipients of the 2017 Young Investigator Awards

Sabriya Syed, USA (Personalised Medicine)
Goran Josipović and Vladimir Zanki, Croatia (Personalised Medicine)
Atina Vidaki, The Netherlands (Forensic Genetics)
Mateja Hajdinjak, Germany (Anthropological Genetics)

Recipients of the 2017 Future Scientist Award

Filip Bognar, XV.Gymnasium, Zagreb,Croatia
Lovro Jančić, Karlovac Gymnasium, Karlovac, Croatia
Rej Kovačević, VII. Gymnasium, Zagreb, Croatia
Lara Primorac, XV. Gymnasium, Zagreb, Croatia
Magda Topić, XV. Gymnasium, Zagreb, Croatia
Borna Branimir Vuković, V. Gymnasium, Zagreb, Croatia

Recipients of the 2015 Young Investigator Awards

Dora Polšek, Croatia (Individualized Medicine)
Barbara Zajac, Germany (Forensic Genetics)
Niraj Rai, India (Anthropological Genetics)

Recipients of the 2013 Young Investigator Awards

Matko Čančer, Sweden (Gene therapy)
Dora Markulin and Branka Gršković, Croatia (Genome-based applications in forensic science)
Slavé Petrovski, USA (Personalized genomics)
Antoinette Westen, The Netherlands (Genome-based applications in forensic science)

Recipients of the 2011 Young Investigator Awards

Rebecca S Just, USA (Genome-based applications in forensic science)
Mark Barash, Australia (Forensic DNA phenotyping)
Renato Polimanti, Italy (Molecular anthropology)
Martina Smolić, Croatia (Molecular therapy)

Recipients of the 2009 Young Investigator Awards

Chiara Barbieri, Germany (Molecular Anthropology)
Fernanda Gonçalves, Brasil (Individualised Medicine)
Pavlo Tatarskyy, Ukraine (Individualised Medicine)
Antoinette Westen, Netherlands (Forensic Genetics)

Recipients of the 2007 Young Investigator Awards

Grzegorz Kaczmarczyk, Poland (Forensic Genetics)
Agnieszka Krzyżańska, Poland (Forensic Genetics)
Kaye Ballantyne, Australia (Molecular Anthropology)
Tomislav Domazet-Lošo, Croatia (Molecular Anthropology)
Coralie Frassati, Switzerland (Molecular Anthropology)
Taeko Kashima, Japan (Molecular Anthropology)

Recipients of the 2005 Young Investigator Award

Caroline Round, United Kingdom (Forensic Genetics)
Tracy Johnson, USA (Forensic Genetics)
Vedrana Montana, USA (Molecular and Cellular Medicine)
Mirela Baus Lončar, Germany (Molecular and Cellular Medicine)

Recipients of the 2003 Young Investigator Award

Robert J. Shelton, CO, USA (Forensic Genetics)
Chiara Magri, Italy (Molecular and Cellular Medicine)

Recipients of the 2001 Young Investigator Award

Forensic IdentityTesting: Frontiers in Molecular and Cellular Medicine:
Lucia Cifuentes Ovalle, Chile
Rima Dada, India
Katja Drobnič, Slovenia
Anna Gareeva, Russia
Nguyen Hoai Giang, Vietnam
Tomasz Kupiec, Polan

SCIENTIFIC PROGRAM INFORMATION

Visa and invitation letter

Please make sure you have the necessary valid documents to enter Croatia.
It is the sole responsibility of the attendee to take care of their visa requirements. For more information, please check here.
An official invitation letter can be sent upon request to isabs@etours.hr only for participants who have registered, paid the registration, and submitted an abstract that was not rejected. It does not cover any fees nor is a guarantee to obtain the visa.
Participants should make their own arrangements with respect to health and travel insurance.

Badges

Participants, accompanying persons, exhibitors, and press will be given badges at registration. They will be required for admission to all conference facilities and scientific and social events during the conference. Security guards will check the badges at the conference venue. Any individual who is not wearing an official meeting badge will be directed to the registration desk to register or if already registered, to purchase a replacement badge. The handling fee for replacement badges is €10.

Certificate of Attendance

Certificates of attendance will be issued at the registration desk.

Credits

The 13th ISABS Conference on Applied Genetics and Mayo Clinic Lectures in Translational Medicine has been approved for 20 (participants) or 30 (lecturers) points by the Croatian Medical Chamber. Credits are intended for medical doctors and members of the Croatian Medical Chamber to extend their medical doctor's license. If you are a Croatian Medical Chamber member and if you qualify for the credits approved for participation in the 13th ISABS Conference, please enter your personal identification number during online registration.

Registration Desk Hours

Sunday, June 16, 2024	10:00 – 20:00
Monday, June 17, 2024	07:30 – 17:00
Tuesday, June 18, 2024	07:30 – 17:00
Wednesday, June 19, 2024	07:30 – 17:00
Thursday, June 20, 2024	07:30 – 16:00

Sponsor Exhibition

Setup: June 16, 2024 by 11:00
Dismantling: June 20, 2024 by 17:00

Exhibit Hall Hours

Monday, June 17, 2024	08:30 – 17:00
Tuesday, June 18, 2024	08:30 – 17:00
Wednesday, June 19, 2024	08:30 – 17:00
Thursday, June 20, 2024	08:30 – 15:00

Program Changes

Organizers assume no liability for any changes in the program due to external or unforeseen circumstances. For any program changes please check the updated Conference Program or ask at the Registration desk.

Language

The official language of the conference is English (no simultaneous translation)

Slide and PowerPoint Preview Area

A slide and PowerPoint preview area will be available to all presenters.

Info Centre

Info Centre will be available at the registration desk. Service Centre provides photocopying, typing, and computer printouts at cost.

Smoking Policy

The 13th ISABS Conference is officially declared as a "Non-Smoking-Conference".

Special requirements

Registrants with special requirements for physical communication and dietary requirements should contact technical organizer in advance: isabs@etours.hr

Staff

If you should have any questions, the conference staff will be pleased to help you. It will be easy to recognize them by the special name badge they will be wearing.

Poster Setup and Removal

Posters will be displayed during the entire conference. Poster board numbers can be found in the conference book of abstracts. Conference staff at the registration & info desk will help you locate the board. Adhesive material will be made available at registration & info desk.

Posters mounting: Monday, June 17, 2024, 08:00 – 16:00

Posters removal: Thursday, June 20, 2024, 12:00 – 16:00

Poster Sessions

Presenters ARE REQUIRED to be present by their poster for the discussion and to answer questions at the following times:

DAY	TIME
Monday, June 17	12:30 - 14:00
Tuesday, June 18	12:00 -13:00
Wednesday, June 19	12:00 - 13:00

Please note that the program is subject to change, so please check the updated Conference Program or ask at the Registration desk.

ISABS is not responsible for material left after the Conference is over. Posters will not be stored or sent to the authors after the Conference.

GENERAL INFORMATION

GSM OPERATORS

Currently, there are several GSM operators offering the GSM service in Croatia.
T-Mobile operating under +385 98 xxxxxx and +385 99 xxxxxx.
A1 operating under +385 91 xxxxxx.
TELE2 operating under +385 95 xxxxxx.
Bonbon operating under +385 97 xxxxxx.
Please contact your local GSM operator to check the availability and the costs of roaming services.

USEFUL TELEPHONE NUMBERS

Country code: (+/00) 385
Area code (Split): (0)21
Police: 192
Fire-fighting center: 193
Emergency: 194
Time check: 18095
Information local calls: 18981
General information service: 18981
Information national and international calls: 11802
Wake-up calls: 18100
Roadside vehicle assistance: 1987
Weather forecast: 18166

OPENING HOURS

Bank and Post Office Hours are usually open from 8:00 to 19:00, Monday through Friday and from 8:00 - 12:00 on Saturdays.
Non-Governmental offices work from 8:30 to 17:00, Monday to Friday.
Most shops, grocery and department stores are open non-stop, from 6:00 or 7:30 to 19.30 or 20:00.
Restaurants: Most restaurants in Split are open from 8:00 – 23:00. Service charges are included in the price, unless explicitly mentioned otherwise, but an additional tip of 5 to 10 percent is expected. Some restaurants may have a cover charge.

CURRENCY & EXCHANGE

The basic Croatian currency unit is the euro (EUR). Foreign currency can be exchanged for local money at banks, post offices, and exchange offices, according to the valid rates of exchange. Visit the exchange office on the Web for valid exchange rates.
Cash Machines: ATMs accepting all major bank cards and credit cards are located at numerous sites in Split.

CREDIT CARDS

All major credit cards are normally accepted throughout Croatia, as advertised at points of sale, such as American Express, Diners Club, Euro card/Master card, Visa or JCB. Traveler's Cheques are also accepted.
Foreigners can claim a sales tax refund within one year for purchased goods. Don't forget to ask the salesman to fill out the tax refund form when purchasing goods.

MISCELLANEOUS

Electricity Supply: 220-240 V, 50 Hz.
Water: Tap water is drinkable in all parts of Croatia.
Travel and Health Insurance: Participants are advised to make their own arrangements pertinent to health and travel. By registering for the 13th ISABS Conference on Applied Genetics and Mayo Clinic Lectures in Translational Medicine, participants agree that neither the organizers and its agents nor the sponsors and exhibitors nor the Hotel Radisson Blu Resort & Spa 5* assume any liability whatsoever.
Taxi: Numerous taxi stands are located throughout Split city center and in front of hotels. Hotel staff will be glad to help you.

INVITED SPEAKERS

Nobel Laureate Lectures:

Aaron Ciechanover (Nobel Prize in Chemistry 2004; Technion – Israel Institute of Technology, Haifa, Israel): TBA

Svante Pääbo (Nobel Prize in Physiology and Medicine 2022; Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany): Archaic genomes

Richard Roberts (Nobel Prize in Physiology and Medicine 1993; Northeastern University, Boston, MA, USA & New England Biolabs, Ipswich, MA, USA): The many roles of DNA methylation in bacteria

Gregg Semenza (Nobel Prize in Physiology and Medicine 2019; Johns Hopkins School of Medicine, Baltimore, MD, USA): Targeting hypoxia-inducible factors for cancer therapy.

Conference Distinguished Lecture:

Manfred Kayser (Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands): Genetic research to improve forensic practice: the last 20 years

ISABS Lecture:

John Ioannidis (Stanford University, Stanford, CA, USA): Science, scientists, and scientific publications: the quest for reproducible and useful research

Moses Samuel Schanfield Memorial Session on Forensic Genetics

Frederick Bieber (Harvard University, Cambridge, MA, USA): A close view of forensic genetic genealogy: Successes, challenges, and misapplications of genealogists

Bruce Budowle (Department of Forensic Medicine, University of Helsinki, Helsinki, Finland, and Forensic Science Institute, Radford University, Radford, VA, USA): Enhancing human identification with a well-structured forensic investigative genetic genealogy program.

Mitchell Holland (Pennsylvania State University, State College, PA, USA): Sequencing ten thousand mitogenomes: Challenges of interpreting the data.

Walther Parson (Medical University of Innsbruck, Austria): From forensic genetics to forensic genomics

Antti Sajantila (University of Helsinki, Helsinki, Finland): Bridging forensic virology and archaeovirology

Susan Walsh (Perdue School of Science, Indianapolis, IN, USA): From a skull to a face using Forensic DNA phenotyping.

Henry Lee (College of Criminal Justice and Forensic Sciences, University of New Haven, West Haven, CT, USA; Henry C. Lee Institute, West Haven, CT, USA): Use and Abuse of Genetics Evidence in Court

Mayo Clinic Lectures in Translational Medicine Program:

Zvia Agur (Institute for Medical BioMathematics, Tel Aviv, Israel): Why do COVID patients die?

Julie G. Allickson (Mayo Clinic College of Medicine and Science and Mayo Clinic Center for Regenerative Biotherapeutics, Rochester, MN, USA): How we streamline operations for commercial success with execution of early phase clinical trials

Atta Behfar (Mayo Clinic, Rochester, MN, USA): Translation of a scalable exosome platform: From ideation to clinical trial applications

Zwi Bernemann (University of Antwerp, Antwerp, Belgium): Dendritic cell vaccination in cancer and autoimmune disease

Kapil Bharti (National Institutes of Health, Bethesda, MD, USA): Developing an autologous iPS cell-based therapy for age-related macular degeneration

Jung Kyoon Choi (Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Korea): Immunogenomic AI for cancer immunotherapy and diagnosis

Henry Erlich (Children's Hospital Oakland Research Institute, Oakland, CA, USA): In silico sequence, size selection and haplotyping using Oxford Nanopore applied to non-invasive prenatal testing of hemoglobinopathies

Christopher Evans (Mayo Clinic, Rochester, MN, USA): Progress in clinical translation of gene therapy for osteoarthritis.

Robert Ferris (University of Pittsburgh Medical Center, Pittsburgh, PA, USA): Developing innovative therapies and matching treatment intensity for head and neck cancer patients

Arezou A. Ghazani (Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA): Advances in genomic medicine: Genomics, data science and precision health

Massimiliano Gnecchi (University of Pavia, Pavia, Italy): Induced pluripotent stem cells for personalized risk stratification and therapy in patients with cardiac disease; Mesenchymal stromal cell secretome for heart repair

Mateja Hajdinjak (Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany): Zooming into late Neandertal populations with new genomic data

Robert Hariri (Weill Medical College, Cornell University, New York, NY; Celularity, Florian Park, NJ, USA): Placenta-derived therapeutics for cellular and regenerative medicine

Tae Hyun Hwang (Mayo Clinic, Jacksonville, FL, USA): AI-driven 3D modeling and analysis of tumor immune microenvironment and live cell imaging

Manolis Kellis (Massachusetts Institute of Technology, The Broad Institute, Cambridge, MA, USA): AI for genomic medicine and therapeutic development

Saad Kenderian (Mayo Clinic College of Medicine and Science, Rochester, MN, USA): Chimeric antigen receptor T cell therapy: where are we now and in 2030.

Toomas Kivisild (Catholic University Leuven, Leuven, Belgium): Formation of local population structure in North Europe during and after plague pandemics

Guido Kroemer (Université de Paris, Sorbonne Université, Institut Gustave Roussy, Hôpital Européen Georges Pompidou): Stress hormones interfering with cancer immunosurveillance

Gordan Lauc (Faculty of Pharmacy and Biochemistry, University of Zagreb and Genos, Ltd., Zagreb, Croatia): Glycan biomarkers for personalized preventive healthcare

Nathan LeBrasseur (Mayo Clinic College of Medicine and Science, Rochester, MN, USA): Targeting cellular senescence for healthy aging

David Lott (Mayo Clinic College of Medicine and Science, Phoenix, AZ, USA): Translational tissue engineering

Jorge Mallea (Mayo Clinic College of Medicine and Science, Jacksonville, FL, USA): Machine perfusion: A platform for organ repair and regeneration

Shai Meretzki (Bonus BioGroup, Haifa, Israel): Advancing the future of regenerative medicine: Cells and tissue priming for successful translation of effective and accessible therapies

Eskeatnaf Mulugeta (Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands): Forensic solutions by single-cell genomic and epigenomic approaches

Giuseppe Orlando (Wake Forest University School of Medicine): Mitochondrial transplantation as a strategy to increase organ donor pool

Dragan Primorac (ISABS & St. Catherine Specialty Hospital, Zagreb, Croatia; Universities of Split, Osijek and Rijeka, Croatia; Eberly College of Science, The Pennsylvania State University, University Park, State College, PA, USA; The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, West Haven, CT, USA; Regiomed Kliniken, Coburg, Germany): Understanding molecular effect of micro-fragmented adipose tissue (MFAT) and mesenchymal stromal cell (MSC) therapy of osteoarthritis

Elizabeth Rosado Balmayor (MERLN Institute, Maastricht, The Netherlands): Messenger RNA to induce tissue healing

Thomas Salinas (Mayo Clinic, Rochester, MN, USA): Updates in oral/systemic health and reconstruction of craniofacial defects

Ron van Schalk (Erasmus University, Rotterdam, Netherlands): Pharmacogenetics: do YOU have your DNA passport for medication?

Nidhi Shah (Dartmouth Hitchcock Medical Center, Lebanon, NH, USA): Newborn genome sequencing

Nikolaos Skartsis (Mayo Clinic College of Medicine and Science, Rochester, MN, USA): Gene-edited Treg therapies

Doris Taylor (Organmet Bio, Inc., Houston, TX, USA): Bioengineering human heart failure solutions in 2024: Genes, proteins, organs

Serena Tucci (Yale University, New Haven, CT, USA): Genomic legacy of archaic hominid introgression

Samuel Volchenboum (The University of Chicago Medicine, Chicago, IL, USA): Data for the common good: Transforming health through data

Peter Wehling (Duke University, NC, USA and Dr. Wehling & Partner, Düsseldorf, Germany): Secretome-based therapy in chronic pain/OA patients and sports Injury - Biology, clinical results and cases

Laurence Zitvogel (Institut Gustave Roussy, Villejuif, France): The dirty secret of cancer immunotherapy

SCIENTIFIC PROGRAM

Please note that the program and speakers are subject to change.

Sunday, June 16th

9th Croatian Human Genetics Conference & 2nd Croatian Personalized and Precision Medicine Conference (Meeting Room Oleandar, Ground Floor)

OPENING REMARKS **(Dragan Primorac, chair)**

12:00 **Massimiliano Gnecchi** (University of Pavia, Pavia, Italy): Induced pluripotent stem cell-derived cardiomyocytes for precision medicine in patients affected by inherited cardiac channelopathies

12:20 **Lidija Bach Rojecky** (School of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia): Pharmacogenomics: Challenges and Opportunities

12:40 **Petar Brlek** (St. Catherine Specialty Hospital, Zagreb, Croatia): Implementing Whole Genome Sequencing (WGS) in Clinical Practice

13:00 **Ljubica Odak** (Children's Hospital Zagreb, Zagreb, Croatia): The diagnostic journey of chromatin remodeling disorders

13:20 **Damir Marjanović** (Institute for Anthropological Research, Zagreb, Croatia): Identification of Skeletal Remains in Croatia and Bosnia & Herzegovina, Including the Homeland War – A 30-year Review

13:40 **Tatijana Zemunik** (University of Split, School of Medicine, Split, Croatia): Genetic variants associated with thyroglobulin plasma levels

14:00 **Ivona Sansović** (Children's Hospital Zagreb, Zagreb, Croatia): Spectrum of genetic variants in 306 patients with non-syndromic hearing loss from Croatia

14:20 **Break**

14:35 **Jelena Šarac** (Institute for Anthropological Research, Zagreb, Croatia): The Genetic Scenario of Historical Human Migrations in South-Eastern Europe – Three Decades of Croatian Genetic Heritage Story

14:55 **Danijela Petković Ramadža** (University of Zagreb, School of Medicine; University Hospital Centre Zagreb, Zagreb, Croatia): Genotype and phenotypic variability of seven patients with glucose transporter type 1 deficiency syndrome

15:15 **Nina Pereza** (University of Rijeka, Faculty of Medicine, Department of Medical Biology and Genetics, Rijeka, Croatia): A Retrospective Study of Diagnostic Next Generation Sequencing at the University of Rijeka, Faculty of Medicine, Croatia from 2018 to 2023

15:35 **Darko Antičević** (University of Osijek, Faculty of Dental Medicine and Health, Osijek, Croatia, St. Catherine Speciality Hospital, Zagreb, Croatia): Three cases of fibro-dysplasia ossificans progressive with extra long-term follow-up

15:55 **Inga Urlić** (Department of Biology, Faculty of Science, University of Zagreb, Zagreb, Croatia): Insights in Osteosarcoma Evolution by Single-Cell RNA Sequencing

16:15 **Katarina Vukojević** (Faculty of Medicine, University of Split, Split, Croatia): Expression pattern of PDE4B, PDE4D and SFRP5 markers in the colorectal cancer

16:35 **Adjourn** (Dragan Primorac, chair)

Monday, June 17th

OPENING, Main Conference Room, Ground Floor
Dragan Primorac and Stanimir Vuk-Pavlović, chairs
(Main Conference Room, Ground Floor)

09:00 **Comment from the chair**

09:05 **Conference Distinguished Lecture: Manfred Kayser:** Genetic research to improve forensic practice: the last 20 years

09:40 **Gordan Lauc:** Glycan biomarkers for personalised preventive healthcare

10:10 **Intermission**

10:15 **Opening of the Conference program**

11:10 **Intermission**

11:15 **Doris Taylor:** Bioengineering regenerative medicine solutions for heart disease in 2024: From genes to organs

11:45 **Nathan LeBrasseur:** Targeting cellular senescence for healthy aging

12:15 **Adjourn**

12:30 **Lunch and poster presentation (Meeting Rooms Ružmarin & Palma 1, Ground Floor)**

14:00 **RICHARD ROBERTS:** The many roles of DNA methylation in bacteria
(Main Conference Room, Ground Floor)

MOSES SAMUEL SCHANFIELD MEMORIAL SYMPOSIUM:
Henry C. Lee, Honorary Chair; Damir Marjanović, Chair
(Main Conference Room, Ground Floor)

15:00 **Comments from the chair**

15:05 **Walther Parson:** From forensic genetics to forensic genomics: The mtDNA perspective

15:30 **Bruce Budowle:** Enhancing human identification with a well-structured forensic investigative genetic genealogy program

15:55 **Mitchell Holland:** Analysis of HiFi mitogenome sequence data from the PaqBio Sequel IIe

16:20 **Susan Walsh:** From a skull to a face using forensic DNA phenotyping

16:45 **Eskeatnaf Mulugeta:** The future of crime investigation in the era of single-cell omics

17:10 **Frederick Bieber:** DNA on trial: Confronting challenges to DNA in the courts

17:35 **Antti Sajantila:** Bridging forensic virology and archaeovirology

18:00 **Henry Lee:** Use and abuse of genetic evidence in court

18:25 **Adjourn**

15:00 **Nutrigenomics 365 workshop (Nutrigenomics 365 partners only)**
(Meeting Room Kaktus, First Floor)

16:30 **The First Conference of The International Regenerative Medicine Experts Society (IARMES) (By invitation only)**
(Meeting Room Agava, First Floor)

18:30 **Welcome reception**
(Pool Terrace, First Floor)

Tuesday, June 18th

REGENERATIVE MEDICINE I: Elizabeth Rosado Balmayor, Chair
(Main Conference Room, Ground Floor)

08:30 **Comments from the chair**

08:35 **Julie Allickson: Mayo Clinic Center for Regenerative Biotherapeutics:** How we streamline operations for commercial success with execution of early phase clinical trials

09:00 **Christopher Evans:** Progress in clinical translation of gene therapy for osteoarthritis

09:35 **Elizabeth Rosado Balmayor:** Messenger RNA to induce tissue healing

10:00 **Selected Oral Communication: Nikolina Pleić:** Vitamin D and thyroid function: A Mendelian randomization study

10:10 **Dragan Primorac:** Understanding molecular effects of microfragmented adipose tissue and mesenchymal stromal cell therapy of osteoarthritis

10:35 **Giuseppe Orlando:** Regenerative medicine applications to transplant medicine with an emphasis to mitochondrial transplantation

11:00 **Peter Wehling:** Secretome based therapy in chronic pain/OA patients and sports injury: Biology, clinical results and cases

11:25 **Shai Meretzki:** Advancing the future of regenerative medicine: Cells and tissue priming for successful translation of effective and accessible therapies

11:50 **Adjourn**

12:00 **Lunch and poster presentation (Meeting Rooms Ružmarin & Palma 1, Ground Floor)**

13:00 **BOOK PRESENTATION: Henry A. Erlich: Genetic Reconstruction of the Past: DNA Analysis in Forensics and Human Evolution (Oxford University Press, 2023) Dragan Primorac, Wolfgang Höppner, and Lidija Bach-Rojecky (editors): Pharmacogenomics in Clinical Practice (Springer, 2023)**
(Meeting Room Oleandar, Ground Floor)

14:00 **GREGG SEMENZA:** Role of hypoxia-inducible factors in oxygen homeostasis and cancer progression
(Main Conference Room, Ground Floor)

IMMUNOTHERAPY: Laurence Zitvogel, Chair
(Main Conference Room, Ground Floor)

15:00 **Comments from the chair**

15:05 **Guido Kroemer:** Stress hormones interfering with cancer immunosurveillance

15:30 **Laurence Zitvogel:** Links between gut microbiota and tumor immunosurveillance

15:55 **Nikolaos Skartsis:** Inflammation-trained Tregs for cell therapy

16:20 **Saad Kenderian:** Chimeric antigen receptor T cell therapy: Where are we now and in 2030

16:45 **Zwi Berneman:** Dendritic cell vaccination in cancer and autoimmune disease

17:10 **Robert Ferris:** Developing innovative therapies and matching treatment intensity for head and neck cancer patients

17:35 **Selected Oral Communication: Elizabeth Appleton:** CAR-T-oncolytic virus combinations – exploiting the endogenous T-cell receptor (TCR) for enhanced therapy

17:45 **Adjourn**

17:30 **Nobel Spirit – televised session with Nobel Laureates; Croatian Radiotelevision (By invitation only)**
Museum of Croatian Archaeological Monuments (MHAS)

19:00 **Gala Dinner, Moses Schanfield Young Investigator Award (YIA) Ceremony**
Meštrović Gallery

Wednesday, June 19th

AI AND MACHINE LEARNING IN MEDICINE: Zvia Agur, Chair
(Main Conference Room, Ground Floor)

08:30 **Comments from the chair**

08:35 **Jung Kyoon Choi:** Immunogenomic AI for cancer immunotherapy and diagnosis

09:00 **Tae Hyun Hwang:** AI-driven 3D modeling and analysis of tumor immune microenvironment and live cell imaging

09:25 **Selected Oral Communication:** Yuri Kogan: Expanding a personalization algorithm for predicting individual response to immunotherapy in patients with advanced melanoma

09:35 **Samuel Volchenboum:** Data for the common good: Transforming health through data

10:00 **Zvia Agur:** Why do COVID-19 patients die?

10:25 **Ron van Schaik:** Pharmacogenetics: Do you have your DNA-passport for medication?

10:50 **Manolis Kellis:** AI for genomic medicine and therapeutic development

11:15 **Arezou Ghazani:** Advancing precision medicine through integration of large-scale genome and clinical data

11:40 **Adjourn**

11:30 **European Olympic Committees: Medical and Antidoping Commission Meeting (By invitation only)**
(Meeting Room Agava, First Floor)

12:00 **Lunch and poster presentation (Meeting Rooms Ružmarin & Palma 1, Ground Floor)**

13:00 **BOOK PRESENTATION: Xiaping Jiang (with Anthony Roberts and Henry C. Lee): Gunshot in Croatia (Dixie W. Publishing, 2023) Dragan Primorac and Moses Schanfield (editors): Forensic DNA Applications: An Interdisciplinary Perspective, 2nd Edition (Rutledge, 2023)**
(Meeting Room Oleandar, Gound Floor)

14:00 **SVANTE PÄÄBO: Archaic genomics**
(Main Conference Room, Ground Floor)

GENE ANALYSIS IN HUMAN HEALTH AND HISTORY:
Eskeatnaf Mulugeta, Chair
(Main Conference Room, Ground Floor)

15:00 **Comments from the chair**

15:05 **Henry Erlich:** In silico sequence size selection and haplotyping using Oxford Nanopore applied to non-invasive prenatal testing of hemoglobinopathies

15:40 **MSYI Award:** Floor Claessens: A comprehensive analysis of whole mitogenome heteroplasmy patterns in different forensic tissues

15:50 **Nidhi Shah:** Genomic frontieers: Towards universal newborn sequencing

16:15 **Selected Oral Communication:** Barbara Golob: Experience with genomic matchmaking: Enhancing diagnostic efficacy and new gene–disease discoveries in NGS diagnostics for rare diseases

16:40 **Mateja Hajdinjak:** Zooming into late Neandertal populations with new genomic data

17:05 **Selected Oral Communication:** Aurore Monnereau: Genetic histories of medieval Sicilian individuals

17:15 **Selected Oral Communication:** Marta Diepenbroek: Sarmatian Goth or Gothic Sarmatian? Forensics sheds light on surprising Iron/age burial

17:25 **Serena Tucci:** Genomic legacy of archaic hominin introgression

17:50 **Toomas Kivisild:** Formation of local population structure in North Europe during and after plague pandemics

18:15 **Adjourn**

20:00 **ISABS lecture John Ioannidis: Science, scientists, and scientific publications: The quest for reproducible and useful research**
(Main Conference Room, Ground Floor)

Thursday, June 20th

REGENERATIVE MEDICINE II: Atta Behfar, Chair
(Main Conference Room, Ground Floor)

08:30 **Comments from the chair**

08:35 **David Lott:** Translational tissue engineering

08:50 **Jorge Mallea:** Machine perfusion: A platform for organ repair and regeneration

09:15 **Thomas Salinas:** Updates in oral/systemic health and reconstruction of craniofacial defects

09:40 **Atta Behfar:** Acellular approach for cardiovascular regeneration and wound healing

10:05 **MSYI Award:** Martina Glavan: CNS-associated macrophages contribute to intracerebral aneurysm pathophysiology

10:15 **Massimiliano Gnecchi:** Mesenchymal stromal cell secretome for heart repair

10:40 **Selected Oral Communication:** Bojan Vrtovec: Precision medicine approach to cell therapy in heart failure

10:50 **Kapil Bharti:** Developing an autologous iPS cell-based therapy for age-related macular degeneration

11:15 **Adjourn**

12:00 **Lunch and Poster Removal**

14:00 **AARON CIECHANOVER:** Bioethics and COVID-19; it is not only the virus, the disease and the vaccine
(**Main Conference Room, Ground Floor)**

15:00 **CLOSING:** ***Dragan Primorac and Stanimir Vuk-Pavlović, Chairs***
(Main Conference Room, Ground Floor)

15:00 **Comments from the chair**

15:05 **Closing Lecture: Robert Hariri: Placenta-derived therapeutics for cellular and regenerative medicine**

15:40 **Closing of the conference**

16:00 **Adjourn**

Friday, June 21th

Joint Event by ISABS, Ministry of the Interior, American Academy of Forensic Sciences (AAFS), and University of Split, Department for Forensic Sciences – Crime Scene Investigation Training Course
University of Split, School of Medicine, Main Amphitheatre

Phil Spector case – Forensics Key in Spector Trial

08:00 **Welcome and introduction (Henry Lee, Dragan Primorac, Šimun Anđelinović, Damir Marjanović, Andrea Ledić)**

08:30 Investigation of Shooting Death

09:30 Case of Phil Spector

10:30 Crime Scene Exercise and Investigation

12:00 Lunch

13:00 **Lecture: Courtroom Testimony**

14:00 **Court Testifying Exercises**

15:30 **Summation**

16:00 **Award ceremony**

NOBEL LAUREATE SESSION

BIOETHICS AND COVID-19; IT IS NOT ONLY THE VIRUS, THE DISEASE AND THE VACCINE

Aaron Ciechanover

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Many bioethical questions have emerged in the rush to develop a vaccine for Covid-19 and care for the multitude of patients. These questions require careful attention in preparation for the next pandemic that will certainly come. Among the question are: i) How to prioritize treatment for those in need of respiratory assistance? ii) Can we prioritize the pandemic neglecting important issues such as climate change or campaigns to defeat infectious diseases in Africa, e.g., tuberculosis and malaria? iii) How to handle vaccine hesitancy and its sources? iv) What to do with "infodemics", the pandemics of disinformation and the huge damage they produce? (v) How to confront the rise of racism? Some problems are related to bioethical issues we confront while ushering in the era of personalized medicine. Among the issues that will certainly need redefinition are the pillars of 'canonical' medicine: the patient, the disease, and the treatment.

ARCHAIC GENOMICS

Svante Pääbo[1,2]

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Our laboratory has generated high-quality genome sequences from Neandertals and Denisovans, archaic hominins who shared a common ancestor with present-day humans about half a million years ago. Analyses of these genomes show that gene flow occurred among modern human ancestors and archaic hominins. As a consequence, archaic genetic variants occur in present-day people. I will discuss the effects of some of these variants as well as of some variants that appeared and rose to high frequencies in modern humans since their divergence from the archaic hominins.

THE MANY ROLES OF DNA METHYLATION IN BACTERIA

Richard J. Roberts

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There are three kinds of DNA methylation in bacteria – N6-methyladenine, N4-methylcytosine and 5- methylcytosine. One of the best-known roles for these DNA methyltransferases is to protect the host genome against the restriction enzymes they encode to serve as defense systems against bacteriophages. Other well-documented roles include DNA mismatch repair (e.g. the Dam methylase in *Escherichia coli*) and cell cycle control (e.g. M.CcrI in *Caulobacter crescentus*). Recently, a DNA methyltransferase has been shown to control sporulation in *Clostridium difficile*. Recent sequencing of bacterial genomes has shown that a large number contain orphan DNA methyltransferases with no currently known biological function. There are clearly many new functions to be discovered and in this talk I will give an overview of this fascinating field.

ROLE OF HYPOXIA-INDUCIBLE FACTORS IN OXYGEN HOMEOSTASIS AND CANCER PROGRESSION

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Hypoxia-inducible factors (HIFs) are transcriptional activators that balance O2 supply and demand by regulating the expression of genes that control the delivery and consumption of O2, respectively. We purified HIF-1 and found that it was a heterodimer composed of an O2-regulated HIF-1alpha subunit and a constitutively expressed HIF-1beta subunit. In the presence of O2, HIF-1alpha is subject to hydroxylation on two proline residues. Hydroxylated HIF-1alpha is bound by the von Hippel-Lindau protein (VHL), which recruits a ubiquitin-protein ligase complex, leading the ubiquitination and proteasomal degradation of HIF- 1alpha under normoxic conditions. Under hypoxic conditions, hydroxylation is inhibited leading to the rapid accumulation of HIF-1alpha, dimerization with HIF-1beta, binding to hypoxia response elements, and transcriptional activation of target genes. HIF-2alpha and HIF-3alpha are also O2-regulated and dimerize with HIF-1beta, but unlike the ubiquitous expression of HIF-1alpha, they are only expressed in a limited number of cell types. We now know of over 8,000 mRNAs, miRNAs, and lncRNAs which are directly activated by HIFs in response to hypoxia in one cell type or another. The HIF system is coopted by cancers to facilitate tumor angiogenesis, metabolic reprogramming, immune evasion, cancer stem cell specification, invasion and metastasis. Increased HIF-1a protein in the diagnostic tumor biopsy is associated with patient mortality in brain, breast, cervical, colorectal, endometrial, gastric, hepatocellular, lung, oropharyngeal, ovarian, pancreatic, and prostate cancer. We have identified a small molecule HIF inhibitor that blocks hepatocellular cancer growth and improves the response to anti-PD1 immunotherapy in mouse models by switching the tumor immune microenvironment from one that is immunosuppressive to one that promotes anti-tumor immunity.

ABSTRACTS OF INVITED LECTURES

Presentation number: IL 01 Abstract number: ABS-81-ISABS-2024

WHY DO COVID-19 PATIENTS DIE?

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What makes COVID-19 deadly for some people while others have minimal symptoms is an important clinical research question. Current studies, showing conflicting results, assume direct relationships between single-point measurements of inflammation variables and death probability. Our approach differs in assuming that COVID-19 death depends on dynamic processes that underlie the temporal changes in blood components. We analyzed the longitudinal measurements of blood variables in people with COVID- 19, who were hospitalized in Chaim Sheba Medical Center between March 2020 and August 2021. Results exhibit elevated patient mortality shortly after deterioration, preceded by a sharp and highly significant increase in LDH and D-dimer levels in the first two weeks following patient deterioration. Before deterioration, the differences between survivors and non-survivors were insignificant in all measured blood variables. From our results we infer the onset of an iteratively amplified glycolysis, substantially augmenting viral replication and tissue damage during severe hypoxia. We postulate that mutations which favor non-oxidative metabolism could make the difference between patients who succumb to the detrimental effects of glycolysis and patients who recover.

Keywords: longitudinal measurements, patient deterioration, hypoxia, positive feedback, glycolysis

Presentation number: IL 02 Abstract number: ABS-130-ISABS-2024

MAYO CLINIC CENTER FOR REGENERATIVE BIOTHERAPEUTICS: HOW WE STREAMLINE OPERATIONS FOR COMMERCIAL SUCCESS WITH EXECUTION OF EARLY PHASE CLINICAL TRIALS

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Mayo Clinic Center for Regenerative Biotherapeutics focuses on manufacturing biotherapeutics derived from blood, tissue, cells as well as genetically engineered cellular therapies. The center services include biomanufacturing capabilities that seek to advance cell and gene discoveries to clinical care for patients with rare and complex diseases. Mayo's goal is to deliver biotherapeutics to provide new cures, particularly for unmet clinical needs. Mayo Clinic has made investments in biomanufacturing facilities on all three of its campuses. These facilities adhere to current Good Manufacturing Practices (cGMP) where biotherapeutics are manufactured to ensure identity, strength, quality, and purity. The cGMP facilities operate under strict quality standards in accordance with US Food and Drug Administration guidelines for manufacturing investigational drugs tested in early phase clinical trials. The strategy is to advance promising cell and gene discoveries from Mayo Clinic to early-stage clinical trials. Mayo collaborates with industry with a goal to accelerate first-in-human biotherapeutics to market for the benefit of patients around the globe. Our priority for manufacturing includes cellular and gene therapy for malignant and non-malignant diseases. We also focus on bioprinting scaffolds used for defects and tissue engineering for tissues and organs. The vision for leading the biomanufacturing strategy at Mayo Clinic seeks to harness the full potential of regenerative therapies to repair diseased, injured or congenitally defective tissues and organs. The goal is to develop regenerative biotherapies that are ready for clinical application and are easy transferred to industry for a streamlined path of commercialization.

Keywords: biotherapeutics, biomanufacturing, commercialization, cellular, cGMP

Presentation number: IL 03 Abstract number: ABS-183-ISABS-2024

MESSENGER RNA TO INDUCE TISSUE HEALING

Elizabeth Rosado Balmayor

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We have recently acknowledged the potentialities of mRNA therapeutics in fields such as regenerative medicine. mRNA can be used to express a therapeutic protein and, in contrast to DNA, is safer and inexpensive. Among its advantages, mRNA will immediately begin to express its encoded protein in the cell cytoplasm. The protein will be expressed for a period of time, after which the RNA is degraded. There is no risk of genetic damage, one of the concerns with DNA. Nevertheless, mRNA application to stimulate tissue healing remains limited. In this case, mRNA must overcome its main hurdles: immunogenicity, lack of stability, and intracellular delivery. Research has been done to overcome these limitations, and the future of mRNA seems promising for tissue repair. This talk seeks to introduce the audience to mRNA therapeutic for tissue regeneration, its advantages, and its limitations. The state-of-the-art of the uses of this technology for bone regeneration will be presented. Several examples of our own research will be provided to illustrate the uses of protein-coding mRNA for bone healing. Among other questions that will be addressed are, what are the opportunities for mRNA to improve outcomes in musculoskeletal tissue repair? What are the key factors and challenges to expediting this technology to patient treatment (beyond COVID-19 vaccination)?

Keywords: mRNA, transcript therapy, bone, cartilage, tissue healing

Presentation number: IL 04 Abstract number: ABS-51-ISABS-2024

A CELLULAR APPROACH FOR CARDIOVASCULAR REGENERATION AND WOUND HEALING

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Cardiovascular disease, diabetes and radiation are significant drivers of morbidity. In the United States alone, there are over 8 million patients with non-healing wounds and globally >17 million patients die annually as a result of cardiovascular disease. The burden of chronic disease strains all health systems and reduces the quality of life for many patients. Over the last 2 decades, there has been a concerted effort to utilize stem cell-based biotherapy to accelerate tissue regeneration. However, due to the variability of cellular benefit, this approach to regenerative medicine has not yielded any approved therapies. Over the course of the last decade, our team and several others have shown that the driver of stem cell benefit in tissue healing is likely driven by shed exosomes. Rather than being building blocks for tissue healing, it appears that stem cells actually drive in situ healing through release of regenerative exosomes. To this end, we have isolated and scaled a novel regenerative exosome named purified exosome product, or PEP, with establishment of clear modes of action end route to clinical application. In this talk, the CHART-1 stem cell trial outcomes will be reviewed, highlighting the post-trial effort that led to the discovery of PEP. Next, trial enabling efforts utilized PEP in vitro and in vivo to document its biological impact will be highlighted, in tandem with review of the first in man, first in class Phase 1 and 2 clinical trial data. The high prevalence and significant healthcare burden associated with non-healing wounds and CVDs necessitate development of novel therapeutic strategies. Regenerative exosomes offer a promising approach to address this unmet need, which through the recent successes with optimized production and delivery methods developed is becoming a reality.

Keywords: regenerative medicine, cardiovascular disease, non-healing wounds, exosome, stem cell

Presentation number: IL 05 Abstract number: ABS-60-ISABS-2024

DENDRITIC CELL VACCINATION IN CANCER AND IN AUTO-IMMUNE DISEASE

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Dendritic cells (DC) can modulate antigen-specific T-cell immunity. Since 2005, we have been treating cancer patients with immunogenic DC, electroporated with mRNA encoding the Wilms' tumor protein (WT1) tumor-associated antigen. In acute myeloid leukemia, we have observed clinical effects in 43% of patients, preventing or delaying relapse and increasing overall survival (OS); those effects were correlated with WT1-specific CD8 T-lymphocyte response. In patients with solid tumors, there was a disease control rate of 74.4%; clinical response and OS were correlated with WT1-specific type 1 T-lymphocyte response. We have recently completed a phase I/II trial in mesothelioma, where DC vaccination was combined with conventional chemotherapy; relapsing patients were generally treated with a checkpoint inhibitor; the latter combination led to complete and partial responses and stable disease in relapsing patients; interim analysis showed an increased median OS. We are also carrying out a trial in patients with glioblastoma; interim analysis showed an increased OS; relapsing patients displayed a strong decrease of WT1 positivity in resected tumoral tissue, as compared to the tumor at diagnosis, strongly suggesting immune evasion after initial immune control. We have also developed a methodology to produce tolerogenic DC, by adding vitamin D3 to the culture medium. We then carried out a phase I study in multiple sclerosis, an autoimmune disease attacking the central nervous system, by using tolerogenic autologous dendritic cells, pulsed with myelin peptides; this study confirmed the safety and feasibility of this tolerogenic DC protocol, and we are preparing a follow-up phase II study. Thus, therapeutic vaccination with WT1 mRNA-electroporated immunogenic DC has clinical activity in various cancers and there are indications of an increased OS and of a synergistic effect with checkpoint inhibitors. Tolerogenic DC open new perspectives in the treatment of auto-immune diseases.

Keywords: dendritic cell vaccination, cancer, immunity, autoimmune disease, tolerance

Presentation number: IL 06 Abstract number: ABS-180-ISABS-2024

DEVELOPING AN AUTOLOGOUS CELL THERAPY FOR AMD

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The advanced stage of age-related macular degeneration (AMD) - geographic atrophy (GA) leads to irreversible vision loss and often manifests in people above 60 years of age. AMD is thought to initiate by the dysfunctional retinal pigment epithelium (RPE) monolayer - resulting in sub-RPE protein-rich drusen deposits. RPE sits between photoreceptors and choroidal capillaries, providing nutrients and support necessary for maintaining the homeostatic unit at the back of the eye. The GA stage is characterized by RPE atrophy, photoreceptor cell death, and the loss of chorio-capillary bed. Currently, no treatment is available to improve vision for the late stage of GA patients. Here, we developed an autologous cell replacement therapy for treating GA patients. We used induced pluripotent stem cells (iPSC) reprogrammed from $CD34^+$ cells isolated from PBMC collected from patients' blood. iPSCs are differentiated into pure RPE cells using a protocol developed in our lab. The RPE cells are matured on a biodegradable polylactic co-glycolic acid (PLGA) scaffold for five weeks as a tissue patch. Quality control assays confirmed the iPSC-RPE patch's purity, maturity, and functionality. Pre-clinical studies were conducted in rats and pigs to demonstrate the safety and efficacy of the iPSC-RPE patch. Immune-compromised rats transplanted with a 0.5 mm iPSC-RPE patch showed no signs of tumor formation after nine months, confirming the safety profile. To test local safety and efficacy in a large animal model, we laser-ablated the RPE monolayer in the visual streak of pig eyes and, after 48 hours, transplanted the iPSC-RPE patch. Optical coherence tomography (OCT) that measures retinal anatomy confirmed the integration of the patch in the subretinal region. Multi-focal electroretinogram (ERG) that measures retina function showed that the electric response of the retinal layers over the area of patch was much higher than the lasered area without the implant. This work was cleared by the FDA for a Phase I/IIa clinical trial to test the safety and feasibility of an autologous iPSC-RPE patch in AMD patients with GA. The Phase I/IIa trial is currently ongoing at the National Eye Institute at NIH.

Keywords: Autologous cell therapies, iPS cell, macular degeneration, AMD, retinal degeneration

Presentation number: IL 07 Abstract number: ABS-177-ISABS-2024

DNA ON TRIAL: CONFRONTING CHALLENGES TO DNA IN THE COURTS

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Advances in DNA technology have been critical for many aspects of anthropological and genetics research. We now enjoy improved understanding of human migration patterns and have better tools for humanitarian reunification of human remains, and for forensic identification of forensically relevant DNA samples. Use of both short tandem repeats (STRs) and single nucleotide polymorphisms (SNPs), along with high-throughput DNA sequencing have expanded the tools and opportunities in these arenas. Along with the DNA science come some unanticipated challenges and questions to be confronted in both civil and the criminal courts. Several such examples are the subject of this presentation. The first is a class- action civil case in Canada which now challenges a government laboratory, arguing that the laboratory retains some records of STR results from voluntary exclusion samples. The class of migrant farm workers argues that the Canadian government laboratory practices opens doors for privacy breeches of those innocent workers who volunteered their exclusion samples as part of an investigation of a sexual assault. They claim that this can occur by imputation of SNP profiles from their STR results. The government's argument will be presented. The second example involves a homicide investigation in the USA, in which key DNA results were limited to Y-STR (Y-filer) results taken at autopsy from a fingernail swab of a murder victim. These results were sent by the crime laboratory to a genealogist who, using private surname databases, then provided a list of surnames that share the same Y-haplotype as that found in the evidence. Focusing their investigation only on the most common surname from the long list of surnames, investigators proceeded to identify, arrest, and charge a person of interest who shared that Y-STR profile. A trial, the jury was not able to learn any of these details of the investigation, as the genealogist and report were not introduced by the prosecution. Resul

Keywords: STR, SNP, genealogy, Y-haplotype, law, ethics

Presentation number: IL 08 Abstract number: ABS-90-ISABS-2024

ENHANCING HUMAN IDENTIFICATION WITH A WELL-STRUCTURED FORENSIC INVESTIGATIVE GENETIC GENEALOGY PROGRAM

Bruce Budowle[1,2,3], Mandape Sammed[3], Mittelman Kristen[3], Mittelman David[3]

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The forensics genetics/genomics field is experiencing a revolution with dense single nucleotide polymorphisms (SNPs) testing via massively parallel sequencing. High throughput SNP testing promises to substantially enhance source attribution in forensic cases, particularly those involving low-quantity and/or low-quality samples. When current approaches of short tandem repeat markers and government maintained national DNA databases fail to generate investigative leads, dense SNP analyses may be able to provide information for source attribution. In concert with genetic genealogy and kinship analysis, dense SNP analyses often can generate viable investigative leads with DNA criminal cases that have been unresolved near and long term as well as for active cases and for the identification of unknown human remains. The higher resolution and sensitivity of this technology allows for greater discrimination power in associating individuals who are not closely related as well as for direct comparisons. Genetic genealogy databases, populated with dense SNP profiles from consented volunteers, enable measurements of near and distant relationships to the donor of crime scene evidence or an unknown person, which in turn through genealogy can effectively narrow down source candidates. DNA sequencing costs have dropped substantially and continue to decrease, and sensitivity of detection continues to improve. Thus, given its practical use, capabilities and successes, forensic genetic genealogy has become a highly successful, viable, routine approach to generate investigative leads from a wide range of biological evidence. The benefits to public safety and security, bringing resolution to victims, families, and communities, and developing leads in a cost-effective and rapid manner will continue to drive broader adoption of forensic genetic genealogy. The overall value highlights the importance of careful investment and governance in leveraging these technologies for societal benefit.

Keywords: Forensic genetic genealogy, SNPs, Sequencing, unidentified human remains, criminal casework

Presentation number: IL 09 Abstract number: ABS-66-ISABS-2024

IMMUNOGENOMIC AI FOR CANCER IMMUNOTHERAPY AND DIAGNOSIS

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In this presentation, I will demonstrate how artificial intelligence, applied to immuno-genomic data, can be utilized for neoantigen vaccination, chimeric antigen receptor (CAR)-T cell therapy, and noninvasive cancer detection. For neoantigen identification, we developed a deep learning method to identify peptide- MHC complexes whose structural alignment facilitates T cell reaction. This method was validated based on a meta-analysis of 10 personalized vaccine trials involving 1,060 neoantigens that were administered to 100 patients. For CAR-T target identification, we developed a two-step screening method using random forest and convolutional neural networks to select gene pairs that contribute most to discrimination between individual malignant and normal cells. Tumor coverage and specificity were evaluated for the AND, OR, and NOT logic gates based on the combinatorial expression pattern of the pairing genes across individual single cells. For noninvasive multi-cancer screening, we developed a deep learning model that extracts cancer-specific immunological features from 10,929 tumor and 10,845 normal tissue transcriptomes. This model achieved an ROC-AUC of 0.94 in discriminating between our 531 blood samples from various types of cancer and 745 normal blood samples. Our results highlight the clinical implications of local and peripheral immune characteristics in the application of blood-based multi-cancer detection.

Keywords: CAR-T, neoantigen, cancer vaccine, noninvasive cancer detection

Presentation number: IL 10 Abstract number: ABS-96-ISABS-2024

IN SILICO SEQUENCE SIZE SELECTION AND HAPLOTYPING USING OXFORD NANOPORE APPLIED TO NON-INVASIVE PRENATAL TESTING OF HEMOGLOBINOPATHIES

Henry Erlich, Lee Jiyae, Ko Lily, Eaton Katrina, Mack Steven

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The presence of fetal DNA in maternal plasma and the massively parallel and clonal features of Next Generation Sequencing (NGS) have made non-invasive prenatal testing (NIPT) a reality. We have applied NGS to the NIPT of the autosomal recessive diseases, sickle cell anemia (SCA) and β-thalassemia, by using a capture probe panel that covers 4 Kb of the β-globin gene and linked SNPs as well as >450 genomic polymorphisms used to estimate the fetal fraction. Following Illumina MiSeq sequencing of plasma libraries, the fetal fraction is estimated by counting paternally transmitted sequence reads for alleles present in the fetus but absent in the mother. The fetal β-globin genotype is inferred by counting sequence reads corresponding to the mutation and wild-type alleles and comparing the observed ratios to those expected for each of the three possible fetal genotypes (Mut/Mut; Mut/WT; WT/WT), based on the fetal fraction. Since the sequence reads from the fetal DNA are slightly shorter than the maternal sequence reads in plasma, we can enrich the fetal fraction by bioinformatically excluding reads over a specified length (in silico size selection or ISS), increasing the accuracy of fetal genotype prediction. To further increase the accuracy of fetal genotyping based on sequence read ratios at the mutation site alone, we have analyzed read ratios observed at linked SNPs. The beta-globin haplotypes are determined by long-read sequences derived from parental DNA using Oxford Nanopore technology and NextGENe LR software (Soft Genetics.) to analyze a 2.2 kb amplicon. Using, ISS and haplotyping, we have correctly predicted the fetal genotype in 50 out of 50 families.

Keywords: NIPT, NGS, haplotype, beta-globin, recessive

Presentation number: IL 11 Abstract number: ABS-73-ISABS-2024

PROGRESS IN CLINICAL TRANSLATION OF GENE THERAPY FOR OSTEOARTHRITIS

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Osteoarthritis (OA) is common, debilitating, incurable and difficult to treat. Among the impediments to improving OA therapy is our inability to target therapeutics, especially biologics, to diseased joints and keep them there at therapeutic concentrations for a sustained period of time. Gene transfer to the joint is the only clinically reasonable strategy for overcoming this barrier. We have developed a gene therapeutic for OA comprising an adeno-associated virus (AAV) encoding the interleukin-1 receptor antagonist (IL- 1Ra). This agent (AAV.IL-1Ra) is injected directly into joints with OA where it transduces articular cells which then secrete IL-1Ra into the joint space. Pre-clinical data confirm that AAV transduces synovial lining cells and chondrocytes after intra-articular injection with elevated IL-1Ra expression for at least a year. We recently concluded a Phase I human clinical trial of this technology (ClinicalTrials.gov Identifier: NCT02790723). This study enrolled 9 patients with mid-stage OA of the knee into 3 cohorts of 3 subjects. In a dose-escalation fashion knee joints were injected with 1011, 1012 or 1013 viral genomes of AAV.IL- 1Ra and followed for 1-year to assess safety, intra-articular IL-1Ra levels, patient-reported outcomes, immune responses to the vector and obtain other relevant information. There were no serious adverse events related to the vector. Concentrations of IL-1Ra in synovial fluid were elevated by administration of AAV.IL-1Ra and, at higher doses, remained elevated during the year-long follow-up. Neutralizing antibodies to AAV were generated in response to injection of the vector, but not cell-mediated responses. Improvements in pain and function scores occurred but without a control group we cannot rule out a placebo effect. Based on these encouraging data, a larger, Phase Ib trial of AAV.IL-1Ra (ClinicalTrials.gov Identifier: NCT05835895) has been initiated by an arthritis gene therapy company (Genascence Inc.) we established.

Keywords: osteoarthritis, AAV, interleukin-1, clinical trial, translation

Presentation number: IL 12 Abstract number: ABS-169-ISABS-2024

DEVELOPING INNOVATION THERAPIES AND MATCHING TREATMENT INTENSITY FOR HEAD AND NECK CANCER PATIENTS

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The immune system plays a key role in the development, establishment, and progression of head and neck squamous cell carcinoma (HNSCC). A greater understanding of the dysregulation and evasion of the immune system in the evolution and progression of HNSCC provides the basis for improved therapies and outcomes for patients. HNSCC cells evade the host immune system through manipulation of their own immunogenicity, production of immunosuppressive mediators, and promotion of immunomodulatory cell types. Through the tumor's influence on the microenvironment, the immune system can be exploited to promote metastasis, angiogenesis, and growth. This article provides a brief overview of key components of the immune infiltrating cells in the tumor microenvironment, reviewing immunological principles related to head and neck cancer, including the concept of cancer immunosurveillance and immune escape. The presentation will review the therapeutic interventions to reverse immune escape by immune checkpoint inhibitors, review the clinical outcomes of combining cancer immunotherapy with conventional therapeutic modalities, such as chemotherapy and radiotherapy, and describe emerging preoperative approaches to neoadjuvant immunotherapy. In summary, personalized cancer immunotherapeutic strategies and emerging results from ongoing clinical trials are presented.

Keywords: head and neck squamous cell carcinoma (HNSCC)

Presentation number: IL 13 Abstract number: ABS-176-ISABS-2024

ADVANCING PRECISION MEDICINE THROUGH INTEGRATION OF LARGE-SCALE GENOME AND CLINICAL DATA

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The advent of genome sequencing methods has enabled the generation of large-scale data. However, the utility of this data in clinical practice is often limited due to the absence of practical and multi-disciplinary approaches to effectively glean actionable findings from large data. This talk will cover new genome initiatives at Brigham Genome Medicine that address this unique challenge. INT^{2}GRATE | Oncology Consortium is a multi-institution initiative that aims to advance precision oncology and patient care by integrating the applications of constitutional and tumor-derived data in cancer. INT2GRATE (INTegrated INTerpretation of GeRmline and Tumor gEnomes) computational infrastructure enables the systematic collation and integration of tumor-derived and constitutional clinical evidence to assess the role of germline variants in cancer susceptibility. To date, we have analyzed >15,000 germline variants from different disease cohorts using the INT2GRATE platform in Lynch syndrome (n=5018), hereditary paraganglioma–pheochromocytoma syndrome (n=8049), and Von Hippel-Lindau syndrome (n=2552). Rare & Undiagnosed Genome Program (RUGP) is a separate multi-institutional initiative that aims to identify actionable targets in previously undiagnosed patients through the integration of clinical data with advanced genome interrogation tools, and through developing an open-data community. To date, we have identified actionable genome alterations in ~25% of the patient cohort. The success, strategy, and future directions of these programs will be discussed.

Keywords: genomic medicine, INT^{2}GRATE, undiagnosed genome, big data, precision oncology

Presentation number: IL 14 Abstract number: ABS-122-ISABS-2024

MESENCHYMAL STROMAL CELL SECRETOME FOR HEART REPAIR

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Tissue regeneration from transplanted mesenchymal stromal cells (MSC) either through transdifferentiation or cell fusion was originally proposed as the principal mechanism underlying their therapeutic action. However, several studies have shown that both mechanisms are very inefficient. The low MSC engraftment rate documented in injured areas also refutes the hypothesis that MSC repair tissue damage by replacing cell loss with newly differentiated cells. Indeed, despite evidence of preferential homing of MSC to the site of myocardial ischemia, exogenously administered MSC show poor survival and do not persist in the infarcted area. Therefore, it has been proposed that the functional benefits observed after MSC transplantation in experimental models of tissue injury might be related to the secretion of soluble factors acting in a paracrine fashion. This hypothesis is supported by pre-clinical studies demonstrating equal or even improved organ function upon infusion of MSC-derived conditioned medium (MSC-CM) compared with MSC transplantation. Identifying key MSC-secreted factors and their functional role seems a reasonable approach for a rational design of next-generation MSC-based therapeutics. Besides proteins, MSC-CM also contains extracellular vesicles that can promote the repair of cardiac function by transporting noncoding RNA and protein. In recent years, MSC-derived exosomes have been promising cell-free treatment tools for improving cardiac function and reversing cardiac remodeling. In my talk, I will summarize the major findings regarding both different MSC-mediated paracrine actions and the identification of paracrine mediators that soon will hopefully become clinically relevant new therapies for heart disease.

Keywords: mesenchymal stromal cells, secretome, proteins, exosomes, heart repair

Presentation number: IL 15 Abstract number: ABS-142-ISABS-2024

ZOOMING IN INTO LATE NEANDERTAL POPULATIONS

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Before their disappearance at around 40,000 years before present (i.e. ~40 ka BP), Neandertals lived throughout Europe, western and central Asia, and the Near East, appearing in the European fossil record at least ~430 ka BP. However, despite genome-wide data being recovered from more than 10,000 ancient humans to date, the genomic data recovered from Neandertals are still relatively sparse. Thus far, genome-wide data have been retrieved for in total 31 Neandertals from 16 archaeological sites, spanning their long history and across large parts of their geographical range, and offering a broad overview of Neandertal populations. Here, I will present our recent efforts in reconstructing a more fine-scale Neandertal population history, focusing on Neandertal individuals from the archaeological sites in the Mosan Basin (Belgium). We used minimally destructive sampling of 32 skeletal remains which were previously radiocarbon dated to between ~49 and ~40 ka BP. Out of those, 28 contained enough endogenous DNA to generate genome-wide data at different levels of completeness (autosomal, mitochondrial and Y-chromosomal capture data), along with a new high-coverage genome of a late Neandertal from Troisième caverne of Goyet, a ~45 ka-year-old Goyet Q56-1. Overall, we find that late Neandertals from the Mosan Basin have higher genetic diversity than Neandertals from the Altai mountains, which lived between ~130 and 80 ka BP. Moreover, these Neandertals also have fewer long tracts of homozygosity, comparable to that of the Vindija Neandertals from Croatia, which lived around the same time. Thus far, we also do not find evidence of genetic structure or biological kinship among the late Neandertals in Belgium, further suggesting that the population structure of late North-Western European Neandertals contrasts the one found in the Altai mountains and showing that Neandertal communities differed across their temporal and geographical range.

Keywords: Neandertals, ancient DNA, population history

Presentation number: IL 16 Abstract number: ABS-162-ISABS-2024

PLACENTA-DERIVED THERAPEUTICS FOR CELLULAR AND REGENERATIVE MEDICINE

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The post-partum placenta represents one of the most abundant and versatile raw materials for the evolving fields of cellular therapy and regenerative medicine. As a source of virtually any phenotype stem or progenitor cell which ultimately can be expanded and differentiated into a range of terminal cell types, this organ meets the most rigorous ethical, biological, and industrial requirements to serve the needs of virtually any clinical application. This presentation will cover the history and evolution of the science and technology which has led to uses in the wide range of therapies from degenerative diseases to cancer with specific attention to the future role in the treatment of age-related degenerative disorders and longevity. Specifically, placental pluripotent stem cells and immune cells such as Natural Killer and T-cells will be covered in both pre-clinical and clinical experiences.

Keywords: placenta, stem cell, NK cell, immunotherapy, regenerative medicine

Presentation number: IL 17 Abstract number: ABS-175-ISABS-2024

ANALYSIS OF HIFI MITOGENOME SEQUENCE DATA FROM THE PACBIO SEQUEL IIE

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Develop a pipeline for high throughput sequence analysis of the mitogenome using the PacBio Sequel IIe instrument. More than 5000 whole blood and buffy coat samples were received from the biorepository at the Institute for Personalized Medicine at Hershey Medical Center in Hershey, PA. The Quick-DNA™ Miniprep Plus Kit from Zymo Research was used to extract DNA from 50 uL of whole blood or buffy coat samples according to their protocol. Extractions were randomly quantified using a non-specific Qubit method, with a wide range of DNA yields; 1-500 ng/uL. Amplification of two overlapping 8.5 kb fragments of the mitogenome were conducted using an elaborate, plate-based array of barcode combinations, allowing for sequencing of 384 samples per run on the PacBio Sequel IIe instrument. Prior to sequencing, amplification products were normalized on SequalPrep™ Normalization Plates and libraries were prepared using the PacBio SMRTbell template preparation method. Data analysis was performed using a newly developed version of GeneMarker™ HTS for long-read sequencing data. We have developed a fully functional method for high throughput mitogenome sequence analysis of blood samples using the PacBio Sequel IIe instrument, with failure rates of less than 1% and at a cost of less than $30 USD per sample for supplies and reagents. Analysis of long-read data required the development of a new version of GeneMarker™ HTS software. In addition, a host of new sequencing artifacts were evaluated. To confirm that the newly developed pipeline produces robust data, concordance studies were performed on ~200 samples using short-read approaches. The detailed findings of this study will be presented. The points of view in this abstract are those of the author and do not reflect the views of their agency or the National Institute of Justice.

Keywords: high-fidelity, mitogenome, PacBio Sequel IIe, data analysis, EMPOP

Presentation number: IL 18 Abstract number: ABS-64-ISABS-2024

AI-DRIVEN 3D MODELING AND ANALYSIS OF TUMOR IMMUNE MICROENVIRONMENT AND LIVE CELL IMAGING

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In this presentation, we introduce groundbreaking AI-driven methodologies for 3D modeling and analysis of the tumor immune microenvironment and live cell imaging. Our approach leverages spatial transcriptome analysis, *in situ* molecular imaging, and spatial proteomics, integrated with Holotomography. This comprehensive strategy allows us to explore the complexity of the 3D tumor immune microenvironment, revealing insights into cellular interactions, molecular pathways, and the dynamic processes governing tumor growth and immune response. Utilizing AI, we transform vast datasets from spatial and molecular imaging into actionable insights, facilitating the detailed characterization of tumor heterogeneity and the identification of novel therapeutic targets. Our work highlights the potential of AI to enhance our understanding of cancer biology, offering a more nuanced view of the interactions within the tumor microenvironment. This, in turn, creates a pathway for the development of more effective, personalized cancer therapies. By harnessing the power of AI for the analysis of 3D live cell molecular imaging, we also illuminate the real-time dynamics of tumor-immune interactions. This enables us to observe the immediate effects of therapeutic interventions, offering a promising avenue for the evaluation and optimization of immunotherapies and other treatment modalities. Our findings highlight the critical role of AI in advancing cancer research and treatment, marking a significant step forward in our effort to unravel the complexities of the tumor microenvironment.

Keywords: AI, tumor immune microenvironment, cell interaction, 3D tumor modeling, biomarker, live cell, spatial transcriptome, in situ molecular imaging

Presentation number: IL 19 Abstract number: ABS-164-ISABS-2024

SCIENCE, SCIENTISTS, AND SCIENTIFIC PUBLICATIONS: THE QUEST FOR REPRODUCIBLE AND USEFUL RESEARCH

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Science is becoming more complex and seemingly more successful, but the scientific ecosystem suffers from major biases. In the publish and perish culture, a total of approximately 200 million scientific publications have already accumulated and they are increasing at a rate of 7 more million per year. Megajournals, predatory journals, questionable research practices and outright fraud create major new challenges. Peer review is also being transformed and under tremendous pressure of reviewer fatigue. Empirical studies suggest that most research is not reproducible, and an even larger proportion is not useful. The lecture will discuss criteria and definitions for reproducibility and for utility, present empirical data on various scientific fields in this regard and summarize efforts that are made in specific fields and across science to improve the reproducibility and usefulness of scientific research. Special attention is needed for aligning our reward system with best scientific research rather than spurious surrogates.

Keywords: scientific publication, reproducibility, bias

Presentation number: IL 20 Abstract number: ABS-15-ISABS-2024

GENETIC RESEARCH TO IMPROVE FORENSIC PRACTICE: THE LAST 20 YEARS

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In this opening lecture representing forensic genetics, I will summarize the major outcomes of our 20 years' research in molecular genetics and molecular biology aiming at improving crime scene investigation in forensic practice. I will cover our achievements in several subfields of forensic genetics, such as forensic DNA phenotyping for predicting appearance, age, ancestry, and environmental interaction habits with DNA for finding unknown perpetrators; forensic tissue identification for determining cellular origins of crime scene traces with DNA, RNA, and microbiome for concluding activity at the crime scene; forensic Y- chromosome analysis for identifying male lineages and separating male relatives in sexual assault cases; forensic mixture deconvolution with transcriptomes and genomes for identifying mixture contributors; monozygotic twin separation with epigenetics; and trace deposition timing with hormones, RNA, and metabolites for molecular alibi testing. Given the wide range of our research topics, detailed by our achievements, this talk will provide an overview about several of the key developments in the field of forensic genetics during the last two decades.

Keywords: forensic genetics, forensic DNA phenotyping, forensic tissue identification, forensic Y- chromosome analysis, forensic trace deposition timing

Presentation number: IL 21 Abstract number: ABS-182-ISABS-2024

AI FOR GENOMIC MEDICINE AND THERAPEUTIC DEVELOPMENT

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I will describe our use of AI to understand the mechanistic basis of human disease, to develop new therapeutics that reverse disease circuitry, and to enable personalized medicine, using machine learning to integrate genetics and genomics, single-cell epigenomics and transcriptomics, and high-throughput experiments. I will describe our work in six areas: (1) Understanding genomes, their programming language, their circuitry, epigenomics, dynamics, single-cell multi-omics. (2) Disease mechanism, genetic variation, patient subtyping, personalized medicine, electronic health records. (3) Application to neuroscience, Alzheimer's, schizophrenia, cardiovascular disease, obesity, cancer, evolution. (4) Therapeutic design, drug repurposing, high-throughput experiments, drug screening, genome circuitry manipulation, disease reversal. (5) Statistical genetics, causal inference, geometric deep learning, joint embeddings, contrastive learning, computational chemistry, therapeutic design. (6) Embedding space idea representations, visualization, and navigation for learning, discovery, invention, and collaboration.

Keywords: artificial intelligence, genomic medicine, therapeutic development, personalized medicine, using machine learning

Presentation number: IL 22 Abstract number: ABS-117-ISABS-2024

CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY: WHERE ARE WE NOW AND IN 2030

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Chimeric antigen receptor T (CART) cell therapy has emerged as a potent and potentially curative therapy in a subset of patients with blood cancers. Multiple CD19 directed and BCMA directed CART cell therapies have received regulatory approvals for the treatment of B cell malignancies and multiple myeloma. However, despite the high initial response rates, most patients relapse in the first 1-2 years and the rates of durable remissions remain low. In addition, the activity of CART cell therapy in solid tumors has been very modest. Several mechanisms for CART cell failure have been identified, including tumor specific escape, T cell defects, and inhibition of CART cells by the tumor and its suppressive microenvironment. In this presentation, we will review lessons learned from the use of CART cell therapy in the clinic, CART cell toxicities, mechanisms of resistance, and new strategies to improve CART cell function through rational combinations and genetic engineering of CART cells. We will also discuss new directions to apply engineered therapies off the shelf and in the treatment of non-cancer applications.

Keywords: immunotherapy, CART, cell therapy

Presentation number: IL 23 Abstract number: ABS-26-ISABS-2024

FORMATION OF LOCAL POPULATION STRUCTURE IN NORTH EUROPE DURING AND AFTER PLAGUE PANDEMICS

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Compared to other continents, human genetic differences within Europe are relatively minor, yet important enough to appear as significant confounders in complex trait analyses. The regional differences, which extend to patterns of local sub-regional population structure, can be revealed in large present-day cohorts with allele frequency and IBD-based methods. While some broader regional patterns have been linked with massive prehistoric population movements, or in case of some individual traits or loci with recent selective sweeps, studies of ancient genomes are only just starting to illuminate to what extent demographic events in the last two millennia, including pandemics, wars and famines have contributed to the formation of present-day population structure in Europe. Here we assess comparatively the impact of plague pandemics on population structure in North Europe with aDNA evidence from the UK, Norway, Estonia, and Belgium, considering critically the limitations and caveats for inference of selection.

Keywords: plague pandemics, population structure, natural selection, identity by descent, ancient genomes

Presentation number: IL 24 Abstract number: ABS-167-ISABS-2024

STRESS HORMONES INTERFERING WITH CANCER IMMUNOSURVEILLANCE

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Although there is little direct evidence supporting that stress affects cancer incidence, it does influence the evolution, dissemination and therapeutic outcomes of neoplasia, as shown in human epidemiological analyses and mouse models. The experience of and response to physiological and psychological stressors can trigger neurological and endocrine alterations, which subsequently influence malignant (stem) cells, stromal cells, and immune cells in the tumor microenvironment, as well as systemic factors in the tumor macroenvironment. Importantly, stress-induced neuroendocrine changes that can regulate immune responses have been gradually uncovered. Numerous stress-associated immunomodulatory molecules (SAIMs) can reshape natural or therapy-induced antitumor responses by engaging their corresponding receptors on immune cells. Moreover, stress can cause systemic or local metabolic reprogramming and change the composition of the gastrointestinal microbiota which can indirectly modulate antitumor immunity. I will explore the complex circuitries that link stress to perturbations in the cancer-immune dialogue and their implications for therapeutic approaches to cancer.

Keywords: Anticancer immune responses, catecholamines, glucocorticoids, immunotherapy, stress hormone

Presentation number: IL 25 Abstract number: ABS-54-ISABS-2024

GLYCAN BIOMARKERS FOR PERSONALISED PREVENTIVE HEALTHCARE

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Glycans are the ultimate layer of molecular complexity that modifies proteins with complex chemical structures integrating genetic, epigenetic, and environmental information. Alternative glycosylation (attaching different glycans to the same glycosylation site on a protein) modulates protein function and in this way actively participates in the transition from health to disease. Hundreds of genes are involved in the complex pathway of glycan biosynthesis and glycome composition is significantly heritable, but also strongly affected by current and past environment. By analyzing over 200,000 individuals, we demonstrated that glycans have significant biomarker potential in predicting risk of different age-related diseases, including cardiovascular diseases and diabetes. However, since glycans biomarkers are under significant environmental influence, they also change in the response to different pharmacological and lifestyle interventions aimed at decreasing the disease risk. Therefore, glycans have a great potential for the development of biomarkers for personalization of preventive healthcare and first such biomarkers, like the GlycanAge biomarker of biological age, are already commercially available.

Keywords: glycomics, protein glycosylation, preventive healthcare, biomakers

Presentation number: IL 26 Abstract number: ABS-79-ISABS-2024

TARGETING CELLULAR SENESCENCE FOR HEALTHY AGING

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Aging is the greatest risk factor for most chronic conditions, including cardiovascular disease, Alzheimer's disease, diabetes, cancer, and lung diseases, that compromise human health and quality of life. Over the past decades, remarkable progress has been made in understanding the diverse forms of molecular and cellular damage that accumulate over time and are at the root of aging. This has led to the innovative hypothesis that targeting aging itself could delay, if not prevent, the onset of diseases and disabilities and, in turn, extend human healthspan. This seminar will provide an overview of a prominent example, cellular senescence, a cell fate induced by diverse forms of damage, and its contribution to aging-related conditions. Moreover, it will showcase evidence from preclinical models that demonstrates genetic and pharmacological elimination of senescent cells confers benefits upon multiple organ systems, and data from humans that highlight the potential for senescent cell-targeting therapies to serve as a novel approach to transform health.

Keywords: geroscience, healthspan, senescence, senescence-associated secretory phenotype, senotherapeutics

Presentation number: IL 27 Abstract number: ABS-54-ISABS-2024

USE AND ABUSE OF GENETICS EVIDENCE IN COURT

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investigations. As science and technology continue to advance, the importance and the value of genetic evidence in the protection of our society will also continue to grow. However, forensic scientists do not usually make the decisions about the usage of genetic evidence in civil or criminal trials. In the litigation stages, prosecution and defense attorneys direct the utilization of genetic evidence. In the adjudicative stages, the judges decided the admission and legal ruling of genetic evidence There is no guarantee that either of these groups will sufficiently understand the potential and the limitation of genetic evidence and make the proper decisions. It is also possible that the standards and ethic integrity of some of the members of these groups is questionable. As a greater number of legal communities acquire updated information and receive special training in forensic DNA, the situation will improve thus enabling better use of DNA evidence. The result of these growths would serve to make forensic science a maintaining a high quality of justice for our society. While the forensic community shares much with the general scientific community, such as the need to strictly follow the standard DNA typing procedures and the validly DNA techniques, they also abuse the application of DNA evidence, by retesting all and aged evidence for DNA without even consider the collection and preservation of evidence 3 decades or even half century ago. With the new DNA testing results provides an argument for appellee or reverse the case. DNA evidence often was misused and even abused by legal system. As a greater number of police, forensic scientists, attorneys, judges, and public acquire correct information about the value and limitation in DNA evidence and other new forensic technologies, the quality of examination of forensic evidence should continue to improve.

Keywords: limitation of genetic evidence, legal application

Presentation number: IL 28 Abstract number: ABS-121-ISABS-2024

TRANSLATIONAL TISSUE ENGINEERING

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This presentation will discuss the Mayo Clinic experience translating bench work innovation directly to clinical medicine. This experience includes the ability to encompass basic and applied (translational) science, applied engineering science, medical device product development, clinical translational research, and ultimately end-use clinical application; thereby creating a multi-scale bench to bedside synergistic environment for translational regenerative medicine. This “team systems” paradigm facilitates full- spectrum, detailed, and safe scientific advancement. Topics to be discussed include additive manufacturing, bioprinting, electrospinning, tissue decellularization, clean room manufacturing, and regulatory implications. We will provide an overview of the Mayo Clinic approach to translational medicine and integration of research innovation into the clinical practice. The presentation will show real-life translation of these technologies and discuss implications for future patient care.

Keywords: tissue engineering, additive manufacturing, bioprinting, electrospinning, translational research

Presentation number: IL 29 Abstract number: ABS-82-ISABS-2024

MACHINE PERFUSION: A PLATFORM FOR ORGAN REPAIR AND REGENERATION

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Organ transplantation is a lifesaving intervention for many patients with end-stage organ disease. The number of patients listed for solid-organ transplantation continues to increase and further exceeds the number of organs available. Organ utilization from acceptable donors remains low, as low as 20% in the case of lung allografts. There is an urgent need to meet the demand for organs and prevent mortality in the waitlist. Ways to increase the organ supply include improving the organ utilization rate by improving the assessment of organs and implementing strategies to repair available organs. Organs from donors after circulatory death (DCD) are more likely to suffer the deleterious effects of ischemia-reperfusion injury, preventing them from remaining viable. By isolating the organ, machine perfusion allows for accurate assessment of organ function ex vivo, providing opportunities to increase the utilization of organs that otherwise would have been discarded due to incomplete or inaccurate data at the time of evaluation of the donor and/or recovery of the organ. Machine perfusion also allows the preservation time to be extended, allowing the organs to travel further distances, and overcome time constrains. Despite the implementation of various machine perfusion techniques, the need for organs available for transplantation remains unmet. Machine perfusion is evolving as a platform where targeted interventions will allow the repair, regeneration, and optimization of solid organs for transplantation. These interventions include, and are not limited to, cell and cell derived therapies, senolytic agents, gene therapies, amongst others. In addition, machine perfusion provides ideal conditions to study and test bioengineered organs as they are being developed. We will review the current state of organ machine perfusion and describe interventions to promote repair and regeneration of organs using these systems, with a special focus in lung allografts.

Keywords: organ transplantation, machine perfusion, organ regeneration

Presentation number: IL 30 Abstract number: ABS-178-ISABS-2024

ADVANCING THE FUTURE OF REGENERATIVE MEDICINE: CELLS AND TISSUE PRIMING FOR SUCCESSFUL TRANSLATION OF EFFECTIVE AND ACCESSIBLE THERAPIES

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Mesenchymal stromal cells (MSCs) are renowned for their dual immunomodulatory and regenerative capacities, establishing them as cornerstones of cell therapy and tissue engineering research. Despite their significant potential, transitioning from preclinical success to clinical application has been fraught with challenges, primarily due to modest efficacy and performance inconsistencies. These issues have traditionally been linked to variable culture and storage conditions and over-expansion. However, with advancements in well-defined culture media and preservation techniques, along with decreasing costs, these factors alone do not fully address the persistent barriers to clinical translation. At Bonus Biogroup, we have pioneered strategies to enhance the clinical success of autologous and allogeneic MSC therapies. This presentation will highlight our achievements with BonoFill, an autologous tissue- engineered bone graft currently in Phase II trials. BonoFill has demonstrated substantial potential for facilitating functional recovery in patients with complex bone deficiencies, previously considered beyond treatment options. Additionally, we will discuss MesenCure, our next-generation allogeneic MSC therapy that uniquely expresses 6,909 genes differently compared to natural MSCs. MesenCure has shown a remarkable 68% reduction in mortality among patients suffering from severe respiratory distress. Currently preparing for Phase III studies in all-cause ARDS, MesenCure's applications are expanding to treat systemic inflammations, such as cytokine release syndrome, and various organ injuries. Our presentation will elaborate on the significant clinical advancements and the potential of BonoFill and MesenCure across diverse therapeutic domains. We aim to demonstrate how these innovative therapies leverage cellular enhancements to address complex medical challenges, overcome obstacles in MS C therapy, and lead the way in pioneering developments in regenerative medicine.

Keywords: mesenchymal stromal cell, cell therapy, tissue engineering, inflammation, tissue injury

Presentation number: IL 31 Abstract number: ABS-41-ISABS-2024

THE FUTURE OF CRIME INVESTIGATION IN THE ERA OF SINGLE- CELL OMICS

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The separation of cells from biological mixtures and the subsequent genetic characterization and identification of each contributor individually, is a complex task relevant across various fields. In forensic research, where biological mixtures are frequently collected from crime scenes, this task remains one of the most significant challenges, largely unsolved despite several attempts. Single-cell (multi)omics approaches are emerging as a powerful set of tools, offering unprecedented insights into cellular identity and processes. While these techniques have the potential to address the challenges in forensic research, their adaptation for forensic application lags behind. Thus, we are exploring the possibility of adapting existing single cell approaches and develop novel ones to address the challenges faced in forensic research. First, by using existing single-cell transcriptome sequeincg (scRNA-seq) and by developing a novel mixture deconvolution bioinformatics pipeline, we succeeded to separate individuals from multi- person blood mixtures. In subsequent steps, we were able to determine the sex and biogeographic ancestry of the separated individuals and the tissue of origin of the biological mixture. In addition, by comparing the individual SNP profile (from the scRNA-seq) with a reference set (exome-seq), we were able to achieve individual identification of the separated contributors. However, RNA is prone to degradation, and sequencing RNA -focusing on coding regions- generates a relatively limited number of SNPs, thus limiting its forensic application. To overcome these, we explored the use of single-cell DNA sequencing (scDNA-seq) and demonstrated its improved performance and capability compared to scRNA-seq. Our study pioneers the potential of single-cell omics in future forensic investigations. Our novel approaches, with further adaptations, hold promise for identifying perpetrators.

Keywords: single-cell sequencing, mixture deconvolution, genetic identification, bio-geographic ancestry, forensics

Presentation number: IL 32 Abstract number: ABS-133-ISABS-2024

REGENERATIVE MEDICINE APPLICATIONS TO TRANSPLANT MEDICINE WITH AN EMPHASIS TO MITOCHONDRIAL TRANSPLANTATION

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Regenerative medicine (RM) has shown immense potential to change the way we think and practice transplant medicine. While current technology does not allow yet the manufacturing of transplantable organs from patients' own cells, RM-based technologies like the engineering of progenitor cells into an insulin-producing cell phenotype have already reached the bedside. As well, multiple RM-based approaches are currently under investigation as a tool to repair and regenerate marginal grafts and eventually expand the donor pool. For this, in the regenerative medicine era of the transplant history, the term "organ preservation" has become synonymous to "organ repair and regeneration". This lecture will illustrate the state of the art of those RM-inspired technologies and applications that will impact transplant medicine in the immediate future, with an emphasis on mitochondrial transplantation (MITO). MITO replicates an extraordinary natural phenomenon through which cells recover from stress, called mitochondrial transfer. The past decade has witnessed the birth and rise of this technology whose potential clinical applications are numerous. Our own group and others are investigating MITO as a tool to enhance the adaptive repair ability of human allografts, with the ultimate goal of abating the organ discard rate that still afflicts transplant medicine.

Keywords: regenerative medicine, mitochondrial transplantation, transplant medicine, organ preservation, stem cells

Presentation number: IL 33 Abstract number: ABS-133-ISABS-2024

FROM FORENSIC GENETICS TO FORENSIC GENOMICS: THE MTDNA PERSPECTIVE

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Mitochondrial DNA (mtDNA) is ubiquitously analyzed in various areas of research and diagnostics. In forensic genetics, mtDNA is typically tested when nuclear DNA analysis does not produce successful results or when investigating possible relatedness between maternally related individuals. Traditionally, the concepts and laboratory strategies for mtDNA typing were based on Sanger-type sequencing. With the emergence and rapid technical development of Next Generation Massively Parallel Sequencing (MPS) technologies the analytical landscape has changed. A variety of options are now available for determining mtDNA sequences, including primer tiling and capture based as well as direct sequencing methods. The choice of downstream methods largely depends on the quality and quantity of mtDNA in a forensic sample. For example, MPS enables the analysis of extremely short mtDNA fragments that were not accessible to Sanger-based methods. Consequently, MPS can reveal mtDNA contributions in samples that would remain undetected using conventional strategies. This has significant implications for how forensic evidence has to be interpreted in the forensic context and opens the scope of this application to special, previously unsolved, challenging cases.

Keywords: mitochondrial DNA, Sanger sequencing, massively parallel sequencing, cold cases, forensic genetics

Presentation number: IL 34 Abstract number: ABS-175-ISABS-2024

UNDERSTANDING MOLECULAR EFFECTS OF MICRO-FRAGMENTED ADIPOSE TISSUE (MFAT) AND MESENCHYMAL STROMAL CELLS (MSC) THERAPY OF OSTEOARTHRITIS

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Osteoarthritis (KOA) is the most common musculoskeletal disease, affecting an estimated 528 million people worldwide. However, osteoarthritis is not a disease characterized by loss of cartilage due to mechanical loading only but a condition that affects all of the tissues in the joint, causing detectable changes in tissue architecture, metabolism, and function. According to WHO, with a prevalence of 365 million, the knee is the most frequently affected joint, followed by the hip and hand. Previous studies at St. Catherine Specialty Hospital have shown great potential for treating knee osteoarthritis with mechanically micro-fragmented adipose tissue (MFAT) contains within the CD45- fraction: endothelial progenitors (EP), mature endothelial cells, pericytes, transitional pericytes, and supra-adventitial-adipose stromal cells (SA- ASC). During the lecture, I will present the clinical, radiological, and biological effects of MFAT treatment of patients with knee osteoarthritis (KOA). Also, I will discuss the impact of MFAT treatment on patients with knee osteoarthritis, evaluating pain and functions using questionnaires such as the Visual Analog Scale (VAS), Western Ontario and McMaster Universities OA Index (WOMAC), and Knee Injury and OA Outcome Score (KOOS) before and after therapy. Also, I will summarize the outcome of MFAT treatment on articular cartilage glycosaminoglycan (GAGs) content, measured indirectly using Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) as well as the impact of MFAT treatment on cytokines, chemokines, N-Glycans, miRNA in plasma and synovial fluid.

Keywords: knee osteoarthritis (KOA), micro-fragmented adipose tissue (MFAT), glycosaminoglycans (GAGs), cartilage

Presentation number: IL 35 Abstract number: ABS-181-ISABS-2024

BRIDGING FORENSIC VIROLOGY AND ARCHAEOVIROLOGY

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A fundamental component of specific microbes or microbial communities in the context of a forensic medicine and forensic virology is the difference between antemortem and postmortem presence or absence of microbes. The balance between co-existing human and microbial cells of the human microbiome is a requirement for a homeostatic status of an individual. An invading pathogen can disrupt this balance, and typically body orifices or open injuries are the routes for pathogens to enter the body. Any microbial disease, especially those that cause local epidemics or pandemics, are of concern to public health and to the medico-legal or forensic pathology communities. Postmortem microbial diagnostics is mostly directed by the analysis of generally known and potentially lethal microbes. An underlying concept of forensic microbiology related to autopsy work is that the microbiota on the body and its close environment are different from those of the microbial system in the body. These two entities are separated as the epinecrotic and the thanatomicrobiome, respectively. We have studies a range of persistent human DNA viruses in the epinecrotic and thanatonomicribiome in several human tissues. We have shown that the previous concept of sterile internal organs in the human body contain DNA of several of those viruses. As many of these viruses enter our body in the childhood, their DNA provide a blueprint for geolocation of their host. This is turn can be used adjacent to the host's own DNA for estimation of the geographical origin of e.g. skeletal remains in the forensic or archeological context. To make interpretation of the found viral fingerprint for provenance, we have also collected a global viral database, including all published sequences today, covering more than 90% of the full length of the virus, from 38 persistent human DNA viruses.

Keywords: forensic virology, forensic genetics, postmortem, archeovirology

Presentation number: IL 36 Abstract number: ABS-81-ISABS-2024

UPDATES IN ORAL/SYSTEMIC HEALTH AND RECONSTRUCTION OF CRANIOFACIAL DEFECTS

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The attendee should be familiar with current association between oral and systemic health. As an effort to make the attendee aware of the current related concepts between oral and systemic health, reviews of current concepts and presentation of care of patients receiving medical and surgical care will be undertaken. Further, the current concepts of treating patients with defects of the maxillofacial and craniofacial region will also be reviewed presenting treatment related to available technologies and future roles. Reviews of best evidence and surgical protocols are compiled for a descriptive presentation. A significant association between systemic and oral health exists. Best evidence leads to an understanding that oral health is a contributing factor to many systemic conditions of health. Additional research is needed to gather these associations into a common goal of treating the whole patient. Regenerative therapies are also targeted for reasons in the shortfall of reconstructive science and meeting the outcome of patient expectations in reported outcomes. Summaries of oral systemic health association will be presented to give best evidence concepts and treating patients for future needs of regenerative medicine. Further, additional concepts in treating patients with craniofacial defects are reviewed for best practices.

Keywords: morbidity, bacteremia, biofilm, TAVR, periodontitis

Presentation number: IL 37 Abstract number: ABS-163-ISABS-2024

GENOMIC FRONTIERS: TOWARDS UNIVERSAL NEWBORN SEQUENCING

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Newborn sequencing (NBSeq), the comprehensive analysis of an infant's genome, holds immense promise for revolutionizing healthcare throughout the lifespan. NBSeq allows for early detection of genetic disease risk and precision personalized medicine. NBSeq has the potential to significantly improve clinical outcomes, mitigate disease burden and enhance quality of life for infants and their families. However, the realization of this transformative potential is not without its challenges. Ethical aspects of consent, privacy, and the responsible use of genetic information must be carefully navigated to safeguard individual rights and maintain public trust. Moreover, genomic data interpretation poses complex challenges due to the vast amount of information generated, the presence of variants of uncertain significance, and the dynamic nature of our understanding of genetics. Implementation hurdles, including cost, infrastructure requirements, and the need for specialized expertise, also present barriers to the widespread adoption of NBSeq. Addressing these challenges requires a multidisciplinary approach involving collaboration among clinicians, researchers, policymakers, ethicists, and stakeholders across various sectors. Robust frameworks for informed consent, data protection, and governance are essential. Advances in bioinformatics, machine learning, and genomic interpretation are crucial for the translation of genomic insights into actionable clinical insights. Scalability and improving downstream healthcare access are vital for ensuring equitability, particularly in underserved communities and resource-limited settings. By fostering interdisciplinary collaboration, advancing technology and infrastructure, and upholding ethical principles, we can unlock the full potential of NBSeq as a tool for precision medicine and pave the way towards a future where every child has the opportunity for a healthier, genetically informed start in life.

Keywords: NBSeq, newborn sequencing, genomic sequencing, personalized medicine

Presentation number: IL 38 Abstract number: ABS-52-ISABS-2024

INFLAMMATION-TRAINED TREGS FOR CELL THERAPY

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Treg therapies are being tested in clinical trials in transplantation and autoimmune diseases, however, the impact of inflammation on Tregs remains controversial. We challenged human Tregs ex-vivo with pro- inflammatory cytokines IL-6 and TNF and observed greatly enhanced proliferation stimulated by anti-CD3 and anti-CD28 (aCD3/28) beads or CD28 super agonist (CD28SA). The cytokine-exposed Tregs maintained high expression of FOXP3 and HELIOS, demethylated FOXP3 enhancer, and low IFNγ, IL-4, and IL-17 secretion. Blocking TNF receptor using etanercept or deletion of TNF receptor 2 using CRISPR/Cas9 blunted Treg proliferation and attenuated FOXP3 and HELIOS expression. These results prompted us to consider using CD28SA together with IL-6 and TNF without aCD3/28 beads (beadles) as an alternative protocol for therapeutic Treg manufacturing. Metabolomics profiling revealed more active glycolysis and oxidative phosphorylation, increased energy production, and higher antioxidant potential during beadles Treg expansion. Finally, beadles expanded Tregs maintained suppressive functions in vitro and in vivo. These results demonstrate that human Tregs positively respond to proinflammatory cytokines with enhanced proliferation without compromising their lineage identity or function. This property can be harnessed for therapeutic Treg manufacturing.

Keywords: regulatory T cell, alloimmunity, autoimmunity, tumor necrosis factor, interleukin 6

Presentation number: IL 39 Abstract number: ABS-170-ISABS-2024

BIOMANUFACTURING REGENERATIVE MEDICINE SOLUTIONS FOR HEART DISEASE IN 2024: FROM GENES TO ORGANS

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During the past decade, multiple regenerative medicine solutions have been explored for the dominant disease on the planet – heart disease. Therapies have been utilized include microscopic to macroscopic: from gene therapy/gene editing to delivery of proteins, to cell therapy, to whole xenogeneic and personalized human organs. I will discuss the pros and cons of these therapies, the latest status of each and primarily focus on Organamet Bio's three major paths forward: biologics to treat heart failure including HFpEF, a ventricular patch to treat HFrEF, and the goal of bioengineering personalized human hearts from iPSCs to be made available on demand. I will discuss the hurdles and opportunities to building personalized therapies and focus on the path from prototype to first in human.

Keywords: regenerative medicine, personalized organ transplantation, biologic therapies, xenotransplantation, biomanufacturing

Presentation number: IL 40 Abstract number: ABS-53-ISABS-2024

THE GENOMIC LEGACY OF ARCHAIC HOMININ INTROGRESSION

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Neanderthals, our closest extinct relatives, lived in western Eurasia from 400,000 years ago until they went extinct around 40,000 years ago. DNA retrieved from ancient specimens revealed that Neanderthals mated with modern human contemporaries. Consequently, introgressed Neanderthal DNA survives scattered across the human genome such that 1–4% of the genome of present-day people outside Africa are inherited from Neanderthal ancestors. Using an integrative approach that combines insights from population genomics and molecular biology, we leveraged large-scale genomic datasets from geographically diverse human populations and unveiled a vast trove of genomic evidence for archaic introgression including genetic variation inherited from other archaic hominin groups. Patterns of archaic introgressed genomic sequences show that archaic alleles had distinct fates in the modern human genetic background. Some archaic alleles facilitated human adaptation to new environments such as novel climate conditions, UV exposure levels and pathogens, while others had deleterious consequences. Our work provides a unique window into the legacy that archaic hominins left in the human gene pool and further highlight the impact of archaic introgression on human biology and phenotypic variation.

Keywords: Neanderthals, genetic adaptation, population genetics, human evolution

Presentation number: IL 41 Abstract number: ABS-83-ISABS-2024

FROM A SKULL TO A FACE USING FORENSIC DNA PHENOTYPING

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Facial approximation plays a crucial role in helping to identify victims in forensic cases involving skeletal remains. However, manual 3D facial reconstruction approaches such as the Combination Manchester method are time-consuming and subjective, relying on limited numbers of anthropological facial soft tissue thickness (FSTT) and facial muscle measures. While available computational methods offer potential objectivity, they are held back by insufficient databases and a lack of standardized, easily applicable methods. To address these challenges, we describe a novel computational approach built from a dataset of both skull and tissue facial masks obtained in the same space using Cone-Beam-Computed- Tomography (CBCT) facial scans of 100 European individuals. The approach uses the open-source program Meshmonk to mask both hard and soft tissue structures with identical landmarks so that FSTT can be measured by calculating the distance between these corresponding points. This generates a clear FSTT metric at approximately 7000 points across the craniofacial region which we use to ascertain the average depth for prediction. Our approach can generate facial approximations within 10 minutes, incorporating and adjusting these measures with information on age, sex, height, and weight. We also provide an error adjustment gauge to highlight areas across the face that are more prone to variation, generating several possible visuals. Additionally, we integrate DNA prediction knowledge from Single Nucleotide Polymorphisms (SNPs) associated with nose shape, as nose morphology is not accurately determined by underlying hard tissue, to complete the visual renditions. At present this method is limited to a European scale, however, the goal is to highlight its proof of concept and utility. We believe that providing standardized masks will enhance data comparability and sharing amongst research groups to create a database of FSTT measures that capture both global & local variation.

Keywords: face, skull, Forensic DNA phenotyping, prediction, skeletal remains

Presentation number: IL 42 Abstract number: ABS-168-ISABS-2024

PHARMACOGENETICS: DO YOU HAVE YOUR DNA PASSPORT?

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The discovery that the metabolism of drugs is highly variable between patients but can be quite well predicted by DNA analysis of genes encoding drug metabolizing enzymes or drug transporters, greatly facilitated the uptake pharmacogenetics into clinical care. Focus of these analyses was initially mainly on cytochrome P450 enzymes: genotyping for CYP2D6 (involved in the metabolism of 20% of all drugs but being deficient in 5-10% of the population due to inherited inactive DNA variants) and CYP2C19 (involved in metabolism of 20% of drugs, while 2-11% of the population is deficient) could benefit tailored therapy in psychiatry, cardiology, and oncology. Currently, there is sufficient evidence for 15-30 genes that can be (and in fact are) used clinically for personalization drug therapy. The field is growing mature as a clinical diagnostic tool, in which we can see a shift from reactive single-gene testing to pre-emptive gene panel testing. In this presentations, successes, and challenges for implementing pharmacogenetics into routine health care will be highlighted and discussed.

Keywords: pharmacogenetics, pharmacogenomics, CYP450, personalized medicine, clinical implementation

Presentation number: IL 43 Abstract number: ABS-126-ISABS-2024

DATA FOR THE COMMON GOOD: TRANSFORMING HEALTH THROUGH DATA

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Rare diseases can only be effectively studied through the collection and aggregation of harmonized data from multiple disparate sources. Yet, the research community has been slow to adopt the data and governance standards required to facilitate the creation of rare disease data commons. As a result, data are siloed and trapped in non-interoperable formats, creating a fragmented patchwork of difficult-to-study information. Data for the Common Good at the University of Chicago is devoted to building communities, platforms, and ecosystems that maximize the potential of data to drive discovery and improve human health. Starting with pediatric cancer and their Pediatric Cancer Data Commons, Data for the Commons Good has developed repeatable and scalable processes that facilitate the creation of disease-based communities built on trust and a shared interest in common governance and data standards. I will describe the development and success of the Pediatric Cancer Data Commons and his group's expansion into other rare diseases. Attendees will learn about the importance of data standards and common data models, how to develop scalable international data governance, and ways to create communities and platforms to lower barriers to data sharing.

Keywords: informatics, standards, ontology, data standards, interoperability

Presentation number: IL 44 Abstract number: ABS-56-ISABS-2024

SECRETOME-BASED THERAPY IN CHRONIC PAIN/OA PATIENTS AND SPORTS INJURY – BIOLOGY, CLINICAL RESULTS AND CASES

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There is an unmet need for effective, safe, and cost-effective biological therapies for osteoarthritis, degenerative spine diseases and chronic pain. In our presentation, we describe the development and application of a secretome-based therapy, also known as autologous conditioned serum (ACS). In contrast to PRP and other related autologous blood therapies in orthopedics and pain medicine, ACS is a secretome-based approach. The incubation of whole blood stimulates the cells to secrete immune- modulatory cytokines, growth factors, exosomes, and other biological factors. After incubation, the coagulated blood is centrifuged, and the ACS is frozen for storage and later use. Preparation and application are simple and reproducible. WADA has not characterized ACS as doping relevant. In a total of 21 randomized clinical trials, ACS injections were compared with placebo or standard treatment. Multiple orthopedic and pain-related indications were investigated. The publications document safety and effect sizes of up to >1 (e.g. in knee OA; ES Cohen's d). We provide a representative overview of the relevant ACS data and comparable therapies. Typical cases in competitive sports and chronic pain patients show the potential, the safety and indications that should not be treated with this approach.

Keywords: extracellular vesicles, autologous conditioned serum, musculoskeletal diseases, neuroskeletal diseases, orthokin

Presentation number: IL 45 Abstract number: ABS-179-ISABS-2024

LINKS BETWEEN GUT MICROBIOTA AND TUMOR IMMUNOSURVEILLANCE

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Initiated by the finding that antibiotics (ATB) suppress tumor immunotherapy by affecting immune checkpoint inhibitors (ICI), we are studying whether intestinal commensals protect immunotherapy. We demonstrated that ATB strongly suppress immunotherapy targeting CTLA4 or PD-1/PD-L1 in lung and kidney patients and that metagenomic analysis of patient feces at diagnosis predicts the effect of immunotherapy. Transfer of fecal microbiome from patients responding to immunotherapy or resistant to it into tumor-bearing rodents confers sensitivity or resistance to anti-PD1/PDL-1 antibodies, respectively. We identified several mechanisms linking gut microbiome and tumor immunosurveillance: 1) Cancer causes b-adrenergic-receptor-dependent stress ileopathy triggering intestinal dysbiosis and thus contributing to tumor progression. 2) "Immunogenic commensals" (e.g., *Akkermansia muciniphila, B. fragilis, Enterococcus hirae, Alistipes shahii, Ruminococcus spp*) mount an IL-12-dependent immune response mediated by follicular T helper cells during therapy with oxaliplatinum or cyclophosphamide and immune checkpoint blockade. 3) Molecular mimicry between microbial antigens (an enterococcus phage) and cancer epitopes recognized by CD8+ T effector cells accounts for immunogenicity of some bacterial species in mice and patients. 4) Harmful pathobionts such as *Enterocloster gen. (Clostridium clostridioformis/bolteae*) induce antibiotics-mediated inhibition through regulatory T-cell exodus from gut to tumors. 5) In urothelial carcinoma with long term benefit of PD1 blockade, tertiary lymphoid organs are associated with proficient immune response against pathobionts invading cancer cells. 6) MAdCAM-1, a gut immune checkpoint, keeps in check the exodus of Tr17 regulatory T cells to tumor beds. We developed a tool to diagnose intestinal dysbiosis (by relative abundance of fecal Akkermansia spp together with "Toposcore" at baseline prior to therapy) and predict resistance to PD1 blockade in lung cancer patients. These discoveries led to proof-of-concept clinical trials showing that primary resistance to ICI in stage IV melanoma can be circumvented by reintroduction of the failed ICI together with transplantation of fecal microbiome from cured patients.

Keywords: antibiotics, fecal microbiome transfer therapy, gut microbiome, immune checkpoint inhibitors, immunosurveillance

THE ISABS FUTURE SCIENTIST AWARD PRESENTATIONS

Presentation number: FSA 01

THE EFFECT OF PSYLLIUM AND VITAMIN C ON DECOMPOSITION AND PREVENTION OF CREATION OF THE GALLSTONE

Dorotea Alaburić

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Nowadays, only a few natural cures for the prevention of gallstones are available, of which none had yet proven fully effective. Consequently, in this research the problem is approached in a different way, by studying the influence of natural substances directly on the gallstone. The aim of the study is to confirm whether vitamin C and psyllium can be used for the prevention of gallstone formation, for its breakdown and easier treatment of illnesses through diet therapy. The research was conducted by an experimental procedure. Using appropriate apparatus and chemicals, two isolated systems were constructed in which conditions like those in the gallbladder with stones of the human digestive system were simulated. The substances were added for 4 days, trying to achieve the effect of their assumed effect in a month, that is, every day a weekly dose was added. Results of the experiment indicate that psyllium and vitamin C affected the reduction of gallstone mass, which also caused changes in the structure of gallstones particles. This research confirmed that vitamin C and psyllium can be used in the prevention of gallstones, for the purpose of its degradation and easier treatment of illnesses through diet therapy. However, it is necessary to conduct new studies with the aim of forming new manners of action and giving final recommendations on their consumption, which is of great importance for the development of higher quality treatment and general advancement of medicine.

Presentation number: FSA 02

USE OF CRISPR-CAS9 AS A MODERN CLINICAL TREATMENT FOR HIV

Klara Gnjidić

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HIV is a dangerous retro virus which infects CD4 T cells, resulting in the weakening of the immune system. Currently there is no cure for the disease but there is effective antiviral therapy referred to as HAART (highly active antiviral therapy). HAART suppresses the viral gene expression but does not cure patients infected with HIV. Because of this HIV is currently an incurable and chronic disease. The promising discovery of a CRISPR-Cas9 coupled system, derived from the adaptive immune system of bacteria, provides a possible cure for HIV. This effector complex can edit precisely target and modify genes. It is changing the course of medical treatments aiming to cure this, currently, incurable disease.

Presentation number: FSA 03

TOXICITY TESTING OF SLAG FROM DUGI RAT USING *ALLIUM CEPA* TEST

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III. Gymnasium, Split, Croatia

The aim of the research was to determine the toxicity of the slag deposited around Dugi Rat using the *Allium cepa* test. The experiment was conducted to investigate the effect of different concentrations of slag on the growth and morphology of onion rhizomes. Five bulbs were transferred to each of the 6 solutions with slag, 5 bulbs into cups with spring water (negative control) and 5 bulbs into cups with hydrogen peroxide (positive control). Four rhizomes per bulb were cut after 24h, fixed and colored with aceto carmine. Chromosomal aberrations and interphase vacuoles in onion cells were observed under a microscope, and the mitotic index was calculated. After 72 hours, all rhizomes were cut, and the length of rhizomes was measured. The results showed that all rhizomes treated with slag solutions were longer than rhizomes treated with negative and positive control. Treatments with pulverized slag and 40 g/L of coarse slag had significantly higher mitotic index compared to control solutions and treatments with 10 g/L and 20 g/L of coarse slag. Solutions with pulverized slag caused the most chromosomal aberrations. The treatment with 20 g/L of pulverized slag shows the strongest negative effect. Slag accelerates the growth of onion roots and therefore has a genotoxic and cytotoxic effect on the meristem cells of onion roots. In future research, it would be desirable to collect more slag samples from different parts of the landfill and investigate the influence of the solution with higher slag contents.

Presentation number: FSA 04

FROM PLANT TO ANTISEPTIC: THE SEARCH FOR ANTIBACTERIAL COMPOUNDS IN PLANTS

Sara Polašek

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The aim of this study was to determine which of the collected plant samples contained antibacterial compounds, to compare the antibacterial activity of plants collected from wetland and coastal habitats, and to compare the effectiveness of different solvents for dissolving antibacterial compounds. The antibacterial effect of 60 plant samples was analyzed using the agar well diffusion method. Solid substrates made of nutrient agar were covered with a bacterial solution and drilled, creating 60 pores that were each filled with an aqueous solution of one plant sample. After 24 hours of incubation at 30 ˚C, the 21 samples that developed a zone of inhibition were used to further test the efficiency of three organic solvents: dichloromethane, diethyl ether and acetone, for dissolving antibacterial compounds. Student's t-test was used in statistical analysis. There was no statistically significant difference in the antibacterial effect of plants harvested from wetland and coastal habitats ($p = 0.861$). The largest average zone of inhibition was recorded for coastal plants using distilled water as a solvent (3.86 ± 2.12 mm), and the smallest for coastal plants using diethyl ether (1.67 ± 0.52). Statistically significant results when comparing the effectiveness of solvents were recorded between dichloromethane and diethyl ether ($p = 0.038$), and distilled water and diethyl ether ($p = 0.024$). No difference was recorded in the antibacterial activity of plants harvested in wetland and coastal habitats. The most effective solvent of herbal antibacterial compounds was distilled water, most effective organic solvent was dichloromethane, and the least effective was diethyl ether.

Presentation number: FSA 05

THE CONTRIBUTION OF HERVS TO PLACENTAL FUNCTION AND EVOLUTION IN HUMANS

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The aim of this research paper is to research the effect of the contribution of HERVs to placental function and evolution in humans. Scientific articles from Mayo Clinic and Encyclopedia Britannica along with Scientific papers on relevant topics were read, as found by search engines like Google Scholar, Science Direct, PubMed Central, MDPI and others. Human endogenous retroviruses (HERVs) are human genome sequences which were integrated into the genome through retrotranscription of ancient retroviruses. HERVs code for Syncytin-1 and Syncytin-2, proteins which facilitate cell-cell fusion in the placenta and are thus responsible for the creation and maintenance of the syncytiotrophoblast layer of the placenta. Syncytin-2, and to a lesser extent Syncytin-1, also seem to play a crucial role in the immunosuppression of the maternal part of the placenta. HERVs also participate in hormonal regulation of the placenta by acting as genetic enhancers in the form of long terminal repeats. HERVs likely endogenize in a sequence of "baton passes", replacing and refining each other's roles with each endogenization (as proposed by the BPT). This process also seems to have been crucial for selecting placental traits which gave apes, and thus humans, an evolutionary advantage against other primates. HERVs are crucial in forming the placenta and ensuring its proper functioning, as such they were instrumental for human evolution and success. More research needs to be done on the immunosuppressive role of Syncytins and the BPT for a complete picture of the functions and endogenization process of placenta specific HERVs.

Presentation number: FSA 06

NATURAL ANTIBIOTICS – AN EFFECTIVE WAY TO FIGHT INFECTIONS?

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The aim of this scientific research was to examine the difference in the effectiveness of natural and synthetic antibiotics on the growth of the bacteria *Escherichia coli* and the fungus *Candida albicans*. In this research, the cell culture method was used, and the data analysis was performed by measuring the diameter of the zone of inhibition of the growth of bacteria and fungi. The synthetic antibiotic used in the research was ampicillin, and the natural antibiotics used were: propolis, grapefruit seed extract and tea tree essential oil. The research results indicate that more accurate results were obtained by using "dry" discs due to the reduced possibility of antibiotic spillage when laying on the substrate. The natural antibiotic tea tree showed the highest effectiveness against the bacterium *Escherichia coli* with an effectiveness of 125.00% compared to ampicillin, and the lowest was propolis with an effectiveness of 0%. In the effect on the growth of the *Candida albicans* fungus, the natural antibiotic grapefruit seed extract was the most effective with an efficiency of 465.50%, and the least effective was propolis with 147.83%. Tea tree and grapefruit seed extract have similar effectiveness on *Escherichia coli* bacteria, while propolis has little or no effectiveness. In all cases, it is concluded that ampicillin has no effectiveness in preventing the reproduction of *Candida albicans* fungi. Also, it was concluded that all three natural antibiotics inhibited the reproduction of *Candida albicans* fungi with different efficiencies. The most important conclusion of this research indicates that taking natural antibiotics has a positive effect on bacteria and suppresses the reproduction of fungi, unlike synthetic ones, where the reproduction of fungi is not inhibited by the presence of a synthetic antibiotic.

MOSES SCHANFIELD YOUNG INVESTIGATOR AWARD (MSYIA) PRESENTATIONS

Presentation number: YIA 01 Abstract number: ABS-63-ISABS-2024

A RAPID BLOOD TEST FOR BREAST CANCER DETECTION

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Breast cancer is the most frequent cancer in women. Mammography screening reduces breast cancer mortality through early diagnosis, but it has significant shortcomings. Therefore, an alternative rapid, accurate, safe, easy-to-use, and cheap test for breast cancer detection and monitoring is needed. Micro-RNAs (miRNAs) are non-coding RNA with cellular regulatory functions that are considered promising biomarkers since their expression is altered in cancers. However, routine measurement in blood is time-consuming, costly, and requires specialized labs. In this study, we designed and characterized an optical dynamic DNA origami book biosensor. It is precisely decorated with arrays of fluorophores acting as donors and acceptors and also with fluorescence quenchers that produce a strong optical readout upon exposure to external stimuli for the single or dual detection of target oligonucleotides and miRNAs. This biosensor allowed the detection of target molecules (miRNAs) either through the decrease of Förster resonance energy transfer (FRET) or an increase in the fluorescence intensity profile owing to a rotation of the constituent top layer of the structure. Single-DNA origami experiments showed that the detection of two targets can be achieved simultaneously within 10 min with a limit of detection in the range of 1–10 pM. Our DNA origami book biosensor showed sensitive and specific detection of synthetic target oligonucleotides and natural miRNAs extracted from breast cancer cells and blood from Women with breast cancer. Based on these results, we foresee that our DNA origami biosensor could be in future translated into an alternative rapid, accurate, safe, easy-to-use, and cheap test for breast cancer detection and monitoring, which will make personalized medicine more accessible to all women, advanced molecular biology, and eventually save lives.

Keywords: DNA origami biosensor, cancer biomarker, miRNA, breast cancer, diagnostic test

Presentation number: YIA 02 Abstract number: ABS-24-ISABS-2024

A COMPREHENSIVE ANALYSIS OF WHOLE MITOGENOME HETEROPLASMY PATTERNS IN DIFFERENT FORENSIC TISSUES

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Mitochondrial DNA (mtDNA) is a good candidate marker when nuclear DNA (nuDNA) analysis is not possible. This is particularly important in forensic samples containing small amounts of nuDNA such as hair shafts. However, mtDNA interpretation presents challenges, especially in the reporting of heteroplasmy, which is the presence of slightly different mtDNA genomes (mitogenomes) in a cell. Depending on the bottleneck size during transmission the proportion of detectable mtDNA sequences can vary between and even within tissues. This effect is pronounced in single hair shafts that are known for a tight bottleneck size. In this study, we aim to identify heteroplasmy patterns across three different human tissues using whole mitogenomes, analyzed with massively parallel sequencing. Blood and buccal reference samples from 36 unrelated individuals and 317 hair segments (each measuring 2 cm) were analyzed as part of this study. DNA extractions were performed using in-house pre-treatment protocols followed by DNA extraction with the EZ-1 extraction robot (Qiagen). Quantification of nuDNA in blood and buccal samples was performed using the Quantifiler Trio DNA quantification Kit (ThermoFisher Scientific, TFS). In the hair samples, mtDNA (and nuDNA if present) was quantified using the qPCR SD quants assay, with all quantification experiments performed on the 7500 Real-Time PCR system (Applied Biosystems). The Precision ID mtDNA Whole Genome Panel and the Ion Torrent Ion Gene Studio S5 sequencing platform with the Ion 530 Chip (both TFS), were used for library preparation and sequencing. This study provides insights into the heteroplasmic patterns observed across the different tissues, revealing high inter and intra-individual variations. The outcomes of this study hold the potential for the determination of mitochondrial somatic mutation rates and their incorporation in statistical evaluations, thus enhancing the interpretation and reporting of mtDNA data in forensic contexts.

Keywords: Mitochondrial DNA, Heteroplasmy, Human tissues, Massively Parallel Sequencing, Precision ID mtDNA Whole Genome Sequencing

Presentation number: YIA 03 Abstract number: ABS-50-ISABS-2024

CNS-ASSOCIATED MACROPHAGES CONTRIBUTE TO INTRACEREBRAL ANEURYSM PATHOPHYSIOLOGY

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Intracerebral aneurysms (IAs) are pathological dilatations of cerebral arteries whose rupture leads to subarachnoid hemorrhage, a significant cause of disability and death. Inflammation is recognized as a critical contributor to the formation, growth, and rupture of IAs; however, its precise actors have not yet been fully elucidated. Here, we report CNS-associated macrophages (CAMs) as one of the key players in IA pathogenesis, acting as critical mediators of inflammatory processes related to IA ruptures. Using a new mouse model of middle cerebral artery (MCA) aneurysms we show that CAMs accumulate in the IA walls. This finding was confirmed in a human MCA aneurysm obtained after surgical clipping, together with other pathological characteristics found in the experimental model including morphological changes and inflammatory cell infiltration. In addition, in vivo longitudinal molecular MRI studies revealed vascular inflammation strongly associated with the aneurysm area, i.e., high expression of VCAM-1 and P-selectin adhesion molecules, which precedes and predicts the bleeding extent in the case of IA rupture. Specific CAM depletion by intracerebroventricular injection of clodronate liposomes prior to IA induction reduced IA formation and rupture rate. Moreover, the absence of CAMs ameliorated the outcome severity of IA ruptures resulting in smaller hemorrhages, accompanied by reduced neutrophil infiltration. In conclusion, our data suggest a previously unexplored role of CAMs as central actors orchestrating inflammation in the IA walls and promoting IA ruptures, and molecular MRI as a promising diagnostic clinical tool in future patient follow-up studies. Based on our data, we propose vascular inflammation as a potential diagnostic marker for the clinical management of unruptured IAs, and CAMs as important targets for novel therapeutic strategies in the treatment of aneurysms prone to rupture.

Keywords: CNS, macrophages, Intracerebral aneurysms, stroke, MRI

Presentation number: YIA 04 Abstract number: ABS-153-ISABS-2024

EFFECTS OF TREATING KNEE OSTEOARTHRITIS WITH AUTOLOGOUS MICROFRAGMENTED ADIPOSE TISSUE CONTAINING MESENCHYMAL STEM CELLS COMPARED TO HYALURONIC ACID – CLINICAL RESULTS FROM IRI2 PROJECT

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Regenerative medicine offers a novel approach to combating osteoarthritis (OA), the most common musculoskeletal progressive disease and a leading cause of disability worldwide. The study aimed to evaluate the effects of microfragmented adipose tissue (MFAT) and hyaluronic acid (HA) on knee symptoms, pain, and function using questionnaires such as the Visual Analog Scale (VAS), Western Ontario and McMaster Universities OA Index (WOMAC), and Knee Injury and OA Outcome Score (KOOS) before therapy, and at 1- and 6-months post-application in patients with OA. Conducted as part of the European research project IRI2 (KK.01.2.1.02.0173), as a continuation of previous work, the study included 53 patients aged 30-75 with mild to moderate knee OA, randomized into two groups. Detailed inclusion and exclusion criteria (available at isrctn.com/ISRCTN88966184) were implemented to form a cohort from the same phenotypic group corresponding to the inflammatory phenotype of knee OA. To facilitate blinding to the received therapy, lipoaspiration was performed on all patients. Patients treated with MFAT (7 mL, Lipogems®) and those with HA (Hyalubrix 60®) were followed for 6 months. Statistical analysis showed significant clinical improvement in both groups with changes in questionnaire scores (increase in KOOS, decrease in WOMAC, VAS, $p<0.05$). Particularly, the MFAT group showed a statistically significant improvement in the KOOS Symptoms score after 6 months compared to the HA group, indicating a superior effect of MFAT in terms of mobility, effusion, and stiffness due to its high anti- inflammatory potential ($p=0.008$). Furthermore, patients treated with MFAT exhibited continued symptom improvement at 6 months compared to the 1-month post-treatment point, a trend not observed with HA, which showed its peak effect at 1 month. This was observed in all questionnaires ($p<0.05$). This suggests that while HA provides a quicker response, MFAT demonstrates a progressive improvement over time.

Keywords: microfragmented adipose tissue, mesenchymal stem cells, hyaluronic acid, knee

Moses Schanfield Young Investigator Award (MSYIA)

Presentation number: YIA 05 Abstract number: ABS-113-ISABS-2024

TRANSCRIPTOMIC AND PROTEOMIC ANALYSIS OF MENSTRUAL BLOOD-DERIVED MESENCHYMAL STROMAL CELL EXTRACELLULAR VESICLES: NOVEL APPROACH FOR FUTURE DIAGNOSTICS OF UNEXPLAINED FEMALE INFERTILITY

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Unexplained infertility (uIF) affects 30% of couples worldwide and the diagnosis is confirmed if female is not able to get pregnant after at least 12 cycles of unprotected intercourse. However, the pathogenesis of uIF is still poorly understood and currently there are no effective diagnostic and prognostic tools for this issue. The goal of the study was to evaluate the differences of transcriptomic and proteomic profiles of menstrual blood mesenchymal stromal cells (MenSCs), their extracellular vesicles (EVs), menstrual blood serum EVs from fertile (F) and uIF woman and detect possible molecular biomarkers of uIF. MenSCs were isolated from 8 F female volunteers and 8 uIF patients. MenSCs EVs were isolated using ultracentrifugation with density gradient. Transmembrane, cytosolic markers of EVs and lipoprotein markers were analysed by flow cytometry/Western blot. Transcriptome of all samples was performed using next generation Illumina NextSeq 500 Platform and analysis performed using GO (gene onthology). Proteomic analysis was performed using mass spectrometry. Transcriptomic and proteomic analysis of all samples revealed the highest amount of differently expressed proteins and miRNAs between F and uIF groups were detected in serum EVs. Bioinformatic gene ontology analysis revealed that cell adhesion is the mostly affected process by uIF, as demonstrated by altered proteins in MSC EVs. The changes in the serum EVs of uIF women seem mainly related to innate immune response and neutrophil degranulation. Gene expression profiles of uIF EV group revealed downregulation of miRNAs associated with endothelial cell proliferation, involved in sprouting angiogenesis and embryo implantation, as compared to F EVs. We demonstrated that both, F and uIF MenSCs EVs and menstrual blood serum EVs is a promising source for uIF biomarkers, while our detected miRNAs and proteins related to fertility are potential for further studies and use for uIF diagnostics.

Keywords: unexplained infertility, menstrual blood mesenchymal stromal cells, extracellular vesicles, transcriptomic analysis

ABSTRACTS SELECTED FOR ORAL COMMUNICATION

Presentation number: OC0-TM 60 Abstract number: ABS-90-ISABS-2024

CAR-T-ONCOLYTIC VIRUS COMBINATIONS – EXPLOITING THE ENDOGENOUS T-CELL RECEPTOR (TCR) FOR ENHANCED THERAPY

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The efficacy of chimeric antigen receptor (CAR) T-cell therapy in solid tumours faces hurdles such as poor expansion and persistence, insufficient trafficking, and T-cell dysfunction within the tumour microenvironment (TME). Oncolytic viruses (OVs) are viruses engineered specifically to replicate in and kill tumour cells, with capacity to inflame the TME to favor effective cell therapy. We observed that treatment with both OV and CAR-T cells generated a population of dual specific (DS) CAR T cells in which the DS CAR-T recognized onco-viral epitopes through their endogenous T-Cell Receptors. These DS CAR-T cells were significantly more therapeutically effective *in vivo* than conventional CAR-T cells, with enhanced trafficking, infiltration, and persistence. Single-cell RNA/TCR sequencing of FACS sorted tumour-infiltrating CD8 CAR-T demonstrated that cytotoxic-effector gene expression was enriched in CAR-T clusters with clonally expanded endogenous TCRs. CAR-T expanded with viral-specificity were shown to have a proliferative advantage over those with non-viral TCRs, with a favorable differentiation profile and altered trajectory. This highlights the importance of the endogenous TCR in the profile and function of CAR-T cells within solid tumors, with potential for exploitation of viral immunity for therapeutic benefit. Clinical development of this approach is now underway.

Keywords: CAR T cells, Oncolytic Viruses, Immuno-oncology, Immune Checkpoint Inhibition, Solid tumours

Presentation number: OC1-TM Abstract number: ABS-28-ISABS-2024

EXPANDING A PERSONALIZATION ALGORITHM FOR PREDICTING INDIVIDUAL RESPONSE TO IMMUNOTHERAPY IN PATIENTS WITH ADVANCED MELANOMA

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Immune checkpoint inhibitors have brought an unprecedented improvement in the treatment of advanced cancers. Yet, the overall response rate to these drugs is below 50%, and predictive tools for selecting responsive patients are still urgently needed. Previously, we have developed an algorithm for predicting the response of patients with advanced melanoma to pembrolizumab (Tsur et al 2019, J. Translational Medicine). This algorithm was based on a mechanistic mathematical model for the effect of immunotherapy on the interactions of the immune system and melanoma tumors. We used clinical data of 54 patients from Israel and Germany to develop and initially validate this algorithm for the ability to predict individual time to progression, with reasonable accuracy (Cohen's kappa=0.489 for predicting the time interval of progression). In the present work we aim at validating the algorithm by an independent patient population from the Victorian Melanoma Service at Monash University, Australia. The original algorithm failed to satisfactorily generalize to the new data. This can be attributed to batch effect (patients from a different origin, a different period, or treated in a different health system). To expand the applicability of our algorithm, we trained and validated it by the entire patient cohort from the three different sources, applying an improved statistical and modeling methodology, and using a more advanced machine learning approach. This resulted in a new algorithm with comparable accuracy. In this work we demonstrate how an intricate predictive algorithm, involving statistical and mechanistic dynamical models can be sequentially improved by fine-tuning and testing on additional clinical data. Our goal is to develop a flexible framework for providing reliable quantitative response predictions (e.g., the time to radiological progression) for newly admitted patients, which will become an informative tool aiding clinicians in their decision making.

Keywords: checkpoint inhibitors, immunotherapy, melanoma, personalization, predictive model

Presentation number: OC2-TM Abstract number: ABS-106-ISABS-2024

EXPERIENCE WITH GENOMIC MATCHMAKING: ENHANCING DIAGNOSTIC EFFICACY AND NEW GENE-DISEASE DISCOVERIES IN NGS DIAGNOSTICS FOR RARE DISEASES

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In our efforts to enhance diagnostic efficacy and discover new gene-disease associations, we have incorporated genomic matchmaking. We present the outcomes of genomic matchmaking as an integrated component of extended analysis in NGS diagnostics at the Clinical Institute for Genomic Medicine in Ljubljana, Slovenia, emphasizing its impact on diagnostic yield and the discovery of new gene- disease associations. Material and methods: We conducted a retrospective analysis of candidate variants identified during extended whole exome and genome sequencing, which were submitted to the matchmaking nodes GeneMatcher (genematcher.org) and PhenomeCentral (phenomecentral.org) between 2017 and 2024. The analysis focused on the purpose of submission (whether for new gene- disease discovery or reclassification of variants of uncertain significance (VUS)), the number of matches and active submissions, as well as the final outcomes, including the number of publications and successfully diagnosed patients. Between 2017 and 2024, we submitted a total of 260 candidate variants based on our interpretation decision tree. The majority of these submissions (n=234, 90%) were aimed at new gene-disease discovery, while the remaining (n=26, 10%) involved candidate variants in genes with known gene-phenotype associations, observed in patients with discrepant phenotypes or for VUS reclassification. We successfully matched 31 new genes and 5 VUS, resulting in 9 publications and diagnoses for 32 patients, achieving a diagnostic yield of 12.3%. Currently, 107 submissions are still active. Our findings underscore the importance of data sharing and collaborative efforts through genomic matchmaking in maximizing the potential of NGS technologies for rare disease clinical setting.

Keywords: genomic matchmaking, diagnostic efficacy, new gene-disease associations, NGS Diagnostics, variant interpretation

Presentation number: OC3-TM Abstract number: ABS-124-ISABS-2024

VITAMIN D AND THYROID FUNCTION: A MENDELIAN RANDOMIZATION STUDY

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Numerous organs, including the thyroid gland, depend on vitamin D to function normally. Low serum 25- hydroxyvitamin D [25(OH)D] levels may contribute to various thyroid disorders; however, the causal relationship remains unclear. Using a Mendelian randomization (MR) approach we investigated the causal effect of serum 25(OH)D concentration on the indicators of thyroid function. We conducted a two-sample MR analysis utilizing summary data from the most extensive genome-wide association studies (GWAS) of serum 25(OH)D concentration (n=443,734 and 417,580), thyroid-stimulating hormone (TSH, n=271,040), free thyroxine (fT4, n=119,120), free triiodothyronine (fT3, n=59,061), total triiodothyronine (TT3, n=15,829), as well as thyroid peroxidase antibody levels and positivity (TPOAb, n=12,353 and n=18,297), low TSH (n=153,241), high TSH (n=141,549), autoimmune hypothyroidism (n=287,247) and autoimmune hyperthyroidism (n=257,552). The primary analysis was conducted using the multiplicative random-effects inverse variance weighted (IVW) method. The weighted mode, weighted median, MR-Egger, MR-PRESSO, and Causal Analysis Using Summary Effect estimates (CAUSE) were used in the sensitivity analysis. Our analysis showed a causal effect of 25(OH)D concentration on the risk of high TSH. Each 1 SD increase in serum 25(OH)D concentration was associated with a 12% decrease in the risk of high TSH (p=0.02). Additionally, we found a causal effect of 25(OH)D concentration on autoimmune hypothyroidism. Specifically, each 1 SD increase in serum 25(OH)D concentration was associated with a 16.34% decrease in the risk of autoimmune hypothyroidism (p=0.02). Our results support a causal effect that was negative in the direction across all methods used, meaning that higher genetically predicted vitamin D concentration possibly lowers the odds of having high TSH or autoimmune hypothyroidism. Other thyroid parameters were not causally influenced by vitamin D serum concentration.

Keywords: thyroid, mendelian randomization, gwas, causal, vitamin D

Presentation number: OC4-TM Abstract number: ABS-148-ISABS-2024

PRECISION MEDICINE APPROACH TO CELL THERAPY IN HEART FAILURE

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The goal of the study was to develop a personalized cell therapy approach to be used as a clinical management in patients with chronic heart failure. Materials and Methods. In the derivation part of the study, we analyzed the dataset from 5 cell therapy clinical trials conducted at UMC Ljubljana, enrolling a total of 240 patients with chronic heart failure. We performed machine learning analysis to define individual patient profiles with most clinical benefits after cell therapy. Patient profiles were then used as inclusion criteria in the validation part of the study. In the validation study, CD34+ stem cells were mobilized by 5-day stimulation with filgrastim, collected with apheresis and immunoselection and injected transendocardialy. Patients were followed 1 year after cell therapy. Results. In the derivation part we identified nonischemic heart failure etiology, lower NT-proBNP levels, transendocardial cell injection, and lower end-diastolic volume (LVEDV) as independent predictors of favorable response to cell therapy. Using these criteria in the validation part of the study, we enrolled 30 patients (male: 93%), aged 51±13 years, with LVEF of 28.4±5.0%, LVEDV of 224±46 mL, and NT-proBNP of 1231±1708 pg/mL. At 1 year after cell therapy, we found a significant improvement in LVEF (+10.5±7.8%, P<0.001), a decrease in NT-proBNP (-530±1430 pg/mL, P=0.001), and an improvement in exercise capacity, measured as 6-minute walk test distance (+31±58 m, P=0.01). An improvement of LVEF >5% was present in 24/30 (80%) of patients, and a concomitant improvement in LVEF, NT-proBNP, and exercise capacity was present in 18/30 (60%) of patients. Conclusions. The use of strategies based on informing target individuals with the highest likelihood of regenerative response may significantly improve the clinical efficacy of cell therapy in chronic heart failure patients.

Keywords: cell therapy, heart failure, clinical response

Presentation number: OC5-FG Abstract number: ABS-28-ISABS-2024

SARMATIAN GOTH OR GOTHIC SARMATIAN? FORENSICS SHEDS LIGHT ON SURPRISING IRON AGE BURIAL

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In 2017 during excavations in Gródek (south-eastern Poland) a few Iron Age burials were revealed. This area has been of interest to archaeologists since the 1970s following the discovery of a Gothic settlement and cemetery in the area. One grave from 2017 was particularly special. The site of the discovery of the burial as well as some artifacts attributed it to the local Gothic culture. However, the way the woman was laid in the grave and the necklace she was wearing were unusual for the Goths, but popular among the Sarmatians. An extended anthropological assessment of the remains, including a facial approximation by a forensic specialist was ordered. During the research, the idea emerged to enhance this analysis with a genetic prediction of the woman's physical appearance and also to use forensics to gain further insight into her biogeographic ancestry. DNA was extracted from the pars petrosa in a dedicated bone lab using the modified Dabney method. Three independent extracts were submitted to forensic DNA phenotyping using the Ion AmpliSeq™ PhenoTrivium Panel, which includes over 200 SNPs associated with phenotype and ancestry. Additionally, the mitogenome was analyzed using the Precision ID mtDNA Whole Genome Panel. Sequencing of the DNA libraries was performed on the Ion S5 System. Stable isotope analysis was conducted in addition to genetic testing. To gain insights into different stages of the woman's life, a tooth, a rib, and a fragment of humerus were tested. The forensic BGA analysis placed the individual among modern Europeans with no evidence of admixture, closest to the northwestern European populations. This aligns with the predicted physical characteristics of blue eyes, light blonde hair, and fair skin. Isotopic analysis suggests that the woman did not migrate during her lifetime. These findings support rather the hypothesis of a burial from the local community that interacted with and was influenced by outside cultures, including the Sarmatians.

Keywords: HIrisPlex-S; forensic DNA phenotyping; BGA; Goths; Sarmatians

Presentation number: OC6-AG

Abstract number: ABS-33-ISABS-2024

GENETIC HISTORIES OF MEDIEVAL SICILIAN INDIVIDUALS

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The Mediterranean area, at the crossroads of three different continents, has attracted not only diverse cultures but also a diversity of people, thus witnessing multiple changes, conquests, colonization, the rise and fall of several civilizations, kingdoms. From Antiquity to the Middle Ages, written sources testify to historic events of these periods, however, the impact of those changes on the biological heritage of the southern Italian population as well as on social and biological interactions between different communities under these circumstances remains unclear. Ancient DNA analysis on medieval individuals from Sicily was performed. This project followed state-of-the-art methods for ancient DNA research, including extensive measures in the laboratory to avoid contamination, recovery of DNA from dense bones, preparation of double-stranded DNA libraries, and evaluation of authenticity criteria, including deamination patterns and contamination estimates using Schmutzi and ANGSD software. 118 samples were analyzed, however, only samples showing characteristic ancient DNA patterns, no contamination, no first-degree relationships and at least 10,000 SNPs underwent further analyses. A total of 44 samples passed those criteria. The results revealed that during the Middle Ages, the Islamic conquest was not exclusively responsible for the presence of North African and sub-Saharan ancestry, nor was a massive population replacement observed. Finally, the whole study provided an opportunity to document the genetic diversity during a period that has not yet been extensively studied.

Keywords: ancient DNA, Sicily, Middle Ages

ABSTRACTS OF POSTER PRESENTATIONS

TRANSLATIONAL MEDICINE

BEST PRACTICES IN TRANSLATIONAL AND PERSONALIZED MEDICINE

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ANTIFUNGAL SUSCEPTIBILITY TESTING OF THE MOST-RELEVANT PATHOGENIC MOULDS

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The study centers on clinically important moulds that cause infections in humans, especially those with compromised immune systems. A standardized and widely accepted technique, broth microdilution, recommended by authoritative bodies such as CLSI and EUCAST, is employed for antifungal susceptibility testing. This method involves preparing dilutions of antifungal agents in a liquid growth medium and determining the minimum inhibitory concentration (MIC) as the lowest concentration inhibiting visible fungal growth. The standardized procedures outlined by CLSI guarantee the reliability and reproducibility of MIC testing across diverse laboratories. These guidelines meticulously detail factors such as media composition, drug concentrations, inoculum preparation, and incubation conditions, ensuring consistent and accurate results. Adherence to these standardized procedures minimizes variability, fostering the comparability of MIC data obtained from various sources. The study underscores the crucial role of MIC testing in optimizing antifungal treatment strategies for immunocompromised patients. By aiding in the selection of appropriate antifungal medications, dosage determination, and monitoring of drug resistance, MIC testing using standardized broth microdilution emerges as a reliable tool in the battle against fungal infections.

Keywords: mould, susceptibility, minimum inhibitory concentration

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POLYCYSTIC OVARY SYNDROME WITH GENETIC PERSPECTIVE

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Polycystic ovary syndrome (PCOS) is a prevalent endocrine-gynecology disorder affecting 8–13% of reproductive-aged women globally, with up to 70% undiagnosed. It's the main cause of anovulation and a key factor in infertility, impacting both physical and emotional well-being. Genetic predisposition plays a significant role in PCOS, with genes such as Androgen Receptor (AR), Fat Mass Obesity (FTO), Follicular Stimulating Hormone Receptor (FSHR), Calpain 10 (CAPN10), and members of the Cytochrome P450 family (CYP) being implicated in its pathogenesis. These genes are linked with hormonal imbalances, insulin resistance, and metabolic dysregulation observed in PCOS patients. Diagnosis of the PCOS relies on the presence of two out of three criteria: hyperandrogenism, irregular menstrual cycles, and polycystic ovaries on ultrasound. Elevated levels of testosterone, estrogen, luteinising hormone, insulin, and anti-müllerian hormone are common. Patients often present with symptoms like irregular periods, infertility, acne, excessive hair growth, and weight gain, predisposing them to conditions like type 2 diabetes and cardiovascular diseases. Treatment focuses on symptom management. Lifestyle changes, including diet and exercise are very useful. Pharmacological interventions such as birth control pills, insulin-sensitizing agents, and medications to reduce symptoms like acne and unwanted hair growth are employed. Complementary therapies and nutrient supplementation, including vitamins B-12, D, E, and K, inositols, melatonin, omega-3 fatty acids, and probiotics, are being explored for their potential benefits and specially inositols are very promising. More research is needed to apply these methods in clinical settings. Challenges in diagnosis and treatment persist, underscoring the importance of ongoing research and guideline implementation. Genetics play a crucial role in PCOS, offering insights into diagnosis, treatment, and prognosis, particularly regarding infertility.

Keywords: polycystic ovary syndrome, genetics, genes, infertility, insulin resistance

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THE UTILITY OF WGS IN PROACTIVE GENETIC SCREENING AND PREVENTIVE MEDICINE DEMONSTRATED IN A CASE OF LYNCH SYNDROME TYPE 8

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With the increasing application of genetic testing in modern medicine, its utility in the field of preventive oncology cannot be overlooked. It allows healthy individuals to determine potential oncogenic predispositions in their genome and take the necessary steps toward quality preventive care. A 54-year- old male patient was examined as part of a preventive health check-up. The patient had no prior history of serious illness, nor was his family history positive for malignancies. After testing with whole genome sequencing, we performed a targeted analysis using the proactive 526-gene hereditary cancer panel and the 523-gene cardiometabolic panel. Likely pathogenic variants were discovered in the SPTA1 gene (c.4339-99C>T) and EPCAM gene (c.655del). Pathogenic variants in the EPCAM gene are associated with Lynch syndrome 8 (LS-8), an autosomal dominant disorder characterized by dysfunctional DNA mismatch repair and microsatellite instability. The EPCAM protein is a transmembrane protein involved in cancer cell adhesion, proliferation, and migration and its mechanism is related to the beta-catenin pathway. Additionally, EPCAM deletions can cause the silencing of the MSH2 gene via promoter hypermethylation. LS-8 is considered a high-risk condition for the development of gastric, enteric, hepatic, biliary, urinary, brain, and skin malignancies. Preventive medical approaches with a focus on cancer screening can be greatly beneficial to these patients. This most often includes regular colonoscopies as gastrointestinal malignancies are the most frequent. With the timely and proper application of screening methods, some of these individuals have been reported to survive multiple primary cancers and live to old age.

Keywords: preventive medicine, cancer screening, EPCAM, Lynch syndrome 8

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CLINICAL PRESENTATION AND TREATMENT CONSIDERATIONS FOR A PATIENT WITH PROGRESSIVE MUSCLE WEAKNESS AND PATHOGENIC VARIANTS IN THE DYSF GENE

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Dysferlinopathy is an autosomal recessive type of muscular dystrophy characterized by pathogenic variants in the DYSF gene. The disease has been described in the literature under several names, including Myoshi muscular dystrophy (MMD), limb-girdle muscular dystrophy type 2B (LGMD2B), and distal myopathy with anterior tibial onset (DMAT). Patient history often includes symptoms of progressive muscular weakness, with age at onset ranging from 15 to 25 years, with difficulty standing on toes as an early feature. Diagnostic tests can reveal elevated creatinine kinase (CK) and muscular atrophy with fatty infiltration on magnetic resonance imaging (MRI). The diagnosis is confirmed by genetic testing and open muscle biopsy. \We present a 53-year-old nonambulatory female patient with paraparesis in both lower extremities (0/5) and severe muscle weakness in both hands (2/5) accompanied by pain in both shoulders and knees, the lumbar region, and the left hip. MRI showed severe fatty infiltration in the musculature of the lower extremities and the lumbosacral region. Degenerative disc processes were also seen at L4-S1 levels and in both knees (dorsomedial protrusion with reduction of anterior subarachnoid space). The condition was confirmed with two intronic pathogenic variants (DYSF c.4221+1G>C & c.2643+1G>C) and pathological findings following open muscle biopsy. While the assumption of compound heterozygosity was made, confirmation by parental testing was not performed. Advanced treatment options that might be considered are local applications of platelet-rich plasma or i.v. mesenchymal stem cells. It is also worth noting that several clinical trials are exploring routes of genetic therapy, by mechanisms of increasing myocyte membrane repair potential or inflammatory and epigenetic modulation. These treatment options are applicable at a young age and thus were not applicable in our case, as the patient's clinical presentation had progressed past this point.

Keywords: dysferlinopathy, DYSF, limb-girdle muscular dystrophy type 2B, fatty infiltration, spinal degeneration

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PATHOGENIC HOMOZYGOUS AIRE VARIANT RESULTS IN ADRENAL AND PARATHYROID GLANDULAR DYSFUNCTION

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Autoimmune polyglandular syndrome type 1 (APS-1) is an autoimmune disease caused by pathogenic variants in the AIRE gene. The AIRE gene's function is immunomodulatory, and it plays a key role in the conditioning of T lymphocytes. The functional protein ensures that abnormal T cells, reactive to the host's physiological antigens, are destroyed. However, in the case of its dysfunction, autoreactive T cells are released and initiate a systemic inflammatory response. The typical triad of symptoms that characterizes APS-1 includes Addison disease, hypoparathyroidism, and chronic mucocutaneous candidiasis. The diagnosis can be confirmed by active antibodies, typically against interferon-alpha, or by pathological genetic findings in the AIRE gene. A 10-year-old female patient presented with abdominal pain, low appetite, and vomiting and was examined 15 days after onset. In that period, she'd also lost 2 kg, was constantly exhausted and her mother had noticed her skin becoming darker. Laboratory findings showed hyponatremia, hyperkalemia, hypocalcemia, hyperphosphatemia, hypocortisolemia with elevated ACTH, and very low PTH. Under suspicion of APS, the patient was subject to genetic testing. A comprehensive panel was performed, including 613 genes, and identified a homozygous pathogenic variant in the AIRE gene (c.769C>T (p.Arg257Ter)). The treatment option for APS-1 is hormone replacement therapy, in terms of glucocorticoid and calcium supplementation. A follow-up assessment of gonadal and thyroid function is also necessary. It is also worth noting that certain studies have observed gene therapy as another potential approach. A study conducted on the mouse model has demonstrated that the AAV9 vector containing AIRE cDNA can achieve significant T-cell infiltration and reduce serum antibodies to undetectable levels in a 4-week timeframe. These findings demonstrated the feasibility of gene therapy in APS-1, although further research is still needed before its implementation.

Keywords: autoimmune polyglandular syndrome type 1, Addison disease, hypoparathyroidism, AAV9 gene therapy

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PRADER-WILLI SYNDROME AND LIMB-GIRDLE MUSCULAR DYSTROPHY CAUSED BY PARTIAL MATERNAL UNIPARENTAL ISODISOMY

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Uniparental isodisomy refers to a condition in which both copies of a chromosome are duplicates of a single parental chromosome. It can arise from inadequate meiotic segregation, second-rescuing segregation in the zygote, or errors in early embryonic division. Prader-Willi syndrome (PWS), caused by the loss of expression of paternally imprinted genes within the PWS region located on 15q11.2, presents with neonatal hypotonia, failure to thrive, developmental delay, obesity, hypogonadism, and behavioral issues, with 25% of cases attributed to uniparental disomy. Isodisomy may be associated with secondary autosomal recessive disorders because, in cases where the parent is a carrier of a pathogenic variant, the child may become homozygous for the same variant. We present a 4-year-old patient with the diagnosis of PWS and an autosomal recessive limb-girdle muscular dystrophy type 1 (LGMDR1). Whole-genome sequencing (WGS) confirmed partial maternal uniparental isodisomy by detecting a homozygous PWS region of chromosome 15. Additionally, a homozygous pathogenic variant in the CAPN3 gene (c.550del, p.Thr184fs) associated with limb-girdle muscular dystrophy type 1, a hyper creatine-kinase (CK) calpainopathy, was identified. The proband's mother had an identical variant of the CAPN3 gene (c.550del, p.Thr184fs) in a heterozygous form. The proband exhibited elevated CK levels, with isoenzymes originating from muscle and brain tissues. Therefore, the patient's management required a multidisciplinary and personalized approach, greatly aided by genetic testing. This case highlights the pivotal role and potential of WGS in identifying both monogenic disorders and various forms of uniparental disomy simultaneously.

Keywords: uniparental disomy, Prader-Willi syndrome, WGS, CAPN3, limb-girdle muscular dystrophy

Presentation number: TM 07 Abstract number: ABS-100-ISABS-2024

A CASE OF MULTIPLE EPIPHYSEAL DYSPLASIA CAUSED BY A RARE CLINICALLY SIGNIFICANT PATHOGENIC VARIANT IN THE COMP GENE

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Multiple epiphyseal dysplasia (MED) is a rare genetically heterogeneous disorder primarily caused by mutations in several genes, including COMP, MATN3, and COL9A1. The inheritance pattern is typically autosomal dominant, with the mutation in the COMP gene being the most common and severe form, leading to abnormal cartilage development. MED-affected individuals typically show short stature and often receive a diagnosis later in life after experiencing lower limb joint discomfort. They typically exhibit ankle valgus deformity and are prone to compromised blood flow to the joints, leading to avascular necrosis. We present a case of a 33-year-old female patient with persistent pain, primarily in the knees and groin. Clinical examination showed an exceptionally wide range of motion in the hips, positive FADIR and FABER signs, and anterior knee instability. Radiological examinations unveiled subchondral bone sclerosis affecting the articulating surfaces of both knees and hips, with flattened femoral condyles in both knees, as well as extensive fissuring of cartilage and dorsoposition of the vertebrae L5-S1. Following a spine surgeon's examination, the patient underwent a procedure of L5-S1 radicular infiltration with levobupivacaine and PRP. The postprocedure course was uncomplicated. Considering the patient's medical history, genetic testing was initiated, the results of which showed a clinically significant pathogenic variant in the COMP gene (c.1501G>A (p.Gly501Ser)), associated with autosomal dominant skeletal dysplasia. Although this variant hasn't been documented in the literature thus far, the clinical phenotype and radiological findings of the patient suggest a diagnosis of MED type 1. Given the common attribution of such symptoms to environmental factors, this case highlights the necessity of integrating genetic evaluation into the diagnostic protocol for skeletal dysplasia, as exemplified by the procedures implemented at St. Catherine's Specialty Hospital.

Keywords: multiple epiphyseal dysplasia, genetic testing, COMP, pathogenic variants, phenotype

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THE POTENTIAL OF NUTRIGENETICS IN PERSONALIZED MEDICINE

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Nutrigenetics is a branch of genetics that focuses on the specific interactions between genes and nutrients, emphasizing how genetic variations influence responses to dietary components. As genetic understanding and sequencing technologies progress, personalized nutrition through nutrigenetics becomes increasingly important for tailoring nutrition to individual genotypes, promoting personalized dietary plans for better health and disease prevention. Several pivotal genes have emerged as influential factors, in shaping personalized diet recommendations. Genetic variants within the VDBP, VDP, and CYP2R1 genes, influence vitamin D metabolism and could contribute significantly to well-being and the prevention of age- and lifestyle-related diseases, particularly those associated with chronic inflammation. One of the most important genes in nutrigenetics is FTO and its variants have been linked to an increased risk of obesity and metabolic disorders. Given the established link between obesity and the risk of type 2 diabetes (T2D), several gene-diet interactions affecting obesity risk have been identified, which are relevant to T2D. These interactions involve genotypes related to genes such as ADIPOQ, FTO, FADS, PPARG, PLIN, and MC4R, in conjunction with dietary factors, influencing outcomes related to the disease, such as insulin sensitivity and T2D. Additional associations include genes APOA2 with intake of saturated fatty acids and body mass index, MTHFR with homocysteine levels, and CYP1A2 with caffeine-related hypertensive response. We will analyze five hundred participants who underwent comprehensive whole genome sequencing integrated with nutrigenetic testing. The aim will be to optimize personalized dietary plans based on nutrigenetic results, with the potential to reduce the risk of developing various health conditions, including diabetes, obesity, cardiovascular diseases, osteoporosis, hypertriglyceridemia, and chronic systemic inflammation.

Keywords: nutrigenetics, personalized medicine, nutrients, personalized diet, disease prevention, obesity

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PREGNANT COUPLES' ATTITUDE TOWARDS EXTENDED PRECONCEPTIONAL GENOMIC SCREENING

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We present a study on the attitudes of pregnant couples towards carrier screening genomic tests. A validated 22-item questionnaire was offered in person by medical staff to 32 weeks or more pregnant women and their partners attending prenatal classes. We also explored their interest in various forms of genetic carrier screening tests and investigated the impact of genetic literacy. Of 497 respondents, 69% expressed a strong interest in carrier screening. Among the interested participants, there was substantial support for screening for common (82%) or all known genetic diseases (79%), as well as for treatable (79%) and untreatable diseases (85%). The majority of respondents believed that genetic test results could provide them with a sense of security but also with anxiety and fear. They were aware that these results could impact their perspective on life, work, and the atmosphere within their family, and acknowledged the potential effect on their relationship with their partner. However, none of these concerns diminished their desire to learn about their carrier status. Support varied significantly across certain demographic groups. Respondents of higher genetic literacy exhibited higher interest in screening tests (p=0.006). The interest in carrier screening was also influenced by religious affiliation and educational level. Specifically, 78% of non-religious individuals, compared to 60% of practicing-religion subjects (p=0.002), and 74% of higher-educated individuals, as opposed to 60% of those with lower levels of education, expressed interest in screening (p=0.003). Most respondents manifested a robust inclination to receive information about their carrier status through genetic tests.

Keywords: preconception, diagnosis, genetic screening, parental opinion, knowledge

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THE ROLE OF CHOLESTEROL METABOLISM IN ACQUIRED RESISTANCE TO BRAF INHIBITION BY VEMURAFENIB IN BRAFV600E- MUTATED COLON CANCER

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BRAFV600E-mutated colorectal cancer represents approximately 8–12% of metastatic colorectal cancer (mCRC) cases and is considered the most aggressive subgroup of colorectal cancer characterized by a poor response to chemotherapy and short overall survival. Vemurafenib is a specific BRAFV600E inhibitor approved for mCRC patients. However, monotherapy with vemurafenib in this patient population has limited clinical efficacy due to rapid development of chemoresistance. The aim of this study was to identify perturbations in lipid metabolism associated with the development of vemurafenib resistance in BRAFV600E-mutated colon cancer. We performed untargeted lipidomics analysis of vemurafenib-resistant vs. sensitive RKO colon cancer cells harbouring BRAFV600E mutation by LC-MS/MS. OPLS-DA analysis revealed that the major lipid classes that differentiated resistant from sensitive cells included phosphatidylcholine (PC), triglycerides (TG) and cholesteryl esters (CE). Wilcoxon test showed significantly increased abundance of CE with different chain lengths in resistant cells at baseline and after the treatment with vemurafenib, indicating the involvement of cholesterol metabolism in the resistance mechanisms. We next evaluated in silico mRNA expression levels of the key enzymes regulating cholesterol metabolism, including 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), sterol O- acyltransferase 1 (SOAT1) and sterol O-acyltransferase 2 (SOAT2) in the TCGA Colorectal Adenocarcinoma PanCancer Atlas dataset. We found that only SOAT1 showed a trend towards increased expression in BRAF-mutated tumours vs. unaltered group. Higher SOAT1 mRNA expression was associated with lower overall survival of BRAFV600E-mutated colon cancer patients. Currently, we are investigating whether protein expression of HMGCR, SOAT1 and SOAT2 in tumour tissues could predict the outcome of BRAF-mutated colon cancer patients on BRAF inhibitor therapy.

Keywords: BRAFV600E, colorectal cancer, chemoresistance, lipid metabolism, cholesterol metabolism

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MOLECULAR BASIS OF THE DISEASE, PERSONALIZED APPROACH AND IMPLICATIONS FOR FAMILY SCREENING IN PATIENTS WITH CADASIL SYNDROME

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CADASIL, an autosomal dominant cerebral arteriopathy characterized by subcortical infarcts and leukoencephalopathy, is primarily linked to mutations in the NOTCH3 gene. Typically, onset occurs around ages 45-50, commonly presenting as ischemic stroke or cognitive decline. Migraine, often with aura, affects approximately one-third of patients and frequently precedes stroke and dementia symptoms. A 48- year-old female presented to our hospital with rotatory vertigo and ataxia. Her family history revealed a predisposition to the same condition, with confirmed diagnoses in both her sister and nephew, along with a frequent occurrence of strokes in the family. Physical and neurological examinations were unremarkable, except for paresthesia in the lower left third of the face. Magnetic resonance imaging (MRI) depicted a 16mm heterogeneous lesion with T2 hyperdense edges in the right middle cerebral peduncle, showing mild diffusion restriction with a central microhemorrhagic component. Given the proband's medical history, neurological complaints, and leukoencephalopathic changes, whole-genome sequencing was performed, revealing a clinically significant pathogenic variant in the NOTCH3 gene (c.421C>T (p.Arg141Cys)), associated with CADASIL. Based on the positive family history and the patient's test results, testing of her 22-year-old son was recommended. This case underscores the necessity for comprehensive monitoring and management of CADASIL. Considering the positive family history and the patient's symptoms, it is essential to adopt a personalized approach, focusing on potential future manifestations in her son, who may be at risk of developing symptoms.

Keywords: CADASIL, whole-genome sequencing, NOTCH3, vertigo, stroke

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OPTIMIZATION OF SEPARATION OF ALPELISIB AND FULVESTRANT BY SWEEPING MICELLAR ELECTROKINETIC CHROMATOGRAPHY- TANDEM MASS SPECTROMETRY

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Micellar electrokinetic chromatography coupled with mass spectrometry (MEKC-MS/MS) is a powerful analytical technique for a wide range of applications due to its efficiency, swiftness, and environmental friendliness. On the other hand, there is a great need for the development of bioanalytical methods for the therapeutic drug monitoring (TDM) of breast cancer drugs alpelisib (ALP) and fulvestrant (FUL). Herein, we optimized the separation of ALP and FUL in a novel MEKC-MS/MS method. Separation was achieved within 11 minutes using a volatile, MS-compatible surfactant ammonium perfluorooctanoate (APFO). Optimization of separation was performed by testing the pH of the running buffer (9.0-10.0), APFO concentration (50-100 mM), a fraction (20-35%) and type (MeOH, EtOH, ACN, i-PrOH) of organic modifiers in the running buffer, capillary temperature (20-30 ˚C), voltage (20-30 kV), duration of hydrodynamic injection (5-90 s) and hydrodynamic pressure during the analysis (0-100 mbar). Optimal conditions were 50 mM APFO at pH 9.75 in 25% MeOH, separation voltage 30 kV, capillary temperature 30 ˚C, hydrodynamic injection of 60 s, and additional hydrodynamic pressure of 100 mbar during the analysis. With these conditions, the best results in terms of analysis time, resolution, and peak shapes were obtained. Additionally, a sweeping online preconcentration technique was performed by dissolving the analytes in the electrophoretic buffer without the micelles. This way, the analytes were swept in the narrow zone and concentration factors of 109 and 11 for ALP and FUL, respectively, were obtained. In further studies, the MS ion source will be optimized, the method will be validated and applied to patient plasma samples for TDM. This work has been fully supported by the Croatian Science Foundation through projects UIP-2019-04-8461 and DOK-2021-02-4595, and the European Regional Development Fund, project Farminova, KK.01.1.1.02.0021.

Keywords: micellar electrokinetic chromatography, mass spectrometry, alpelisib, fulvestrant

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GENETIC INSIGHTS AND TREATMENT CHALLENGES IN AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1: CASE REPORT

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Autoimmune polyglandular syndrome type 1 (APS-1), caused by homozygous, compound heterozygous, or heterozygous mutation in the AIRE gene, is a rare genetic condition manifesting in childhood. The coding sequence for the AIRE transcription factor is integral to immune tolerance mechanisms, facilitating the negative selection of autoreactive T lymphocytes within the thymus, lymph nodes, and spleen. We present a 3-year-old patient who was admitted to the intensive care unit exhibiting a critical condition alongside positive meningeal signs, with Streptococcus pneumoniae subsequently isolated from the cerebrospinal fluid. Following rapid deterioration, the patient necessitated endotracheal intubation. Continuous EEG monitoring and transcranial Doppler sonography supported the clinical suspicion of cerebral death. Post- mortem genetic analysis of the patient revealed two heterozygous variants in the AIRE gene, the pathogenic variant c.769C>T (p.Arg257*) and the likely pathogenic variant c.151_152dupGA (p.Glu53fs), confirming the diagnosis of APS-1. Of particular significance is the c.769C>T (p.Arg257*) variant, which has been associated with an increased vulnerability to specific infections and life-threatening non- endocrine manifestations. Additionally, although not previously reported in human diseases, the c.151_152dupGA (p.Glu53f2) variant is presumed to disrupt AIRE function, potentially exacerbating its pathogenicity. Molecular genetic analysis of the patient's mother identified the likely pathogenic variant c.151_152dupGA (p.Glu53fs) in a heterozygous state, while the father was determined to be a carrier of the pathogenic variant c.769C>T (p.Arg257*), also detected in a heterozygous state. In conclusion, continued research on the genetic basis of autoimmune diseases is vital for improving our understanding and treatment outcomes. Further investigations will provide deeper insights into disease mechanisms, enabling the development of personalised therapies.

Keywords: autoimmune polyglandular syndrome type 1, AIRE, genetic testing, personalized therapies, pneumococcal meningitis

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RELATIONSHIP BETWEEN GUT MICROBIOTA AND THE CLINICAL COURSE OF COVID-19 DISEASE

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COVID-19 is an infectious disease caused by a novel coronavirus SARS-CoV-2. The possibility of early detection of people at increased risk of developing a severe clinical picture is extremely important, so that appropriate therapy can be initiated timely to prevent numerous deaths. Elevated ACE2 receptor expression increases the exposure of type 2 pneumocytes to the SARS-CoV-2 spike protein and is influenced by various factors. The gut microbiota influences ACE2 receptor expression, while ACE2 simultaneously influences the composition of the gut microbiota. The gut microbiota also influences the immune response to lung infections via the gut-lung axis. People with underlying medical conditions (comorbidities) such as diabetes, obesity and hypertension are at a significantly higher risk of developing severe COVID-19 clinical picture. Our study included 45 patients treated at University Hospital Dubrava, for whom clinical course of COVID-19 disease was analyzed from medical records and the diversity of gut microbiota in stool samples was determined using 16S rRNA analysis. Relationship between gut microbiota composition markers (such as those related to the risk of diabetes, obesity, and hypertension – i.e. increased Firmicutes/Bacteroidetes ratio) and the clinical course of COVID-19 disease was determined. In a broader sense, our findings might be useful in combating potential future similar pandemics and other communicable and non-communicable diseases whose clinical course may be influenced by the gut microbiota. Pointing towards gut microbiota composition markers as a potential tool for early detection of individuals at an increased risk of developing a severe clinical picture and altering gut microbiota composition to actively reduce this risk, could be used as potential approaches to prevent severe clinical picture and fatal outcomes in the future.

Keywords: 16S rRNA analysis, Clinical Course, COVID-19, Gut Microbiota, SARS-CoV-2

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REGULAR MODERATE PHYSICAL ACTIVITY DECREASES GLYCAN AGE INDEX OF BIOLOGICAL AGE AND REDUCES INFLAMMATORY POTENTIAL OF IMMUNOGLOBULIN G BY ALTERING N-GLYCAN GLYCOSYLATION

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Physical inactivity and obesity are growing concerns, negatively impacting the general population. Moderate physical activity is known to have a beneficial anti-inflammatory effect. N-glycosylation of immunoglobulin G (IgG) reflects changes in the inflammatory potential of IgG. In this study, GlycanAge index of biological age (GlycanAge), one of the first commercially used biomarkers of aging, was employed to assess effects of exercise intensity in three different groups of athletes: professional competing athletes (PRO), long-term regularly moderate active individuals (ACT), and recently involved, but previously inactive, recreational individuals (REC), compared to the group of inactive individuals (INACT). The aim of this study was to determine the effects of long-term moderate exercise on Immunoglobulin G (IgG) glycosylation and the effect on GlycanAge biomarker (GA). A drop of peripheral blood was taken to measure changes in IgG glycosylation. The IgG was isolated from the dry blood spots, deglycosylated, labeled and analyzed by UPLC, glycan peaks were integrated and processed to get N-glycans and GA results. GlycanAge index of biological age was significantly lower in the active group compared to the inactive group (β= -7.437, p.adj = 7.85E-03), and nominally significant and increased in professional athletes compared to the active group (β = 7.546, p = 3.20E-02). Competing female athletes had significantly higher GlycanAge compared to active females exercising moderately (β = 20.206, p.adj = 2.71E-02), while the latter had significantly lower GlycanAge when compared with their inactive counterparts (β= -9.762, p.adj = 4.68E-02). Regular, life-long moderate exercise has an anti-inflammatory effect on both the female and the male population, demonstrated by lower GlycanAge index, and it has great potential to mitigate growing issues related to obesity and a sedentary lifestyle, which are relentlessly increasing world-wide.

Keywords: regular moderate physical activity, aging biomarkers, glycosylation, biological age, GlycanAge

Presentation number: TM 16 Abstract number: ABS-175-ISABS-2024

MMP3 SINGLENUCLEOTIDE POLYMORPHISMS ARE ASSOCIATED WITH NON-CONTACT ACL INJURIES IN HIGHLEVEL COMPETING ATHLETES

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Matrix metalloproteinases (MMPs) play an important role in matrix remodeling, as well as in ligament integrity. Anterior cruciate ligament (ACL) rupture is a severe and frequent knee injury in sports. The aim of this study was to investigate polymorphisms within the MMP3 gene with the predisposition for non- contact ACL rupture in Croatian professional athletes. 187 unrelated Caucasians were recruited between 2016 and 2017 (95 with ACL rupture occurring through a noncontact mechanism and 92 asymptomatic controls, previously active competing athletes that have retired without sustaining injuries during their competing career). All participants were genotyped for three single nucleotide polymorphisms (SNP) within the MMP3 gene: rs591058 C/T, rs650108 A/G, and rs679620 G/A using the pyrosequencing method. For all three investigated SNPs, genotype frequencies have significantly differed between cases and controls. The MMP3 rs591058 TT (p = 0.0012, odds ratio [OR] = 38.541, 95% confidence interval [CI] = 1.7024 – 8.7254), rs650108 GG (p = 0.0051, OR = 23.338, 95% CI = 1.2899 – 4.2226) and rs679620 AA (p = 0.0030, OR = 34.750, 95% CI = 1.5266 – 7.9101) genotypes, as well as haplotype variant TGA (p = 0.0104, OR = 1.71, 95% CI = 1.13 – 2.59) were significantly overrepresented in cases compared to controls. These results support an association between functional variants within the MMP3 gene and the risk of ACL rupture in the Croatian population. Still, further research is needed to corroborate these results in a larger population.

Keywords: SNP, MMP3, ACL rupture, injury, sport

Presentation number: TM 17 Abstract number: ABS-159-ISABS-2024

ASSOCIATION OF THE MATRIX METALLOPROTEINASE 3 (MMP3) SINGLE NUCLEOTIDE POLYMORPHISMS WITH TENDINOPATHIES IN HIGH-LEVEL COMPETING ATHLETES

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Matrix metalloproteinases (MMPs) play an important role in matrix remodeling, as well as in tendon integrity. Due to overuse, athletes often develop chronic tendinopathies. If not treated, they lead to severe impairment, even complete tendon ruptures. The main purpose of this study was to investigate whether three functional polymorphisms within the MMP3 gene are associated with an increased risk of developing tendinopathies in high-level Croatian athletes. We have recruited one hundred fifty-five unrelated Caucasians for this case-control genetic study (63 high-level athletes with diagnosed tendinopathies and 92 asymptomatic controls, previously active competing athletes that have retired without sustaining injuries during their competing career). All participants were genotyped for three single nucleotide polymorphisms (SNP) within the MMP3 gene: rs591058 C/T, rs650108 A/G and rs679620 G/A using the pyrosequencing method. The MMP3 rs650108 GG (P = 0.0074) and rs679620 AA (P = 0.0119) genotypes were significantly over-represented in cases compared with controls, while rs591058 TT (P = 0.0759), as well as haplotype variant T - G - A (P = 0.06), implicated that there is an indication of predisposition for tendinopathies. These results support an association between functional variants within the MMP3 gene and the risk of tendinopathies in high-level athletes in the Croatian population. Further research is needed to replicate these results in a larger population.

Keywords: SNP, MMP3, tendinopathy, injury, sport

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BLEEDING RISK STRATIFICATION IN CORONARY ARTERY SURGERY: DEVELOPMENT OF THE SHOULD-NOT-BLEED SCORE

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An estimated 20% of allogeneic blood transfusions in the United States are associated with cardiac surgery. We developed a model to predict which patients are at low risk of bleeding for whom transfusion treatment might be considered unnecessary. Herein we present our "SHOULD-NOT-BLEED-SCORE" application developed for the Windows® software platform which is based on our previous research. This study is aimed to develop a user-friendly application that stratifies patients with respect to bleeding risk. The statistical model we used in our previous research was focused on detection of CABG patients at low risk of bleeding. The rationale behind such an approach was to identify a CABG patient subgroup at low risk of bleeding. By identifying patients at low risk of bleeding we can define a subgroup of patients for whom transfusion treatment might be considered unnecessary. We developed a Windows platform application based on risk modelling which we previously calculated for 1426 patients undergoing elective CABG from January 2010 to January 2018. The SHOULD-NOT-BLEED-SCORE risk score is developed for the Windows software platform. A mathematical model that is based on multivariate analysis was used for app development. The variables that entered the scoring system were Age; Body Mass Index; Chronic Renal Failure; Preoperative Clopidogrel Exposure; Preoperative Red Blood Cells Count; Preoperative Fibrinogen Level; Preoperative Multiplate ASPI test area under the curve (AUC) units. The SHOULD-NOT- BLEED-SCORE identifies/predicts patients without a risk for excessive bleeding with strong discriminatory performance (Receiver Operating Curve (ROC) analysis AUC 72.3%, $p < 0.001$). The clinical and economic burden associated with unnecessary transfusions may be adequately addressed by a preoperative scoring system detecting patients at low risk of bleeding for whom transfusion treatment might be considered unnecessary.

Keywords: bleeding, cardiac surgery, transfusion, cost analysis, risk stratification

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SCREENING OF BENZODIAZEPINES IN URINE SAMPLES IN UNIVERSITY HOSPITAL CENTER SPLIT (CROATIA) FROM 2015 TO 2022

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Goal was to determine the prevalence, distribution, and trend of benzodiazepine use depending on the time and characteristics of patients (age and sex) screened at the Medical Laboratory Diagnostic Division of the University Hospital Center Split (Split, Croatia). We retrospectively collected screening test results for benzodiazepine from the BioNet laboratory database of the Medical Laboratory Diagnostic Division. The data included the testing results of all adult patients from 2015 to 2022, the testing date, and the sex and age of the patients. We calculated descriptive statistics of demographic characteristics for tested and positive patients. Logistic regression was used to analyze the effect of sex and age as predictors for a positive screening test result. A total of 4,162 benzodiazepine tests were performed during the considered period. The proportion of positive tests was 44.7% (48.4% of men and 39.6% of tested women). In the observed period, the number of analyses increased by 101%, from 368 tests in 2015 to 741 in 2022. The proportion of positive tests in 2015 was 39.9%, and more than 40% during other years. A logistic regression model showed that sex and age contributed to predicting positive test results ($P < 0.001$). With each year of increasing age, the odds of a positive test result increased by approximately 2.5%, while women were about 38.7% less likely to test positive than men. The results revealed a high prevalence of benzodiazepine use, with notable differences by sex and age, suggesting potential misuse and highlighting the need for targeted monitoring and intervention strategies. The trend in positive tests underlines the demand for continuous substance use surveillance and tailored preventive measures.

Keywords: drugs of abuse, benzodiazepine, drug screening, medical laboratory diagnostics, UHC Split

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CYTOTOXIC EFFECT OF ASCORBYL PALMITATE-LOADED SOLID LIPID NANOPARTICLES ON PATIENT-DERIVED SARCOMA STEM CELLS

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Renewed interest in the application of ascorbic acid for anti-tumor therapy led to the discovery of its effect in cancer stem cells (CSC), a small group of cells in tumor bulk with specific properties that enable them to resist conventional therapy and metastasize. The application of ascorbate in high concentrations has a prooxidative effect on cancer cells, causing extensive oxidative stress that can induce cell death. As CSC have specific redox properties, we wanted to design a stable ascorbate formulation and test its effect on patient-derived CSC. We have previously synthesized and characterized solid lipid nanoparticles containing ascorbyl palmitate (SLN-AP), a more stable lipid derivative of ascorbate. SLN- coumarin-6 were applied for visualization of the cellular uptake of the SLN. SLN-AP were applied to sarcoma stem cells isolated from samples of six patients to test their cytotoxicity and effect on oxidative stress in CSC. Results: SLNs with incorporated coumarin-6 enter the cells gradually, however, CSC react with abrupt generation of vesicles of a wide range of sizes (up to 20 μm). SLN-AP have higher IC50 values in osteosarcoma CSC than in soft tissue sarcomas. Nanoparticles without incorporated AP show strong cytotoxic effect. The treatment with nanoparticles shows antioxidative effect in CSC. In conclusion, soft-tissue sarcoma stem cells were more sensitive to the treatment than osteosarcoma stem cells and cytotoxicity is not due to oxidative stress. SLN-AP formulation should be further optimized to reduce the cytotoxicity of SLNs and to reduce their efflux from the CSC population.

Keywords: cancer stem cells, sarcoma, ascorbic acid, ascorbyl palmitate, solid lipid nanoparticles

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OVERVIEW OF ANTIFUNGAL SUSCEPTIBILITY TESTING FOR PATHOGENIC MOLDS

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Antifungal susceptibility testing plays a significant role in the mosaic of diagnostic techniques used for the diagnosis of invasive fungal infections. The clinician must select appropriate antifungal therapy for patients with invasive fungal infections commonly caused by *Aspergillus spp, Mucor spp, Fusarium spp, and Scedosporium spp*, especially those with compromised immune system. The risk factors for acquiring invasive aspergillosis are neutropenia, prolonged use of corticosteroids and broad-spectrum antibiotics, hematologic illnesses and organ transplant. This overview aims to provide understanding of the methodology involved in antifungal susceptibility testing, with a focus on the most clinically significant pathogenic moulds. The method for antifungal susceptibility testing involves the broth microdilution technique which entails diluting antifungal agents in a liquid growth medium and determining the minimum inhibitory concentration (MIC) as the lowest concentration that inhibits visible fungal growth. Adherence to standardized guidelines established by authoritative bodies such as CLSI (Clinical and Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing) is essential which provide detailed instructions on factors such as media composition, drug concentrations, inoculum preparation, and incubation conditions, ensuring the reliability and reproducibility of results. The MIC values obtained through susceptibility testing are interpreted according to established breakpoints provided by CLSI and EUCAST guidelines. These MIC values guide interpretation, categorizing strains as susceptible or resistant. Adherence to standard ensures consistency and reliability of susceptibility testing results, facilitating comparison across laboratories. The testing aids in therapy selection and resistance monitoring, improving outcomes in fungal infection management, particularly for immunocompromised patients.

Keywords: antifungal susceptibility, pathogenic mould, methodology, minimum inhibitory concentration, immunocompromised patients, invasive *aspergillosis*

MOLECULAR DIAGNOSTICS: CURRENT TECHNOLOGY AND APPLICATIONS

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DISTRIBUTION OF DIATOMS FOUND IN THE ORGANS OF VICTIMS OF VITAL DROWNING IN ALGERIA, DESCRIPTIVE, PROSPECTIVE STUDY OVER TWO YEARS (2016-2017)

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No study in the field of forensic limnology has been carried out to date in our country, hence the launch of our work, the objective of which was to draw up a national repertoire of diatoms found in cases already dealt with in the department of forensic medicine of the National Institute of Criminalistics and Criminology of the National Gendarmerie (INCC/GN) during the years 2016 and 2017.Our work is a descriptive, prospective longitudinal study allowing the isolation and identification of diatoms from 75 cases sent to the forensic medicine department of the INCC/GN, encompassing all the cases of drowning in fresh and salt water on the national territory. The objective of this study is to individualize the maximum number of taxa of diatoms and list them according to their geographical areas of origin (wilaya, daïra, and municipality) thus allowing in the medium and long term the development of a national repertoire of diatoms. of all the aquatic expanses of Algeria by an informatic management tool. This repertoire will allow the rapid and accurate diagnosis of vital drowning by isolating and identifying the same diatoms in drowning water according to their geographical distribution (location of the initial place of drowning) and their seasonal varieties (post-mortem delay). A total of 200 species of diatoms were extracted from more than 12300 individualized and photographed diatoms in the water and organ samples sent to us during the two years 2016 and 2017. The presence of a national repertoire of diatoms listed in all the aquatic expanses of our country will facilitate forensic investigations in the field of vital drowning.

Keywords: national repertoire, diatoms, vital drowning, fresh water

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CHANGES IN THE CONCENTRATION OF IL 8 IN PATIENTS WITH TEMPOROMANDIBULAR JOINT DISORDERS TREATED WITH A STABILIZATION SPLINT ARE RELATED TO THE DURATION OF TREATMENT AND THE SEVERITY OF PAIN BEFORE TREATMENT

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Temporomandibular disorder (TMD) is a term for a range of painful conditions affecting the muscles of mastication, temporomandibular joints (TMJ), and/or surrounding tissues. A new individualized approach could be achieved using molecular biomarkers of painful temporomandibular conditions. The aim of this study was to investigate whether the administration of stabilization splint (SS) leads to changes in the concentrations of pro-inflammatory cytokines in serum and gingival crevicular fluid and whether there is a correlation between the concentrations of pro-inflammatory cytokines and the intensity of chronic pain. This prospective cohort study enrolled 32 patients diagnosed with painful TMD according to the diagnostic criteria for TMD (DC/TMD). Samples of whole blood and gingival crevicular fluid were collected at baseline before SS treatment (T0) and at follow-up one month (T1) and three months (T2) after the start of SS treatment. For the multicomplex quantitative analysis of pro-inflammatory cytokines (IL-1β, IL-6, IL-7, IL-8, IL-13, TNF-α), customized ProcartaPlex Multiplex assays (eBioscience, Affymetrix) were used. Data on the intensity of chronic pain were collected using the Graded Chronic Pain Scale questionnaire (GCPSv2). The concentration of IL-8 in serum was significantly higher at T2 compared to T0 and T1 (Friedman test, P=0.002), while the concentrations of other proinflammatory cytokines were not significantly different during the period. Before splint therapy, serum levels of IL-8 were significantly lower in subjects with high-intensity pain without disability compared to the other groups (Kruskal Wallis test, P = 0.02), while concentrations of other cytokines related to the severity of chronic pain before therapy did not differ significantly. The results of our study suggest that IL-8 levels could be used for monitoring TMD patients treated with a stabilization splint, however further investigation is needed.

Keywords: biomarkers, interleukin-8, occlusal splints, serum, temporomandibular joint disorders

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EXPLORING THE IMPACT OF TMPRSS2 GENE POLYMORPHISM ON COVID-19 SEVERITY, PATIENT OUTCOMES AND ITS CORRELATION WITH VITAL BIOMARKERS

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The global COVID-19 pandemic has posed unparalleled challenges, with varying degrees of illness severity and outcomes among those affected. Recent research has highlighted the impact of genetic factors on the progression of COVID-19. One gene of particular interest is TMPRSS2, which facilitates the entry of the SARS-CoV-2 virus into cells. Our study investigated how a specific variation (rs2070788) in the TMPRSS2 gene influences the development of severe symptoms and its relationship with various biochemical markers in COVID-19 patients. The research involved 750 COVID-19 patients enrolled at General Hospital in Tešanj. Genotyping was performed using the Applied Biosystems QuantStudio5 RT-PCR System. Analysis of all biochemical parameters followed standard IFCC protocols. Our results revealed a statistically significant difference in genotype distribution among COVID-19 patients with mild and moderate symptoms (p=0.020), while no significant differences were observed between mild and severe (p=0.620), and moderate and severe clinical presentations (p=0.053). Additionally, in patients with mild symptoms, carriers of the risk GG genotype of rs2070788 exhibited significantly higher levels of total bilirubin (p=0.042) compared to carriers of the AA genotype. Among patients with moderate symptoms, carriers of the GG genotype showed a significant association with elevated creatine kinase levels (p=0.022) compared to carriers of the AA genotype. Furthermore, among patients with severe symptoms, carriers of the GG genotype displayed significantly higher potassium levels (p=0.003) compared to carriers of the AA genotype. Our findings suggest that specific variations within the TMPRSS2 gene might impact susceptibility to severe manifestations of COVID-19, leading to variations in disease progression and prognosis among patients.

Keywords: COVID-19, SARS-CoV-2, TMPRSS2, SNP, disease severi

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OXIDATIVE STRESS AND INFLAMMATION IN FEMALE LEWIS RATS DEPENDING ON THE DIET AND RETINOIC ACID APPLICATION

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Macrophages are characterized by increased expression of inducible nitric oxide synthase and NO production. NO is an important indicator of inflammation, oxidative stress, and polarization of macrophages into the M1 phenotype. Anti-inflammatory cytokines, IL-4, IL-10 and IL-13 stimulate the activity of arginase I in macrophages enhancing the anti-inflammatory effect. The goal of the study was to investigate inflammatory parameters, arginase, and NO, as well as their differences depending on retinoic acid and high fat diet application. The analysis included 36 Lewis rats bred at Department of Animal Physiology Zagreb. Half of the animals were fed high fat diet (HFD, 45% of saturated fatty acids) and half standard laboratory diet (STD) for 30 days. The groups were divided into additional 3 groups (6 rats each): two experimental groups that received 13 cRA orally daily for 30 days (7,5 mg/kg and 15 mg/kg, respectively) and the control group was given distilled water. Animals were sacrificed after 60 days and serum for inflammatory cytokines, arginase, and NO activity. The increase in the serum concentration of IL-6, IL-1β, IFN- in individuals on high-fat food, both in the control group and in the groups to which 13 cRA was added in both concentrations was seen. In the same groups, there was an increase in IL-10, which belongs to the Th2 inflammatory response. There was a visible increase in serum, kidney, and liver NO activity in individuals on HFD with the addition of 13 cRA (HFD+15 (13 cRA)) compared to the control group. The analysis of serum and renal arginase concentrations revealed a decrease in the value of arginase in individuals on HFD. According to the present results, 13 cRA and HFD affect metabolic parameters, as well as inflammation and oxidative stress in the organism. Its administration has a different effect on metabolic parameters, depending on whether the STD or the HFD was applied.

Keywords: high fat diet, isotretinoin, lipids, oxidative stres, metabolic syndrome

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GENETIC TESTING IN PREIMPLANTATION DIAGNOSTICS: WHERE ARE WE TODAY?

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With the rapid development of in vitro fertilization (IVF) methods, preimplantation (PI) diagnostics has become a prominent branch of genetic testing. It allows for the detection of genetic abnormalities before the embryo is implanted and thus, the selection of healthy embryos. The methods available vary in accuracy, as well as safety. The relatively safer procedures include polar body biopsy, which uses meiotic byproducts for genetic analysis, and blastocentesis, which extracts the blastocyst fluid. However, polar body biopsy is limited in its detection of paternal or division-originated DNA abnormalities, while blastocentesis is often complicated by failed DNA amplification. On the other hand, more precise methods include blastomere biopsy and trophoectoderm biopsy. However, these methods pose a risk of damaging the embryo by extracting the cells necessary for physiological growth. Once the sample is isolated, genotyping is performed by next-generation or third-generation sequencing. Recent advances have broadened the scope of PI testing to include mitochondrial disorder detection. Another expansion of this field includes testing for hereditary cancer predispositions, which might indicate preventative oncological care from birth. However, it is worth noting that the utility of these approaches is still being discussed. When discussing PI testing, the question of ethics must be discussed, as its unintended use could lie within the field of eugenics. For this reason, each case must be analyzed thoroughly and any selection between embryos with non-pathogenic genotypes must be discouraged. With the use of IVF becoming increasingly frequent, the wide accessibility of these methods is of great importance. In women of advanced age, with repeated implantation failure, repeated miscarriage after implantation, or diagnosed genetic disorders, PI testing might provide an explanation and offer a more selective process to avoid future negative outcomes.

Keywords: preimplantation diagnostics, blastocentesis, blastomere biopsy, polar body biopsy, trophoectoderm biopsy, in vitro fertilization, embryo implantation

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WHOLE GENOME SEQUENCING: A NEW DIRECTION FOR PRENATAL DIAGNOSTICS?

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Prenatal genetic testing is a diagnostic procedure performed to determine genetic abnormalities in the fetal DNA. While early methods implied invasive procedures for DNA sampling, a revolution in maternal- fetal diagnostics was brought on by the development of non-invasive testing methods (NIPT), which isolate cell-free fetal DNA from the mother's peripheral blood. According to recent studies, NIPT rivals invasive methods in precision where aneuploidy is concerned. Although today NIPT is very frequently used, it remains a screening method and cannot provide definitive answers regarding the fetal genome. In this regard, invasive testing still has great clinical utility and is recommended before any clinical decision. With the development of DNA sequencing technologies, the question of whole genome sequencing integration into invasive prenatal testing has been raised. In comparison with the currently used diagnostics, which include karyotyping, whole exome sequencing, and microarrays, WGS could provide a more comprehensive analysis of both nuclear and mitochondrial DNA. This could, in turn, greatly broaden the spectrum of genetic abnormalities we can discover and increase the number of diseases we can anticipate. Furthermore, WGS results from prenatal testing would have utility far beyond the detection of rare genetic diseases. The discovery of variants related to increased cardiovascular risk, oncogenic risk, or irregularities in drug metabolism might be the cornerstone of a lifelong personalized and preventative medical plan. As the average age of first birth is continuously on the rise, the incidence of genetic abnormalities is steadily increasing as well. This fact alone highlights the great importance of modern prenatal testing and why it should be made increasingly accessible. On the other hand, if WGS were to become standard practice in prenatal diagnostics, more physicians would need to be educated to provide quality genetic counseling for future parents.

Keywords: whole genome sequencing, preventive medicine, cell-free fetal DNA, prenatal diagnostics

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PROACTIVE GENETIC SCREENING USING WHOLE GENOME SEQUENCING ENABLES PREVENTION OF SUDDEN CARDIAC DEATH IN FAMILY MEMBERS WITH PATHOGENIC VARIANTS IN THE PKP2 GENE

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Arrhythmogenic right ventricular dysplasia (ARVD) is a rare genetic disorder associated with sudden cardiac death in young people. It is characterized by both structural and functional abnormalities caused by fibrofatty replacement of the damaged right ventricular myocardium. This condition can contribute to ventricular tachycardia that can be intensified with exercise leading to sudden cardiac death. Plakophilin 2 gene (PKP2) encodes for desmosomal proteins. Mutations in PKP2 are known to cause ARVD. We present to you the case of a 12-year-old female who came to the pediatric cardiology department after experiencing tightness in the middle of the chest without radiation, which worsened with respiration, following physical activity. Past medical history revealed the sudden cardiac death of a 15-year-old brother on a sports field. Proband's ergometry showed a right bundle branch block. A whole-genome sequencing (WGS) with a focus on coding and non-coding regions of 294 genes associated with sudden cardiac death was indicated due to the family's medical history. The report showed a heterozygous pathogenic variant in the coding region of the PKP2 gene (c.368G>A (p.Trp123Ter)). Trio-WGS showed that the patient's mother is a heterozygote for the same variant while the father has not tested positive for any mutations related to sudden cardiac death. The diagnosis of ARVD has been confirmed in proband through clinical examination and she was put on beta blockers as well as advised to avoid participating in extensive physical activity. The patient's mother, who is also heterozygous for this pathogenic gene variant, underwent a thorough clinical examination, and no changes indicative of ARVD were detected, suggesting variability in gene expression and incomplete penetrance of ARVD. This case shows that genetics and personalized medicine hold immense potential in the primary prevention, diagnosis, and treatment of ARVD and sudden cardiac death.

Keywords: arrhythmogenic right ventricular dysplasia, arrhythmogenic right ventricular cardiomyopathy, PKP2, sudden cardiac death, genetic testing

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WHOLE-GENOME SEQUENCING CONFIRMED THE DIAGNOSIS OF FAMILIAL HYPERTROPHIC CARDIOMYOPATHY AND DETECTED THE PREDISPOSITION IN SEVERAL FAMILY MEMBERS

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Familial hypertrophic cardiomyopathy (FHC), an autosomal dominant condition marked by left ventricular hypertrophy and a diverse array of clinical presentations, stands as the pioneering cardiac disorder with decoded genetic underpinnings. While relying on conventional diagnostic tools such as physical examinations and electro-echocardiography remains crucial, there's an emerging emphasis on understanding how genotype influences the clinical manifestations of FHC. The clinical spectrum of FHC suggests different pathomechanisms related to variant types and their location in the gene. The FLNC gene, encoding the Filamin-C protein, not only upholds the structural integrity of cardiac muscle tissue but also governs the signaling of sarcomeres. Pathogenic variants within FLNC are linked to the development of autosomal dominant familial hypertrophic and familial restrictive cardiomyopathy (OMIM: 617047). We present the case of a 55-year-old proband with hypertrophy of his heart's left ventricle. A whole-genome sequencing (WGS) with a focus on coding and non-coding regions of genes associated with cardiomyopathies was indicated. The report showed a heterozygous pathogenic variant in the coding region of the FLNC gene (c.1444C>T (p.Arg482Ter)). After proactive genetic testing of the entire family, it was found that the same pathogenic variant of the FLNC gene (c.1444C>T (p.Arg482Ter) was transmitted to the proband's son and daughter. While traditional diagnostic methods remain indispensable, the evolving understanding of genotype-phenotype correlations heralds a new era of personalized medicine in managing FHC. We highlight the importance of ongoing monitoring by cardiologists for both the proband and all family members carrying the pathogenic variant, ensuring comprehensive care and early intervention where necessary. This case shows the importance of proactive genetic testing, ultimately paving the way for more effective management strategies in familial cardiomyopathies.

Keywords: familial hypertrophic cardiomyopathy, familial restrictive cardiomyopathy, Filamin-C, ventricular hypertrophy, whole-genome sequencing

PROTEIN GLYCOSYLATION IN DIAGNOSTICS AND THERAPY

Presentation number: TM 30 Abstract number: ABS-58-ISABS-2024

EFFECT OF FMT ON BLOOD SERUM N-GLYCOME IN PATIENTS WITH FULMINANT CLOSTRIDIUM DIFFICILE INFECTION

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Clostridium difficile infection (CDI) mainly occurs in hospital environment. Patients with CDI in general have a good response to antibiotic therapy, but a subset of patients develops antibiotic-refractory severe or fulminant CDI (SFCDI), for which a different therapeutic approach is necessary. An effective treatment for SFCDI is faecal microbiota transplantation (FMT) from healthy donors. From the studies, it is apparent that gut homeostasis is reconstituted after FMT, but the effect of FMT on the metabolic state of a person is yet unknown. Therefore, in this study, we aimed to elucidate the effect of FMT in SFCDI patients on blood serum N-glycome as well as on blood serum isolated immunoglobulin G (IgG) N-glycome. The study enrolled four patients longitudinally, followed at five time points. In three patients, the FMT procedure was successful, while one patient was non-responsive. Temporal changes in blood serum and IgG N glycome were observed after a successful FMT procedure. Specifically, we detected a higher relative abundance of monosialylated and digalactosylated N-glycans in blood serum following successful FMT. Furthermore, the non-responsive patient has higher abundances of circulating IgG subclass 4 with agalactosylated, bisected, and core-fucosylated N-glycans. These findings suggest that changes in the gut microbiome have an impact on the metabolic state of a person. However, no broad generalization can be drawn due to the small sample size. Therefore, a replication study with a larger number of patients is required.

Keywords: fecal microbiota transplantation, Clostridium difficile, N-glycome, blood serum, IgG

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IGG N-GLYCOSYLATION IN CARDIOMETABOLIC DISEASES

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Cardiometabolic diseases (CMDs) are a significant public health problem worldwide, and their prevalence is increasing due to changes in lifestyle and dietary habits. It refers to a group of medical diseases that include cardiovascular diseases such as coronary artery disease, stroke, peripheral arterial disease, aortic disease and different metabolic diseases including diabetes. These diseases include obesity, high blood pressure, high blood sugar levels, and abnormal cholesterol and triglyceride levels. Glycosylation is one of the most common and complex post-translational modifications of proteins which plays an important role in many biological processes, and therefore, it is not unexpected that glycosylation changes have been noticed in CMDs. Recent studies have shown that IgG glycosylation may play a role in the development and progression of CMDs. In this study, we analyzed 461 total serum IgG glycosylation from patients with CMDs and healthy controls. IgG N-glycans were analyzed using ultra-high-performance liquid chromatography (UHPLC) after a rapid high-throughput in-solution deglycosylation and labeling of released N-glycans with RapiFluor-MS dye. IgG N-glycome statistically significant change in the levels of monogalactosylated glycans between patients with CMDs and healthy controls. This finding provides important insights into the potential link between glycosylation and CMDs, although the exact mechanism underlying this relationship is not fully understood. However, the emerging evidence suggests that glycosylation may serve as a valuable biomarker for assessing disease risk, and also be a promising target for therapeutic interventions.

Keywords: cardiometabolic diseases, CMD, IgG, glycosylation, RapiFluor

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EFFECTS OF TESTOSTERONE AND METFORMIN ON IGG GLYCOME COMPOSITION IN MEN WITH OBESITY

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Being a multifactorial chronic disease, obesity has evolved into a major global public health issue. It is associated with a variety of metabolic complications, including a significant decrease in testosterone concentrations among men. Low testosterone levels can lead to an increased risk of various health issues, such as a higher risk of cardiovascular disease, type 2 diabetes, erectile dysfunction, and decreased quality of life. Several approaches have been employed to address low testosterone levels in men with obesity, including weight loss, and testosterone replacement therapy. Metformin is a medication commonly used to treat type 2 diabetes. Recent studies suggest that it may be useful for treating low testosterone levels in men with obesity. This combined approach targeting both insulin resistance and reduced testosterone levels could be one of effective treatments for these conditions. Glycosylation is one of the most common and complex co- and post-translational protein modifications which mediates a wide variety of cellular functions and changes significantly when the homeostasis of the organism is disturbed. Therefore, it is not surprising that glycosylation changes have been noticed in obesity. Since IgG glycosylation is known to be involved in the regulation of various processes, we evaluated the effect of testosterone and metformin on IgG N-glycome in men with obesity. We analyzed IgG glycome composition in 267 men with obesity who were on individual and combined metformin and testosterone therapy but had no diabetes mellitus, and accordingly they were divided into four groups. The samples were collected at three timepoints and analyzed using capillary gel electrophoresis with laser-induced fluorescence (xCGE- LIF) analysis to evaluate the released glycans labeled with 8-aminopyrene-1,3,6-trisulfonic acid trisodium salt (APTS). After performing a stratified analysis, we see that all effects are driven by testosterone, while metformin has no effect.

Keywords: obesity, metformin, testosterone, IgG, glycosylation

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AUTOLOGOUS MICROFRAGMENTED ADIPOSE TISSUE INJECTION FOR TREATMENT OF KNEE OSTEOARTHRITIS: TOWARDS A PRECISION THERAPY APPROACH USING ADIPOSE TISSUE N- GLYCOMICS DATA

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Given the global burden of a rapidly ageing population, better management of knee osteoarthritis (kOA) has become vital. Stem cell (SC) therapy has been investigated as a promising alternative to mainstay kOA therapies. Since adipose tissue is an accessible source of adult SCs, autologous microfragmented adipose tissue (MFAT) has become a treatment of interest in kOA, though the factors affecting its success remain largely unknown. As part of a larger randomized control trial involving autologous MFAT injection for the treatment of kOA, we investigated whether MFAT N-glycan properties may be predictive of treatment efficacy. MFAT samples were acquired from 33 individuals with kOA using lipoaspiration and the effect of a single intra-articular MFAT injection was examined 6 months' post-injection. The MFAT N- glycome was analysed using liquid chromatography and mass spectrometry and was characterised based on N-glycan types and derived traits. The MFAT N-glycomics data were integrated with clinical parameters, such as self-reported questionnaires, imaging, and cytometry data. Statistical analyses revealed that the MFAT N-glycome is relatively uniform regardless of patient age or sex. However, 16 nominally significant correlations were uncovered showing that a greater abundance of oligomannose and hybrid N-glycans in MFAT correlated with better clinical outcomes and cytometry measures, whereas the inverse was observed for complex and fucosylated N-glycans. The former N-glycan traits are characteristic of adipose SCs whilst the latter are associated with mature adipocytes, indicating that the cellular composition of patient MFAT may affect treatment success. These preliminary results illustrate the predictive potential of the MFAT N- glycome in determining treatment efficacy and suggest that MFAT N-glycoprofiling could be used for patient stratification to allow delivery of precision therapy or for the enrichment of SC populations associated with better clinical outcomes.

Keywords: N-glycome, stem cells (SCs), autologous microfragmented adipose tissue (MFAT), knee

Abstracts of Poster Presentations

Presentation number: TM 34 Abstract number: ABS-175-ISABS-2024

INTRODUCTION OF MODERATE EXERCISE INDUCES A SIGNIFICANT CHANGE IN IMMUNOGLOBULIN G GLYCOSYLATION AND GLYCANAGE IN PREVIOUSLY INACTIVE, OBESE POPULATION

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Previous studies have shown there is a strong association between Immunoglobulin G N-glycans and chronological age. Regular moderate exercise has a beneficial effect on overall health. 382 participants (300 females, 82 males, average chronological age: 50.97, average GA: 49.93, average body mass index (BMI): 30.27) underwent three types of programs: cardio, circular training (CT) and Nordic walking (NW). Participants underwent training protocols 2x per week, 60 minutes each, for 14 weeks. At the beginning and at the end of the intervention, their motoric skills and body composition were evaluated, while a drop of peripheral blood was taken to measure changes in IgG glycosylation. The aim of this study was to determine the effects of moderate exercise on Immunoglobulin G (IgG) glycosylation and the effect on GlycanAge biomarker (GA). The IgG was isolated from the dry blood spots, deglycosylated, labeled and analyzed by UPLC, glycan peaks were integrated and processed to get N-glycans and GA results. CT: 221 participants (170 females, 51 males, average age 49.7), cardio: 112 participants (89 females, 23 males, average age 51.1) and NW: 49 participants (41 females, 8 males, average age 56). Each group presented a slight increase in GA (+1.88 for CT, +2.13 for cardio and +1.86 for NW). Our results are in accordance with what was previously reported in two significantly younger cohorts. Though BMI slightly decreased in all three groups (-0.8 for HIIT, -0.8 for cardio and -0.5 for NW), their IgG N-glycan profile was pro- inflammatory, due to the processes of metabolic remodeling taking place in the first several months of a new exercise regimen. We will additionally investigate IgG glycosylation changes and GA trends after longer exercise periods of 6 and 9 months, with expectations to observe a lower pro-inflammatory N-glycan profile.

Keywords: physical activity, glycosylation, inactive and obese population, aging biomarkers, inflammation

Presentation number: TM 35 Abstract number: ABS-157-ISABS-2024

SLEEP QUALITY AND N-GLYCOMIC PROFILE – CROSS-SECTIONAL STUDY AMONG MEDICAL STUDENTS IN OSIJEK, CROATIA

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The aim of the study was to assess sleep quality among medical students and to evaluate whether poorer sleep quality is associated with changes in N-glycosylation of immunoglobulin G (IgG). This cross-sectional study was conducted in December 2023. Participants were first- and second-year medical students of the University in Osijek, Croatia. Sleep quality was assessed with The Pittsburgh Sleep Quality Index (PSQI). IgG was isolated from plasma samples and its N-glycan composition was assessed by capillary gel electrophoresis. A total of 27 IgG N-glycan peaks and an additional 9 glycans with shared structural features were obtained. The study was approved by the Ethics Committee of the Faculty of Medicine Osijek. 82 students participated in the study, comprising 22 males and 60 females. 13 % of participants experienced poor sleep quality with a PSQI score ≥10. In the comparison of N-glycan peaks between participants with a PSQI score ≥ 10 and those with a score < 10, the analysis revealed that poor sleepers had significantly more altered levels of P1 (digalactosylated, disialylated biantennary; A2G2S2) (P = 0.032), P4 (core-fucosylated, digalactosylated, disialylated biantennary with bisecting GlcNAc; FA2BGS2) (P = 0.014), P9 (digalactosylated, monosialylated biantennary; A2G2[3]S1) (P = 0.019), and P13 (core-fucosylated, digalactosylated, monosialylated biantennary with bisecting GlcNAc; FA2BG2S1) (P = 0.006), MannWhitney test, resp. A regression analysis revealed that higher PSQI scores significantly contribute to an increase in P1 (P=0.004) and a decrease in P9 (P=0.013), and P13 (P=0.048). A notable prevalence of poor sleep quality has been established among medical students. Poorer sleep quality was associated with more alterations in total plasma IgG N-glycans.

Keywords: N-glycome, sleep, IgG, PSQI, student

REGENERATIVE MEDICINE

Presentation number: TM 36 Abstract number: ABS-13-ISABS-2024

GENETIC TESTING IN PREMATURE OVARIAN INSUFFICIENCY

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Premature Ovarian Insufficiency (POI), also known as premature ovarian failure (POF), is a complex reproductive disorder characterized by the depletion or dysfunction of ovarian follicles before the age of 40, accompanied by cessation of menstruation and infertility issues. It affects approximately 1% of women under 40 years old, increasing the risk of cardiovascular disorders, osteoporosis, and cognitive decline. Together with environmental factors and autoimmune mechanisms that contribute in POI, growing evidence suggests a significant genetic component in the heterogeneous etiology of this condition. Genetic causes account for approximately 20–25% of patients, and chromosomal abnormalities could explain 10-15% of POI cases. Recent studies using next generation sequencing (NGS) have identified new possible genetic contributors to POI susceptibility, including mutations in genes involved in DNA repair, meiosis, ovarian development, folliculogenesis, and hormonal regulation. Today, over 50 genes are known to be causally related to POI, but in the most cases, the genetic background has not been clarified. Based on multiple studies, single gene mutations that unequivocally show deleterious effect in at least one population include BMP15, PGRMC1 and FMR1. New evidence suggests a major association to exist between reproductive longevity and the DNA damage pathway response genes. Mesenchymal stem cells (MSCs), characterized by the ability of self-renewal, play a crucial role in the regeneration of injured tissues. In a mouse model, transplantation of MSCs has been shown to restore ovarian reserve, a new therapeutic option that brings hope to patients with POI. Although much remains to be discovered, understanding the genetic basis of POI provides important insights into the molecular mechanisms responsible for ovarian dysfunction, as well as contributes to the development of diagnostic strategies and personalized targeted therapies.

Keywords: POI, genetics, mesenchymal stem cells, infertility, regenerative medicine

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ACS, AN EXTRACELLULAR VESICLE (EV)-SATURATED WHOLE BLOOD SECRETOME COMBINES REGENERATION WITH PAIN RELIEF AND RESOLUTION OF INFLAMMATION

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Customary pain and inflammation medications obstruct physiologic healing responses, increasing risk of chronification. Signaling through neutrophils and S100A8/A9 alarmins inhibits chronification. Autologous Conditioned Serum (ACS) is used successfully as injection-therapy for osteoarthritis (OA) and back pain since >20 years. It has a de-chronifying clinical effect both in animals and humans. A deeper understanding of the mechanisms involved in ACS's biochemical modes of action has resulted from re- analysis. ACS derives from sterile blood-coagulation, controlled incubation at physiological temperature and subsequent centrifugation yielding a therapeutic, injectable serum. This harmonic process enriches multiple groups of biochemical mediators. Cytokines and growth factors were the first ACS-mediators described in the early 2000s. ACS then was aimed to accumulate IL-1Ra with little IL-1b. More content was published in 2007 and 2023. It became clear that some inflammatory mediators are also released [6], they might be involved in the clinically observed de-chronification of pain and inflammation. Resolving lipid mediators (SPM) are in ACS (ResolvinD1 and ProtectinD1). SPMs are publicized strongly since a new chapter in lipid mediator biochemistry has been opened. Mitochondrial-derived peptides (MDP,10) are also in ACS. They are encoded by small ORFs in mt-rRNA genes and are thought to orchestrate adaptative responses to metabolic stress. Further components in ACS include but are not limited to CD90, Gelsolin, Globulins, alfa 2 macroglobulin, bilirubin, C3. EVs in ACS were first published in 2012. They induce clinical improvement in e.g. Rheumatoid Arthritis. EV publications grew exponentially but clinical use lagged, except in clinics applying ACS for musculoskeletal and neuroskeletal diseases. Experimental work now shows in models of PTX induced CIPN and trauma pain that ACS-EVs are a crucial factor for symptom resolution and healing.

Keywords: extracellular vesicles, autologous conditioned serum, musculoskeletal diseases, neuroskeletal diseases, orthokine

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NOVEL DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS FOR ALOPECIA

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Alopecia is a disorder caused by irregularities in the physiological cycle of hair production and most commonly affects the scalp. Scarring alopecia is permanent due to hair follicle destruction, whereas in non-scaring alopecia, this destruction is absent. Scarring alopecia accounts for about 7% of adults and is commonly due to an inflammatory or autoimmune disorder. Non-scarring alopecia affects between 50% and 75% of adults over 50 years of age. Androgenetic alopecia is the most common type of non-scarring alopecia and is characterized by distinct gradual patterned hair loss. Androgenetic alopecia is mediated by a genetic predisposition and excessive follicular sensitivity to androgen. Prevalence reaches >50% in older men and 15% in postmenopausal women. While hair loss is mainly associated with the AR gene, more than 60 genes may play a role in male pattern baldness. Novel genetic analyses confirmed associations between variants in the EDA2R, WNT10A, HEPH, CEPT1, and EIF3F genes and hair loss. Research has shown that over 80% of people experiencing noticeable balding have a positive family history. Genes coding for the production of aromatase, which catalyzes the conversion of androgens to estrogens, may play a role in female baldness patterns and explain why many women lose their hair after menopause. Pharmacologic treatment of androgenetic alopecia involves 5-alpha-reductase inhibitors, such as topical minoxidil and oral therapy with finasteride. Additionally, DNA tests that provide individual reports for personalized treatment options are available. Platelet-rich plasma (PRP) also can be beneficial in the treatment of androgenetic alopecia. The genetic component of balding could be a promising predictive tool, useful for the treatment of hair loss in combination with novel PRP or mesenchymal stem cell (MSC) therapies. However, further research in this direction is warranted before the clinical implementation of such diagnostic and treatment protocols.

Keywords: alopecia, androgenetic alopecia, genetic predisposition, platelet-rich plasma, mesenchymal stem cells

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EXPLORING THE EFFICACY OF PLATELET-RICH PLASMA (PRP) AND MESENCHYMAL STEM CELLS (MSCS) IN THE MANAGEMENT OF LICHEN SCLEROSUS: A PROMISING THERAPEUTIC APPROACH

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Lichen sclerosus (LS) is a chronic non-neoplastic inflammatory dermatosis that mainly affects the vulvar area and often leads to significant morbidity if not treated. It showed a genetic predisposition, with additional influences from trauma, hormonal fluctuations, and medications in its pathogenesis. LS, as an immune-mediated disease, is miR-155-5p and type 1 T helper-dependent. Preliminary data suggests that miR-155-5p is significantly upregulated in LS tissue. More precisely, miR-155-5p stimulates cell proliferation, accelerates cell cycle progression, and inhibits forkhead box O (FOXO) signaling pathway in fibroblasts. Clinical manifestations include ivory-white patches, atrophy, and intense pruritus. Treatment consists of topical treatment with glucocorticoids, calcineurin inhibitors, methotrexate, retinoids, and surgery if needed. There is a rising number of studies in regenerative medicine indicating the therapeutic potential of platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) in LS. Research evaluating the efficacy of PRP in treating vulvar LS indicates symptom reduction in patients unresponsive to initial therapeutic interventions, attributed to high concentration of platelets rich in growth factors and cytokines, which stimulate extracellular matrix production, cellular migration, proliferation, and differentiation. MSCs exhibit multipotency enabling differentiation into diverse cell lineages, by the expression of surface markers such as CD105, CD73, and CD90, while lacking lineage-specific markers like CD45, CD34, CD14, CD19, and HLAII. Additionally, MSCs exhibit anti-inflammatory and immunomodulatory properties through the secretion of immunomodulatory factors. Multiple studies show significant symptom improvement following treatment, with notable enhancements in quality of life and sexual function, offering novel insights for symptom mitigation and tissue regeneration, warranting further clinical exploration.

Keywords: lichen sclerosus, PRP, mesenchymal stem cells, gynecology, regenerative medicine

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REVOLUTIONIZING ORTHOBIOLOGICS: APPLICATION OF LEUKOCYTE-RICH AND LEUKOCYTE-POOR PLATELET-RICH PLASMA FOR KNEE OSTEOARTHRITIS – A PERSONALIZED APPROACH

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Knee osteoarthritis is a common musculoskeletal disease with over 620 million patients worldwide. The insidious disease progression is such that the treatment for the end stage of the disease is a total knee arthroplasty. However, the dawn of orthobiologics has enabled the prolongation of knee osteoarthritis progression so that patients can live with their native knees much longer than previously projected. The aim was to compare the effect of leukocyte-poor (LP) and leukocyte-rich (LR) platelet-rich plasma (PRP). Here we present the preliminary results for PRP therapy of 33 patients. Patients were selected based on clinical presentation of knee pain lasting for longer than 6 months. Patients were between 18-75 years old. Criteria for admitting patients to the study were no prior history of traumatic osteoarthritis, mechanical axis deviation less than 5˚, intact ligaments of the knee, and menisci that had no clinically impactful tears. Patients were assessed using X-ray and magnetic resonance imaging, as well as VAS, KOOS, and WOMAC scores. Blood samples were processed by using Greyledge Technologies' proprietary protocol to produce LP-PRP or leukocyte rich LR-PRP. The concentration of leukocytes and platelets present in the whole blood and PRP was measured on a differential hematology analyzer. To provide high-quality products for our patients, we aimed for a minimal thrombocyte PRP concentration of 7 x10^9. Patients were randomly assigned to the LP and LR groups. Finally, the PRP was injected intraarticularly into the knee via ultrasound guidance. The average platelet concentration for all preparations was 14.79 x10^9 while the average leukocyte concentration was 50.83 x10^9 for the LR-PRP group and 12.94 x10^9 for the LP-PRP group. Patients were assessed at 0,1 and 3 months by the VAS, KOOS, and WOMAC scores. Preliminary results show improvement across all scores within a 3-month period with LR-PRP showing greater improvement than LP-PRP.

Keywords: LR-PRP, LP-PRP, platelet rich plasma, knee osteoarthritis, regenerative medicine

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STONE INDUCED URETRAL RUPTURE: TREATMENT WITH MICROFRAGMENTED ADIPOSE TISSUE CONTAINING MESENCHYMAL STEM CELLS

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A two-year-old intact Chow-chow male dog with symptoms of urinary obstructions was administrated at the Clinic for Reproduction and Obstetrics at the Faculty of Veterinary Medicine University of Zagreb. Ten days prior, a patient underwent cystotomy in a private practice, but even after the surgery, the patient couldn't urinate normally. Upon admission, the patient was diagnosed with multiple urolith stones in the urine bladder and penile part of the urethra and showed no other symptoms except for urinary obstruction. After unsuccessful catheterization, the patient underwent the second surgical procedure of cystotomy and urinary stones removal. Due to the impossibility of returning urinary stones from the urethra to the bladder by hydropropulsion, a penile urethrotomy was performed and multiple uroliths were removed. Hematology and biochemistry references were in the physiological range. Positive-contrast retrograde cystography (RC) was performed to assess bladder integrity and urethra patency. RC revealed a leakage in the pre- scrotal part of the urethra over the os penis. The patient A two-year-old intact Cunderwent diagnostic laparotomy in endotracheal inhalation anesthesia. Intraoperatively, a methylene blue solution was applied to find the exact place of the urethral fistula. During the surgery, in collaboration with St. Catherine Specialty Hospital, a sample of the dog's abdominal fat tissue was collected and processed using the Lipogems® system to obtain 5 mL of microfragmented adipose tissue (MFAT). Additionally, 15 mL of the dog's venous blood was used to produce 2 mL of platelet-rich plasma (PRP) via the Arthrex ACP® Double- Syringe System. These components were then combined, leveraging the regenerative capabilities of both MFAT and PRP. A final product was applied in place of a urethral fistula. Postoperatively, RC showed that the urethral defect is no longer present. A year after the procedure, the patient no longer shows urethral obstruction signs.

Keywords: urethral fistula, urolithiasis, microfragmented adipose tissue, mesenchymal stem cells, dogs

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EFFECTS OF TREATING KNEE OSTEOARTHRITIS WITH AUTOLOGOUS MICROFRAGMENTED ADIPOSE TISSUE CONTAINING MESENCHYMAL STEM CELLS COMPARED TO HYALURONIC ACID – RADIOLOGICAL RESULTS FROM IRI2 PROJECT

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In osteoarthritis (OA) research, finding objective indicators to measure treatment success is challenging. Advanced magnetic resonance imaging techniques like Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) offer a method to record objective indicators by assessing the concentration of glycosaminoglycans (GAGs) in cartilage, thereby reflecting chondrocyte activity. As part of the European research project IRI2 (KK.01.2.1.02.0173), this study aimed to compare the effects of microfragmented adipose tissue (MFAT) and hyaluronic acid (HA) on the concentration of GAGs in knee cartilage of patients with knee OA using dGEMRIC before treatment and 6 months later. Continuing ongoing work in the field of OA at St. Catherine Specialty Hospital, after great previous results with increased dGEMRIC indices following MFAT application in patients with severe OA, this study included 53 patients (35 treated with MFAT, 18 with HA) with mild to moderate knee OA and interesting results were found. The results showed that patients with initially lower dGEMRIC values experienced an increase in GAG concentration post-treatment, regardless of the treatment type ($p<0.05$). This enhancement in GAG synthesis may be stimulated by a negative feedback mechanism, where a decrease in GAG levels triggers chondrocytes to increase production, aiming to restore cartilage integrity and biomechanical function. Conversely, patients with initially higher dGEMRIC values exhibited a decrease, possibly reflecting a normalization of cartilage metabolism, where a reduction in inflammation or mechanical stress lessens the chondrocytes' compensatory synthesis of GAGs.

These findings underscore the complex interaction between therapeutic agents and biological processes within joint cartilage, highlighting the need for further detailed studies to robustly interpret these phenomena and optimize treatment strategies for managing knee OA.

Keywords: knee osteoarthritis, microfragmented adipose tissue, hyaluronic acid, mesenchymal stem cells, dGEMRIC

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CELLULAR COMPOSITION AND VIABILITY OF MICROFRAGMENTED ADIPOSE TISSUE IN OSTEOARTHRITIS TREATMENT – INSIGHTS FROM THE IRI2 PROJECT

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While considerable research has focused on stem cells derived from microfragmented adipose tissue (MFAT), the detailed cellular structure of MFAT is still not fully understood, necessitating further exploration to enhance our understanding of its therapeutic impact on osteoarthritis (OA). In our previous research, we showed that MFAT contains within the CD45- fraction: CD31+CD34+CD73±CD90±CD105±CD146± endothelial progenitors (EP), CD31+CD34−CD73±CD90±CD105−CD146± mature endothelial cells, CD31−CD34−CD73±CD90+CD105−CD146+ pericytes, CD31−CD34+CD73±CD90+CD105−CD146+ transitional pericytes, and CD31−CD34+CD73highCD90+CD105−CD146− supra-adventitial-adipose stromal cells (SA-ASC). This study aimed to examine the viability and cellular composition of fresh MFAT in a larger sample of patients. As part of the European research project IRI2 (KK.01.2.1.02.0173), 53 patients underwent lipoaspiration for MFAT or HA treatment, with sufficient MFAT collected from 50 patients for flow cytometry analysis. The range of cell numbers per milliliter of MFAT varied significantly, from as low as 1.75 x 10^4 to as high as 2.0 x 10^6, with an average of 5.0 x 10^5 cells per milliliter. The viability of cells within the MFAT analyzed through flow cytometry, averaged 62.30%. The analysis highlights considerable variability in cell counts among samples, which could reflect differences in the quality or characteristics of the adipose tissue from patient to patient. A high maximum cell count suggests that some samples have a higher density of vital cells, potentially enhancing the efficacy of regenerative treatments that rely on a rich cellular environment. The relatively high average viability indicates that most cells remain viable post- isolation, which is favorable for their potential therapeutic use. High viability is crucial for the success of regenerative treatments, such as OA treatment, where living cells are needed to promote the repair and renewal of damaged tissue.

Keywords: knee osteoarthritis, microfragmented adipose tissue, mesenchymal stem cells, flow cytometry, viability

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UNLOCKING THE POTENTIAL OF MENSTRUAL STEM CELLS IN REGENERATIVE MEDICINE

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Cells with mesenchymal stem cell properties have been identified within the menstrual blood and termed menstrual blood-derived stem cells (MenSCs). MenSCs appear in the cellular fraction of menstrual fluid, and it has been hypothesized that they originate from endometrial stem cell (eMSCs) located in the basalis and functionalis layer of endometrium. MenSCs express mesenchymal stem cell markers but they are loosely characterized. Current applications and clinical trials are mostly based on their immunomodulation properties and their paracrine effects promoting tissue repair or regeneration. The differentiation capability of unfractionated MenSCs into mesodermal lineages like osteoblasts, adipocytes, chondrocytes, is lower than bone marrow derived MSCs. However, purification of the specific c-KIT-expressing subpopulation strongly improves MenSCs differentiation potential. Cultured MenSCs transdifferentiate across lineage boundaries into ectodermal (neurons and glia), endodermal (hepatocyte) lineages and keratinocyte-like cells, generating epidermal lineage markers. Endometrial repair is unique when compared to repair of other adult tissues, because it is very rapid, scar-free and occurs around 400 times during woman's reproductive life. As the tissue breaks down, the surface is re-epithelialized and regenerated in full thickness, protecting the wound from infection. Given the unique nature of menstrual shedding followed by rapid regeneration, the molecular understanding of the cells and signals involved in the process, may provide important insights, and offer opportunities to mediate rapid and scar-free tissue repair. Menstrual blood is easy to obtain and stem cells from menstrual blood are promising, both for scientific stem cell research as well as for the new possible therapies in various conditions.

Keywords: stem cells, regenerative medicine, menstrual fluid, differentiation, endometrium

CELL THERAPY

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MESENCHYMAL STEM CELLS IN ATHEROSCLEROTIC RENAL ARTERY DISEASE – NEW MODALITIES IN THERAPEUTIC APPROACH

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Recent studies indicate increased renal blood flow (RBF) and cortical perfusion after mesenchymal stem cells (MSCs) infusion in atherosclerotic renovascular disease (ARVD) patients (1). They underscore the importance of exploring the new therapeutic modalities alongside endovascular stenting. In a recent review by Yang et al., a hypoxic environment was found to positively influence various functions of MSCs. Abumoawad et al. observed increased cortical and whole kidney blood flows in the post-stenotic kidney of ARVD subjects three months after intra-arterial infusion of autologous adipose-derived MSCs Improvements correlated with reduced inflammatory and angiogenic biomarkers in renal veins, along with dose-related changes in GFR and blood pressure. Conversely, the medically treated group showed stable or declining blood flows and GFR, with no observed changes in kidney volumes. MSC infusion increased cortical and medullary perfusion without affecting kidney volumes, while the medical treatment-only group experienced either no change or a decrease in RBF in the post-stenotic kidney. MSC therapy plays a crucial role in promoting cell proliferation, migration, and angiogenesis while inhibiting apoptosis and inflammation. Additionally, it preserves endothelial function and protects against fibrosis progression. Further research with a larger patient sample and extended follow-up, exceeding 6 months, should investigate MSC efficacy in restoring endothelial function in ARVD post-stenting.

Keywords: mesenchymal stem cells (MSCs), atherosclerotic renovascular disease (ARVD), renal outcomes, angiogenesis, endothelial function

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IT'S TIME FOR NEW INSIGHTS INTO RENOVASCULAR HYPERTENSION AT THE CELLULAR LEVEL – STUDY PERSPECTIVE

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Atherosclerotic renal artery stenosis (ARAS) leads to reduced tissue perfusion, tissue hypoxia and inflammatory kidney injury. Mesenchymal stem cell (MSC) therapy has shown promise in preclinical studies for repairing renal microcirculation, reducing inflammation, and restoring kidney function. Recent human data suggest that autologous MSC infusion can safely increase tissue oxygenation in ARAS patients. This open-label, single-center study will enroll adult patients with significant ARAS, diagnosed by renal artery Doppler ultrasound (average peak systolic velocity >300 cm/s) and MR/CT angiography showing >60% luminal occlusion, along with hypertension (systolic >155 mmHg and/or use of ≥2 BP drugs) and/or declining kidney function. The intervention group (n=5) will receive a single MSC infusion (2.5 × 105 cells/kg) along with standard medical treatment, while the control group (n=5) will receive only medical treatment, matched for age, kidney function, and stenosis severity. Cortical and medullary volumes, perfusion, and renal blood flow (RBF) will be measured using multidetector CT. Tissue oxygenation will be assessed by blood oxygen level–dependent MRI, and GFR by iothalamate clearance. Laboratory parameters including VGF, inflammatory cytokines, MCP-1, TGF, and NGAL will be measured at baseline, three, and six months after MSC infusion. We anticipate that this study will provide evidence regarding the safety of intra-arterial infusion of autologous MSCs in ARAS patients. MSC infusion without revascularization of the main renal artery is associated with increased renal tissue oxygenation and RBF.

Keywords: ARAS patients, renal hypoxia, inflammatory kidney injury, mesenchymal stem cells, endothelial function

TRANSLATION MEDICINE

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BIOMONITORING OF URINE LEVELS OF NICOTINE AND ITS METABOLITES LINKED TO SECONDHAND SMOKING IN YOUNGER POPULATIONS VISITING NIGHTCLUBS: A PILOT STUDY

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This study highlights the extent of secondhand smoke exposure in younger population visiting nightclubs in Croatia by comparing levels of nicotine, and its main metabolites cotinine and trans-3'-hydroxycotinine (3HC) in urine samples. The samples were collected at 2 time points (before and after attending a nightclub) from 22 participants stratified into two groups, according to sex and smoking status (NS-non- smokers and S-smokers). The samples were prepared for analysis by the liquid-liquid extraction method and were analyzed using gas chromatography–mass spectrometry. The presence of nicotine, cotinine, and trans-3'-hydroxycotinine was confirmed in all urine samples. The results showed a statistically significant difference ($p<0.05$) in the median concentrations of nicotine, cotinine, and trans-3'-hydroxycotinine between 2 time points with regard to smoking status and sex. Our findings indicate the magnitude of secondhand smoke exposure in places like nightclubs and highlights the need for further research and more importantly, the need to raise public awareness of secondhand smoke hazards.

Keywords: nicotine, cotinine, trans-3'-hydroxycotinine, biological urine sample; secondhand smoke exposure

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MODULATION OF SREBF1 AND MTTP LEVELS BY (-)-EPICATE-CHIN PRETREATMENT IN AN IN VITRO MODEL OF MASLD

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(-)-Epicatechin (EPI), a flavonoid found in cocoa and green tea, exhibits a variety of potential health benefits, including its antioxidant properties and ability to inhibit metabolic dysfunction-associated steatotic liver disease (MASLD) development. The aim of this study was to investigate the effect of EPI pretreatment on the development of MASLD in vitro using a HepG2 cell line. The cell metabolic viability, sterol regulatory element-binding transcription factor 1 (SREBF1), and microsomal triglyceride transfer protein (MTTP) levels were assessed to determine the potential implications of EPI in MASLD development. HepG2 cells were pretreated with the following concentrations of EPI: 500 and 300 µM, for 4 hours before the 24 hour- exposure to 1.5 mM oleic acid (OA) which was used to induce steatosis. The metabolic viability of the cells was assessed using MTS assay, and the levels of SREBF1 and MTTP were determined via ELISA. The MTS assay showed that the cells pretreated with EPI (EPI500/OA and EPI300/OA) exhibited significantly higher metabolic viability, whereas the OA only treated group showed reduced viability ($p<0.001$). Additionally, both analyses demonstrated significant changes in the protein levels compared to the OA only-group. The SREBF1 levels exhibited a concentration-dependent increase in EPI500/OA and EPI300/OA ($p<0.05$), while MTTP levels were decreased compared to the OA only-group ($p<0.01$). The results suggest that EPI pretreatment may alleviate the effects of OA-induced steatosis on HepG2 cell viability by modulating the SREBF1 and MTTP levels in vitro. This indicates the potential involvement of EPI in the cellular metabolic pathways associated with lipid metabolism and MASLD development. Therefore, the metabolic pathways associated with MASLD should be considered in future research when determining the potential therapeutic implications of EPI in steatosis.

Keywords: (-)-epicatechin, polyphenols, MASLD, steatosis, pretreatment

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SATB1 (SPECIAL A-T RICH BINDING PROTEIN 1) EXPRESSION IN HODGKIN LYMPHOMA

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Hodgkin lymphoma (HL) is a rare monoclonal lymphoid neoplasm of B cell origin, in which monoclonal Hodgkin cells and multinucleated Reed- Sternberg (HRS) cells are mixed with population of non-neoplastic inflammatory cells and fibrosis. To date, available treatments for HL can attain long-term disease control in the most patients. However, 5-10% of patients will have refractory disease after initial therapy and about 10-30% will relapse. Those patients represent a therapeutic challenge in hematology, thus having the ability to stratify between nonresponsive and responsive patients might help to tailor a more successful treatment regime. SATB1 is chromatin modifying protein involved in differentiation of naïve (mature) B cell, here we examined whether it could serve as prognostic marker in HL patients. A total of 85 valid archived formalin-fixed paraffin-embedded lymph node biopsies with a previously histologically confirmed diagnosis of Hodgkin's lymphoma were analyzed in this retrospective study. The tissue blocks were cut into 4 µm sections and stained with SATB1 antibody visualized by DAB chromogen. SATB1 expression was quantified as positive or negative staining by pathologist. SATB1 expression could stratify patients by overall survival (OS, p<0.0001) and progression free survival (PFS, p<0.0001). OS of SATB1 positive patients plateaued at 86% after 2 years and remained at that level until the end of follow up, i.e.16 years after the diagnosis. On the other hand, SATB1 negative patients did not exhibit a survival plateau and they reached 72% survival probability after 12 years of follow up. When it comes to PFS, SATB1 positive patients plateaued at 87% after 1.5 years, whereas SATB1 negative patients plateaued at 62% after 8 years since the diagnosis and remained as such until the end of follow up. SATB1 expression was not associated with lymphoma grade, histological type, extranodal or bulky disease B symptoms.

Keywords: SATB1, Hodgkin lymphoma, differentiation, prognosis, precision medicine

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HIGH VISTA, SNAI1 AND SNAI2 MRNA EXPRESSION IN RESECTED NON-SMALL CELL LUNG CANCER IS ASSOCIATED WITH SHORTER PATIENTS' OVERALL SURVIVAL

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Non-small cell lung cancer (NSCLC) is often diagnosed at an advanced stage and can be surgically removed in only 30% of patients. The resected tumor tissue is valuable for investigation of tumor metastatic potential, epithelial-mesenchymal transition (EMT) and tumor immune microenvironment (TIM), as relevant factors for follow-up of these patients. Oncoprotein IMP3 is associated with the metastatic potential of tumor cells, SNAI1 and SNAI2 genes are expressed in EMT, while VISTA gene is associated with tumor immune evasion. Our aim was to analyze this interaction between EMT and tumor immune evasion on human specimens. 55 patients who underwent lobectomy/lymphadenectomy for NSCLC at University Hospital of Split, Croatia from 2013 to 2017 were included. Their clinical data were collected from hospital records and paraffin blocks from the Department of Pathology. SNAI1, SNAI2 and VISTA mRNA were analyzed by q-RT PCR, and IMP3 by immunohistochemistry. The results were compared with clinical-pathological parameters and overall survival (OS). p<0.05 was set as statistically significant. Results: There were 37 (67%) men and 18 (33%) women, median age 64 (range 49-83) years. Histological types were 34 (62%) adenocarcinoma and 21 (38%) squamous carcinoma. 35 (63%) tumors were in stage T1, and 50 (90%) in N1. Lympho-vascular invasion was found in 55% of cases. The resection margin was positive in 6 cases. High SNAI1 and SNAI2 mRNA were associated with lympho-vascular invasion, high SNAI2 with higher T stage, and high VISTA with positive resection margin. IMP3 expression, as well as higher mRNA expression of all analyzed genes were connected with lower OS. High expression of VISTA, SNAI1 and SNAI2 mRNA in surgically resected NSCLC is correlated with shorter patient's overall survival.

Keywords: NSCLC, surgery, overall survival, VISTA, SNAI1, SNAI2, IMP3 oncoprotein

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EFFECT OF UV-C RADIATION ON PROTEIN INTERACTION BETWEEN KRAS AND RAF1 RAS BINDING DOMAIN

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The idea of this research is to describe and clarify how oxidation affects the functional consequences of the interaction of KRAS and the RBD (RAF1 RAS-binding domain) proteins. After lysis of HEK293 cells, proteins were exposed to UV-C radiation treatment. Then various variants were determined in which the proteins entered into protein-protein interactions. The last step was to perform a Western blot analysis using the SIMPL method where the results were visible on film using the chemiluminescence method. UV-C doses were determined: 0.4 J/cm2, 0.6 J/cm2, 0.8 J/cm2 and 1.0 J/cm2. At doses of 0.4 J/cm2 and 0.6 J/cm2 there are no visible changes in interactions between proteins. At a dose of 0.8 J/cm2, a decrease in the intensity of the protein band was visible when KRAS and RBD proteins were treated. The final radiation dose used in this experiment is 1.0 J/cm2, a complete loss of interaction between the treated KRAS and RBD proteins is observed. An additional measure of protein carbonylation was carried out at the already set doses. There is a difference in the appearance of the protein band between the untreated protein and the protein treated with different doses of UV-C radiation. It was observed that the protein band of RBD protein treated with a dose of 1.0 J/cm2 almost completely fades. The results obtained in this study indicate a dose-dependent effect of UV-C radiation on the KRASRBD interaction. The weakening of the bond, observed at the higher dose, implies that protein oxidation may affect the stability of the complex. It is important to point out that the protein bands of untreated protein were the same as those that underwent radiation treatment, suggesting that UV-C radiation alone is not the cause of changes in protein expression. Additionally, oxidative damage was checked by measuring the level of protein carbonylation. This observation supports the idea that UV-C radiation causes oxidation of proteins, which can further affect their interactions.

Keywords: protein-protein interactions, KRAS oncogene, UV-C radiation, oxidative stress, SIMPL method

Presentation number: TM 52 Abstract number: ABS-175-ISABS-2024

PERSONALIZED APPROACH TO CURING GLIOBLASTOMA MULTIFORME – ROLE OF BRADYKININ II RECEPTOR

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Glioblastoma multiforme, GBM, are primary brain tumors derived from glia or glial precursor cells. They are characterized by invasive growth, which represents a significant impediment to successful treatment with standard therapy of surgery followed by radiotherapy and temozolomide chemotherapy. High incidence of recurrent tumor growth and short median patient survival rate of 14 months are result of almost impossible complete surgical removal and, therefore, tumor re-growth and dispersal throughout the brain. Additional obstacle to curing the disease is very heterogeneous nature of the tumor. Hence, similarly to other cancers, a need for more individual and personalized approaches to diagnostics and therapies is emerging. We have identified that bradykinin, through binding to bradykinin 2 receptor, B2R induces calcium excitability followed by vesicular glutamate release which promotes migration and invasion of human GBM patient-derived xenolines (PDX), the best pre-clinical model of GBM. The effects are reduced by blocking the receptor with icatibant, an FDA approved B2R blocker. Furthermore, we found that B2R is overexpressed in a subset of patient's tissue samples, while our analysis of RNAseq data available from The Cancer Genome Atlas (TCGA) indicates that high mRNA expression of B2R in GBM correlates with significantly shorter patient life span. Pre-clinical data indicate that the median GBM tumor volume in the icatibant-treated mice was 58% of that in the sham-treated mice, while survival of icatibant-treated mice was 25% longer than of the sham-treated mice. Taken together, B2R emerges as a therapeutic target and icatibant as the first adjuvant therapy that tempers the invasion of GBM.

Keywords: personalized medicine, glioblastoma multiforme, invasion, glutamate, B2R

IMMUNOTHERAPY

Presentation number: TM 53 Abstract number: ABS-25-ISABS-2024

UNVEILING THE COMPLEXITY: BASAL TRYPTASE LEVELS AND C-KIT MUTATION IN SYSTEMIC ALLERGIC REACTIONS TO HYMENOPTERA VENOM

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In contemporary allergy management, assessing basal serum tryptase levels gains pivotal importance for patients with a history of systemic allergic reactions to *Hymenoptera* venom, particularly those without evident cutaneous manifestations. Elevated basal tryptase levels (>11.4 mcg/L) serve as a crucial indicator, triggering further investigation for potential mast cell disorders. Our study aimed to investigate the frequency of c-kit mutation within our patient cohort undergoing venom immunotherapy for Hymenoptera allergies. A cohort of 22 patients undergoing venom immunotherapy at the Special Hospital for Pulmonary Diseases was analyzed. Tryptase levels (Immunocap, Phadia, Upsala) were measured in the whole cohort, while c-kit D816V mutation (PCR, 2720 Thermal Cycle) was determined in 17 patients. Among the patients, 3 (17.64%) tested positive. Interestingly, 2 out of 3 positive patients exhibited basal tryptase levels below 11.4 mcg/L. However, basal tryptase levels were significantly higher (p = 0.0065) in the c-kit mutation group (median 10.10) compared to the c-kit negative group (median 3.99), and higher basal tryptase levels were associated with an increased likelihood of testing positive for c-kit mutation (OR 2.087,p = 0.0045). The findings affirm the need to explore mast cell disorders in patients with Hymenoptera allergies, even if their basal levels fall below 11.4 mcg/L. This information contributes to the refinement of diagnostic and therapeutic strategies for individuals with mast cell disorders associated with Hymenoptera venom allergies.

Keywords: allergic reaction, immunotherapy, *Hymenoptera* venom, tryptase, c-kit mutation

Presentation number: TM 54 Abstract number: ABS-141-ISABS-2024

NON-SMALL CELL LUNG CANCER – PDL-1 CLONE 22C3 VS CLONE SP263: CORRELATION BETWEEN CYTOLOGICAL AND HISTOLOGICAL SAMPLES

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Non-small cell lung carcinoma (NSCLC) accounts for about 80% of all lung cancers, of which the most common type is adenocarcinoma. In order to determine the patient's´possibility of receving immunotherapy after the diagnosis predictive biomarkers are already almost routinely determined. ALKDF530, ROS1SP384 and PDL-1SP263 and 22C3 are determined immunohistochemically at the Clinical Institute for Pathology and Cytology of Clinical hospital Dubrava. Clone 22C3 is used for immunohistochemical staining of cytological smears, while clone SP263 is used for IHC staining of cytoblocks and histological samples. The interpretation of PDL-1 expression in cytological/histological samples is as follows: PDL-1 present in less than 1% of tumor cells - negative; PDL-1 present in >1% and <50% of tumor cells - positive and PDL-1 present in >50% of tumor cells - positive with strong expression. At the Clinical Institute for Pathology and Cytology, in the period from March 2022 to February 2024, 217 patients underwent IHC staining of PDL-1 cytological and histological samples. 39 patients had 2 types of samples: cytological and histological, which were compared in pairs. In 10% of patients, the cytological preparations did not have enough tumor cells or there were none, but biopsies in these same patients showed PDL-1 positivity in 1% to 50%. In most patients, cytological smears show generally two times weaker expression of PDL-1 compared to histological samples. Pembrolizumab (Keytruda®) is a drug used in the treatment of NSCLC along with chemotherapy or as a first-line therapy if PDL-1 expression is ≥50% TPS.The development and application of targeted therapy significantly increases the quality of life and prolongs life expectancy, and therefore a high-quality and reliable interpretation of PDL-1 expression is necessary.

Keywords: PDL-1, 22C3, SP263, NSCLC, immunotherapy

ARTIFICIAL INTELLIGENCE IN CLINICAL MEDICINE

Presentation number: TM 55 Abstract number: ABS-47-ISABS-2024

MACHINE LEARNING FOR DETECTION OF VERTICALLY TRANSFERRED METABOLITES AND XENOBIOTICS

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Vertical transmission of metabolites, particularly xenobiotics, from mother to child can play a significant role in early-life disease phenotypes. Xenobiotics are foreign substances not naturally present in the body, such as environmental chemicals or drugs, which can be transferred in a multitude of pathways such as pregnancy and breastfeeding. This exposure to xenobiotics can have a significant impact on the child's health from birth, as these compounds can accumulate in the fetal body and lead to various health issues. This study employs an explainable machine learning approach to detect metabolic connections between mothers and children. By utilizing radnom forests (RF), light gradient boosting machine (LGBM) and logistic regression (LR) models, we analyzed metabolic concentration disparities. Based on the disparities, we distinguished genuine mother-child pairs from randomly paired non-relatives with an accuracy of 72%. Both RF and LGBM, in terms of accuracy, AUC and Matthews correlation coefficient, showed superior performance over LR. Our results show that the most relevant feature, as confirmed by statistical tests, was perfluorooctanoate (PFOA). PFOA is absorbed primarily through contaminated food and water as well as through polluted air, to a lesser extent. Their persistent and bioaccumulative nature, coupled with their demonstrated negative effect on health, especially during fetal programming, have raised significant concern regarding early life development. Machine learning approaches have the potential to significantly contribute and play a crucial role in examining the transfer of xenobiotics and other metabolites.

Keywords: machine learning, vertical transfer, xenobiotics, metabolomics, mother-child

Presentation number: TM 56 Abstract number: ABS-30-ISABS-2024

ARTIFICIAL INTELLIGENCE AS A GAME-CHANGER IN CLINICAL PRACTICE

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Clinical practice is one of the crucial areas of possible Artificial intelligence (AI) implementation. AI is based on algorithms that use deep learning techniques in combination with large data sets to analyze, understand, explain, predict, and perform tasks that are usually done by humans. This study aims to explore the AI's status of implementation in today's clinical practice, potential issues, and areas of new development possibilities. The results showed that these tools can decrease human error and costs and improve accuracy in comparison with traditional approaches. One of the crucial AI applications is the early detection and alerting of clinicians for patients with life-threatening conditions because these patients greatly contribute to high mortality rates. The combination of AI and genotype is a base for vast advancement in disease prevention, prediction, and development of precision medicine. Only AI can effectively analyze large population data sets and provide us with the specific genetic markers of various populations. Mentioned large datasets, can enable us to develop predictive models for the identification of specific patients with a higher risk of hospital readmission which can improve patient outcomes and cost- effectiveness of health systems. But this revolutionary clinical practice won't come if we don't tackle some of the issues that relate to AI implementation such as the problem of data quality which leads us to wrong conclusions and unwanted health outcomes; potential security breaches of patient data and the human contribution to the design of AI algorithms and potential biases that could ruin the AI judgment. In conclusion, AI started to revolutionize patient-centered care and treatment outcomes whereas its algorithms are increasing the accuracy, speed, and cost-effectiveness of clinical practice. Continuous work on the development of AI in healthcare is needed to unlock the full potential of this game-changer platform.

Keywords: artificial intelligence, clinical practice, precision medicine, data analysis, patient-centered care

Presentation number: TM 57 Abstract number: ABS-119-ISABS-2024

DEEP LEARNING MODEL FOR TYPE II DIABETES PREDICTION: INSIGHTS FROM AN ISOLATED POPULATION WITH TRADITIONAL LIFESTYLE

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The prevalence of type II diabetes poses a significant health challenge in developed nations due to lifestyle factors. This chronic metabolic disease is on the rise globally, and it poses a burden on the health systems and societies. This study focuses on investigating the risk factors associated with type II diabetes within an isolated population of the Croatian island of Hvar. Little isolated populations, characterized by a traditional lifestyle, serve as valuable source for studying potential genetic factors associated with disease development. The cohort comprises approximately 1,300 subjects from different age groups and villages on the island. Study data includes anthropometric measurements, biochemical parameters, socioeconomic data, and lifestyle habits. Additionally, genome-wide SNP genotyping was performed using the collected blood samples. Bioinformatic and biostatistical methods were implemented for data interpretation. Association analysis and allele frequencies calculations showed a strong association of several SNPs and Type II diabetes. Cross-referencing these results with GWAS catalogue confirmed that six of them had previously been associated with the type II diabetes trait. Based on this genetic information and the study data, we used a deep neural networks algorithm to develop predictive model that can effectively identify individuals at risk for developing Type II diabetes. Artificial intelligence approach offers innovative solutions for diagnostics and patient care. Benefits include early intervention and personalised healthcare approach.

Keywords: diabetes, GWAS, AI, neural networks, diagnostics

PHARMACOGENOMICS

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PHARMACOGENOMICS IN ISOLATED POPULATIONS: EXAMPLE OF CROATIAN ROMA POPULATION

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Genetic distinctiveness is especially pronounced in isolated populations due to their minimal exchange of genes with other populations and due to increasing frequencies of otherwise rare or private alleles. The Roma, transnational minority population of Indian origin, are an example of a founder population with centuries long sociocultural isolation which left traces in their gene pool showing considerable differences compared with other populations. The group of genes that significantly differentiate among populations are those responsible for Absorption, Distribution, Metabolism and Excretion of drugs (ADME genes). The knowledge on their distribution in isolated populations is limited, but these differences are essential for population-stratified pharmacogenomics. In order to fill in the knowledge gap, in 300 samples from three Roma groups in Croatia, we genotyped SNPs from 33 genes, members of the core list of the most important ADME markers by PharmaADME Consortium. The principal aim of the study was to assess the extent to which the population history – including multiple bottleneck/founder events, isolation and endogamy – could have impacted these functionally important genes. Analyses of allele frequencies of investigated SNPs showed genetic distinctiveness of the Roma population in Croatia, while more thoroughly haplotype analyses of the CYP2D6, NAT1, NAT2, ABCB1, CYP2C19 and CYP2B6 genes revealed distinctive metabolizing activity even at the level of different Roma groups in Croatia. Our data confirm that isolated populations have a specific position within the global ADME genetic landscape. This also highlights the fact that pharmacogenetics guidelines of the well-defined majority populations cannot be used in pharmaco-therapeutic practice in population isolates and confirms the necessity for defining their specific genetic profile.

Keywords: Roma population, ADME genes, pharmacogenetics, isolation

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SIGNIFICANCE OF CYP2C9 IN PRESCRIBING SIPONIMOD THERAPY IN PATIENTS WITH MULTIPLE SCLEROSIS

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Siponimod is a medication used in the treatment of secondary progressive (SPMS) and relapsing forms of multiple sclerosis (MS). The drug selectively acts on sphingosine-1-phosphate (S1P1), specifically type 1 and 5 receptors, which are involved in immunomodulation and anti-inflammatory processes, and have promyelinating and neuroprotective effects. CYP2C9 is responsible for the metabolism of approximately 20% of clinically important drugs, including siponimod. The CYP2C9 gene is highly polymorphic, which contributes to significant inter-individual variability of therapeutic response. An individual's ability to metabolize CYP2C9 substrates can be classified into the following phenotypes: normal metabolizer (*1/*1 genotype), intermediate metabolizer (*1/*1; *1/*3; and *2/*2 genotype), and poor metabolizer (*2/*3 and *3/*3 genotype). It is important to consider the genetic polymorphisms of CYP2C9 in patients receiving siponimod therapy, due to contraindications in patients carrying CYP2C9 *3/*3 genotype. Patients with other CYP2C9 genotypes may require dose adjustments. The aim of this study was to determine allelic distribution in the population of patients from Bosnia and Herzegovina, as well as to determine the precise dosage of siponimod according to the CYP2C9*2 and CYP2C9*3 genotypes. Material and methods: The study included 57 patients with MS in B&H. The CYP2C9 genotypes were determined by real-time PCR using Taqman Drug Metabolism Genotyping assays. Results: The prevalence of CYP2C9*2 and *3 alleles was 7.02 and 6.14%, respectively. Based on these frequencies, of the 57 participants 15 (26.32%) were predicted to be intermediate metabolizers (IM), and the remaining 42 (73.68%) were normal metabolizers (NM). The IM required a dose adjustment by 50%. Conclusion: All patients requiring siponimod therapy should be genotyped for these polymorphic variants, due to the high possibility of toxicity and side effects if an inappropriate dosage of a drug is administered.

Keywords: siponimod, CYP2C9, multiple sclerosis, polymorphism, pharmacogenetics

Presentation number: TM 60 Abstract number: ABS-65-ISABS-2024

PHARMACOGENOMIC TESTING IN CROATIA: ALLELE AND GENOTYPE FREQUENCIES OF DRUG-METABOLIZING ENZYMES, RECEPTORS, AND OTHER ASSOCIATED PROTEINS

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This retrospective cross-sectional study investigated the allele frequencies of genes encoding enzymes, receptors, transporters, and other drug metabolism constituents of 28 different genes in a Croatian population. Secondarily, the obtained data was compared to publicly available databases on the European population. A retrospective analysis of patient health records was performed, which included 522 patients who underwent pharmacogenetic testing by the RightMed PGx panel to determine the SNPs in the 28 targeted genes. Allele frequency for each gene was determined by dividing the total count of that allele by the total number of alleles in the patient pool for the respective gene. Genotype frequency was determined for each gene by dividing the total count of each unique allele combination by the total number of genotypes in the patient pool for the respective gene. The analysis demonstrated wild-type alleles to be the most frequent for most of the analyzed genes, consequently demonstrating the normal metabolizer phenotype to be the most frequent for utmost of genes. No statistically significant differences were found between the Croatian and European populations for the majority of analyzed genes. Conclusion: The allele frequencies observed in our study can serve as a valuable reference for future studies investigating drug efficacy and safety in the Croatian population. This study contributes to the growing data on genetic diversity that influences drug response in different populations.

Keywords: : pharmacogenomics, genetics, ADR, population genetics, allele frequency

TISSUE ENGINEERING

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ADVANCEMENTS IN BIO-INK TECHNOLOGY FOR PRECISION DERMATOLOGICAL RECONSTRUCTION IN ACID ATTACK VICTIMS

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This paper introduces a pioneering method for dermatological reconstruction tailored to acid attack victims, merging bio-ink technology with in-vitro tissue engineering and advanced 3D modeling. The process initiates with cultivating healthy skin tissue in vitro to establish a robust cell reservoir, succeeded by digitally replicating burnt area dimensions for customized skin graft fabrication. The bio-ink, comprising hyaluronic acid (HA, $C_{14}H_{21}NO_{11}$) at 2%, collagen ($C_4H_6N_2O_3$) at 3%, fibrinogen ($C_{72}H_{104}N_{18}O_{19}S_2$) at 1%, silver nanoparticles (Ag) at 0.1%, and Transforming Growth Factor-Beta (TGF-β) at 0.05%, is meticulously applied onto the wound bed to foster hydration, structural reinforcement, hemostasis, antimicrobial shielding, and immunomodulation. HA ensures optimal hydration and moisture retention, while collagen provides structural support for tissue remodeling. Fibrinogen promotes clot formation, creating a stable scaffold, and silver nanoparticles confer antimicrobial properties. TGF-β regulates inflammation and promotes tissue regeneration. This specialized bio-ink acts as a scaffold, facilitating cellular infiltration and tissue integration, thereby augmenting wound healing and skin regeneration. Preliminary trials indicate promising success rates surpassing 75% in moderate to severe cases, underscoring the potential of this innovative approach to enhance outcomes and quality of life for acid attack survivors. Through the amalgamation of bio-ink technology, this methodology represents a paradigm shift in dermatological reconstruction, offering a ray of hope and healing to individuals grappling with traumatic skin injuries.

Keywords: acid attack, bioengineering, 3D modelling, bio-ink, tissue

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BIOINFORMATICS AND COMPUTATIONAL APPROACHES IN MICROBIAL BIODEGRADATION

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Increased human activity on energy reserves, dangerous farming methods, and rapid industrialization have all contributed to an increase in environmental contamination over the last few decades. Bioremediation is a convenient solution for environmental issues. Bioremediation is a biological technique for recycling wastes into a form that other species may utilize and reuse. Microorganisms are used in bioremediation to decrease, eliminate, contain, or alter harmful pollutants in soils, sediments, water, and air. The type of bioremediation known as "microbial bioremediation" uses microorganisms and/or their derivatives (enzymes or used biomass) to remove pollutants from the environment. Pollutants are broken down or transformed by microbes using their natural metabolic processes, with or without slight pathway modifications to direct the pollutant into the usual microbial metabolic pathway for breakdown and biotransformation. With a focus on plastic degradation and polyethylane compounds, Ideonella sakaiensis, *Klebseialla pnuemoniae*, and *Pseudomonas* were thoroughly researched using computational and bioinformatic tools. Protein sequences of mentioned bacteria were retrieved from NCBI, and tertiary structures were constructed using the SWISS-MODEL tool. Sequence alignments and comparisons were conducted using BLASTP tool, and the final results showed that enzymes produced by *Ideonella sakainesis* were the most reliable and useful. This is because PETase and MHETase enzymes produced by *I. sakainesis* were thoroughly researched, and identical sequences demonstrated in BLASTP results could be used as possible alternative enzymes for plastic degradation.

Keywords: bioremediation, biodegrading bacteria, *Ideonella sakaiensis, Klebsiella pneumoniae, Pseudomonas*

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MATURATION AND ELECTROPHYSIOLOGICAL PROPERTIES OF HUMAN INDUCED PLURIPOTENT STEM CELL DERIVED CARDIOMYOCYTES (HIPSC-CMS) ON ELECTROMECHANOACTIVE SCAFFOLD

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Heart-on-a-chip for drug testing seems attractive approach to evaluate the possible drug effects on cardiomyocyte viability and electrophysiology. For the advancement of human induced pluripotent stem cell derived cardiomyocyte (hiPSC-CM) maturation, the need in recapitulation of the native cardiac microenvironment becomes increasingly evident. Our aim was to create a 3D hiPSC-CM culture system with a biocompatible electromechanoactive scaffold, coated with electroconductive layer, suitable for long term culturing and maturation of hiPSC-CMs and compatible with electrophysiology measurement techniques. Elastic scaffold was fabricated by electrospinning of gelatin-glucose (Gel/Glu) microfibers followed by the vapor-phase and electrochemical deposition of conductive polymer polypyrrole (PPy) to create electroconductive layer. Electrophysiological properties of hiPSC-CMs were analysed using intracellular calcium imaging (Cal520) and sharp electrodes. Synchronous calcium oscillations were induced using electrical stimuli. Calcein AM and DAPI staining showed high level attachment of hiPSC-CMs to Gel/Glu /PPy scaffold demonstrating its biocompatibility. The cells remain abundant even during long term cultures (5-7 weeks) and increasingly express maturation markers NKX2- 5, Troponin T, etc. Intracellular calcium imaging and analysis with sharp electrodes showed generation of synchronous spontaneous calcium oscillations by hiPSC-CMs on Gel/Glu/PPy scaffolds, while external electrical stimulation synchronised calcium oscillations. Gel/Glu /PPy scaffold is biocompatible for hiPSC-CMs maturation, and suitable for evaluation of cardiomyocyte electrophysiology properties. Such electromechanoactive scaffold can be further employed for development of heart-on-a- chip model and tissue engineering applications.

Keywords: human iPSC derived cardiomiocytes, electrophysiological properties, electromechanoactive scaffold, maturation, electric stimulation

WHOLE GENOME SEQUENCING FOR IMPLEMENTATION OF PRECISION MEDICINE

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COMPREHENSIVE WHOLE-GENOME, BIOCHEMICAL, AND GLYCAN ANALYSIS IN PATIENTS WITH MORBID OBESITY

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Obesity is a growing health problem worldwide, imposing a significant burden on the health-care system and society in general, particularly morbid obesity. It is a multifactorial disease influenced by genetic and environmental factors. Pathophysiologically, obesity represents a chronic inflammatory state that leads to various metabolic disorders such as diabetes mellitus and hyperlipidemia, as well as conditions like hypertension, cardiovascular diseases, and tumors. This study is structured into two phases. Firstly, a case-control study aims to elucidate the molecular basis of morbid obesity and its potential correlation with genes associated with cardiovascular and metabolic diseases, and hereditary cancer syndromes. Sixteen participants of both genders and aged between 20 and 55 years, with morbid obesity (BMI >40 kg/m2), were enrolled. The control group comprised subjects with a normal BMI range (18.5-24.9 kg/m2). Both groups underwent genomic testing for 1130 genes, including panels for cardiometabolic, nutrigenetic and hereditary cancer-related genes. The second phase involves a prospective interventional study focusing exclusively on the group with morbid obesity. The aim is to observe the impact of weight loss on inflammatory conditions and specific metabolic disorders. Initially, participants underwent clinical assessments, laboratory analyses and plasma N-glycom and N-glycom Ig assessments. Subsequently, participants received consultations regarding nutritional plans and exercise regimens for the next 6 months, during which their progress was closely monitored. N-glycom assessments were repeated after 3 months. Another comprehensive clinical assessment was conducted at the 6-month mark, including laboratory analyses and N-glycom assessments. The final clinical assessment is scheduled for 12 months after the commencement of the study. The collected data are currently undergoing analysis, and preliminary results will be presented at a congress.

Keywords: morbid obesity, whole genome sequencing, glycosylation, metabolic disease

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WHOLE GENOME SEQUENCING: ADVANTAGES AND CHALLENGES OF CLINICAL IMPLEMENTATION

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Whole genome sequencing (WGS) is a revolutionary diagnostic method in clinical genetics that allows for a complete and comprehensive analysis of the human genome. On one hand, WGS generates exceedingly large volumes of data, providing the necessary raw information for the detection of more complex genetic variants. On the other hand, the correct interpretation of this data relies on computational statistical algorithms and predictive machine learning models trained on large datasets of genotype- phenotype correlations. This powerful tool has already begun its integration into many areas of applied medicine, the most prominent being cancer genomics, neonatal screening, pharmacogenomics, and rare disease genomics. Another aspect of WGS utility is in biomedical research, as the method has led to the discovery of many new intronic, structural, and copy number variants. By determining everyone's entire genomic profile, WGS has become one of the main pillars of personalized medicine and multi-omics development. Through the integration of data with other -omics branches, such as epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics, a complete biomolecular profile can be determined for each patient. It should be stated that certain limitations of WGS are presenting challenges in particular clinical cases. These include predictive model imperfections, genetic mosaicism, non- Mendelian genetic disorders, and variability in variant penetrance. Additional options, such as 'trio testing', in which the proband's parents' genetic profiles are also determined, can be explored in these cases to provide a more complete picture. However, DNA sequencing technologies are continuously evolving, currently through the development of third and fourth-generation sequencing. With their increasing implementation into clinical practice, these technologies show great potential in revolutionizing the field of medicine.

Keywords: whole-genome sequencing, genomics, multi-omics, pharmacogenomics, cancer-genomics

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SLOVENIAN GENOME PROJECT – A NATIONAL RESOURCE OF POPULATION AND DISEASE-ASSOCIATED GENETIC VARIABILITY IN SLOVENIANS

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Understanding a nation's genetic makeup is crucial for efficient genetic testing and development of national disease screening programs. Recent population sequencing initiatives focused on larger, mostly Anglo-Saxon populations, leaving many populations, including the Slovenians, underrepresented. To address this, we aggregated sequencing data from 8,025 Slovenian individuals, establishing a comprehensive genetic variability database. We combined exome (ES) and genome sequencing (GS) data from 7,566 ES and 459 GS individuals. Variants were called against the hg38 reference genome, following GATK guidelines. Stringent variant quality filters retained accurately genotyped variants in over 90% of ES or GS cohorts, ensuring precise frequency estimations. Variant were annotated via the Variant Effect Predictor, stored in a local SQL database and collected in an on-line genome browser. In the dataset, 26,439,624 distinct variants were identified, mostly (96.3%) in the GS cohort. Notably, 3,070,774 variants (11.6%) were absent in gnomAD 2.1.1, indicating novel human genome variation. Significant variant frequency disparities were observed, with 8.3% variants (MAF>0.01%) showing over two-fold differences compared to global gnomAD populations. For ClinVar variants, 77.0% of pathogenic variants either differed significantly or were absent in gnomAD populations. In conclusion, our study presents a novel resource on Slovenian genetic variability, crucial for understanding this population and the wider European region. Given distinctiveness from commonly used gnomAD populations, our resource is valuable for genetic diagnosis and population screening efforts.

Keywords: genome project, genomics, rare diseases, next-generation sequencing, population genetics

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THE CROSEQ GENOME PROGRAM: THE FIRST LARGE-SCALE PEDIATRIC CROATIAN GENOME ANALYSIS AND AGGREGATE DATABASE

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The genetic diagnosis of Mendelian diseases is often challenging due to their rare nature and complex phenotype. Population-specific variant allele count (AC) and allele frequency (AF) are important parameters for the clinical assessment of variants. Here, we present the development of the CROseq Genome Program in collaboration with the University Hospital Centre Zagreb (UHCZ) and the Brigham and Woman's Hospital (BWH) in the US, funded by the Mila za Sve Foundation, Rijeka. The aim of the CROseq is twofold: 1) analyze complex diseases by the joint genome analysis of the affected children and their unaffected family members to discover disease etiology, and 2) develop the first Croatian Genome Aggregated Database (CGAD) and Croatian Genome-Phenotype Database (CGPD). A total of 754 participants enrolled in the CROseq Genome Program (female=374; male=380; affected=274; unaffected=490). Whole genome sequenced data were analyzed at the BWH using the latest analytical tools. An automated computational infrastructure was developed to transfer the data to Croatia. The aggregate databases were generated using annotated variant parameters including population frequency, in silico scores, zygosity, and inheritance pattern, and a minimum of 20 Human Phenotype Ontology per case. A total of 54.8 million genomic variants have been analyzed. Of those, 16.9x10'6 variants were absent from gnomAD database and exclusively found in the Croatian population. A total of 18.5x10'3 variants absent from gnomAD were frequently observed in the CROseq cohort (AF>0.5). Aggregate databases were generated to enable elastic search by using any unique phenotype or genotype features. CROseq Genome Program is the first collaborative program to address the rare disease and complex genome in the pediatric population in Croatia. The CGAD and CGPD datasets are the first aggregated genome knowledgebases in Croatia. They are an invaluable tool for genetics and population-based studies in Croatia and beyond.

Keywords: CROseq Genome Program, Trio Whole Genome Sequencing, joint analysis, Croatian Genome Aggregated Database (CGAD), Croatian Genome-Phenotype Database (CGPD)

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MIRNA AS A PERSONALIZED MEDICINE TOOL FOR TREATMENT OF KNEE OSTEOARTHRITIS

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Knee osteoarthritis (OA) is a disease characterized by loss of cartilage and inflammation of all tissues in the joint, causing changes in tissue architecture, its metabolism, and function. These changes are mediated by a complex interplay of proinflammatory and anti-inflammatory mediators regulated with miRNA. We explored the miRNA profiles of OA patients who were treated with two types of treatments: with the intra-joint administration of micro-fragmented fat tissue (MFAT) and with hyaluronic acid. We measured the miRNA profiles in plasma, synovial fluid, and MFAT (from the test group) in different time points. The aim was to find miRNAs, predictors of treatment outcomes for the two therapies. miRNA profile was measured with the next-generation sequencing (NGS). NGS QC and absolute quantification of miRNAs were done using spike-ins based on a linear regression model. For the MFAT we didn't find any miRNA that would serve as a good predictor for treatment outcome, even if we stratify the patients by gender. For plasma, we can observe several candidate miRNAs (7 downregulated, 4 upregulated) as predictors for MFAT treatment outcome while no miRNAs were found as a good predictor for HA treatment. For the synovial fluid, no miRNAs were defined as predictors for MFAT treatment, while for HA treatment 13 miRNAs were up regulated and 1 down regulated. These candidate miRNAs need to be validated with other analytical techniques, to check for the possible false positivity. Nevertheless, candidate biomarkers as ones described in our project are of huge interest to orthopedists while knee OA can be treated with different treatments. The personalized approach is needed for the best possible treatment outcome. Conducted as part of the European research project IRI2 (KK.01.2.1.02.0173)

Keywords: knee osteoarthritis, miRNA, marker, treatment outcome, personalized medicin

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CLINICAL AND MOLECULAR ANALYSIS OF BETA-THALASSEMIA MINOR: CASE REPORT OF A PATIENT WITH HETEROZYGOUS HBB VARIANT

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Beta-thalassemias are heterogeneous groups of hereditary anemias characterized by reduced or absent synthesis of the beta-globin chain of hemoglobin (Hb), which is encoded by the HBB gene located on chromosome 11. There are three main forms: beta-thalassemia major (TM), beta-thalassemia intermedia (TI), and thalassemia minor (TMI). The clinical presentation may vary depending on the type of mutation and zygosity. We present the case of a 29-year-old male patient who underwent further laboratory examination due to microcytic anemia with iron and unsaturated iron-binding capacity within the normal range and an enlarged occipital lymph node. Hemoglobin electrophoresis showed the patient's hemoglobin consisted of 71.6% HbA0, 3.5% HbA2, <0.10% HbF, and 25% HbE. HbS was not detected. Finally, whole- genome sequencing revealed a single heterozygous variant (c.79G>A (p.Glu27Lys)) in exon 1 of the HBB gene. This pathogenic variant leads to the synthesis of abnormal HbE, characterized by a change in the amino acid sequence from glutamic acid to lysine. The βE mutation also affects β-globin gene expression by creating an alternate splicing site in the mRNA at codons 25–27. This explains our electrophoresis assessment, confirming the diagnosis of TMI. Although HbE alone does not cause significant clinical problems, its interactions with other thalassemias produce syndromes of varying severity. Despite the lack of a severe clinical presentation, individuals with TMI are carriers of the pathogenic variant, and genetic counseling is recommended for family planning by the patient or biological relatives in whom genetic tests confirm the pathogenic variant.

Keywords: beta-thalassemia, thalassemia minor, HBB, hemoglobin electrophoresis, whole-genome sequencing

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UTILIZING ARTIFICIAL INTELLIGENCE FOR ANALYSIS OF WHOLE GENOME SEQUENCING DATA TO DESIGN PERSONALIZED NUTRITION INTERVENTIONS FOR LIFE QUALITY IMPROVEMENT

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Each individual possesses a distinct genetic composition that profoundly influences various facets of their health and lifestyle, notably impacting nutrient processing mechanisms. The comprehension of these genetic disparities stands as a pivotal element in tailoring nutrition strategies. Leveraging cutting-edge genomics technologies such as whole-genome sequencing (WGS), Nutrigenetics 365 project employs sophisticated algorithms and data analysis methodologies to dissect this genetic landscape. Through meticulous analysis, specific genetic markers dictating nutrient metabolism, dietary inclinations, and the impact of food on health are discerned. These genetic markers may elucidate the efficiency of processing certain vitamins, highlight sensitivities to particular foods (e.g., lactose intolerance), or unveil predispositions to diet-influenced ailments (e.g., heart disease). Armed with this knowledge, nutritionists harness AI-powered platforms to craft bespoke nutrition regimens that harmonize with an individual's genetic blueprint, optimizing nutrient absorption and mitigating the risk of nutrition-related disorders. A crucial component entails the ongoing monitoring of an individual's health and dietary responses, facilitating iterative refinement of the nutrition plan through constant feedback integration into the analytics framework. The overarching objective is to elevate the overall quality of life and health outcomes. Personalized nutrition interventions hold the promise of superior weight management, heightened energy levels, diminished susceptibility to chronic ailments, and holistic wellness. In conclusion, the integration of artificial intelligence and whole-genome sequencing heralds a new era of precision and personalized medicine. By decoding the intricate genetic makeup of individuals, we can tailor nutrition strategies with unprecedented accuracy, optimizing health outcomes and enhancing quality of life.

Keywords: whole-genome sequencing, nutrigenetics, personalized nutrition, artificial intelligence

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RARE LIKELY PATHOGENIC VARIANT ASSOCIATED WITH STARGARDT DISEASE IN THE CROATIAN POPULATION

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Stargardt Disease (STGD) stands as the most prevalent inherited retinal dystrophy, marked by subretinal lipofuscin-like deposition and bilateral vision loss. It is the most common genetic retinal disease, affecting 1 in 10,000 individuals. STGD's phenotypic spectrum spans diverse age-related manifestations, ranging from rapidly progressive cone-rod dystrophy with significant vision loss to late-onset maculopathies with preserved central vision. Autosomal recessive or dominant STGD links to pathogenic variants of ELOVL4, PROM1, BEST1, PRPH2, and ABCA4 genes. A 45-year-old male patient with late-onset maculopathy and preserved central vision came to our hospital for a routine eye check-up. All ophthalmologic diagnostic evaluation for Stargardt disease was made: a personal and family history, visual acuity, slit lamp examination, tonometry, fundus examination, visual field testing, fluorescein angiography, fundus autofluorescence (FAF), electroretinography (ERG) and optical coherence tomography (OCT). A whole- genome sequencing (WGS) was conducted with a focus on coding and non-coding regions of 438 genes related to the most prevalent inherited ocular disorders. The analysis revealed a rare likely pathogenic variant in the coding region of the ABCA4 gene (c.3272G>A (p.Gly1091Glu)). Experimental studies have demonstrated that this missense alteration impacts ABCA4 function. However, further data are requisite to confirm the variant's pathogenicity, hence its classification as likely pathogenic. We highlight the importance of ongoing monitoring by an ophthalmologist for both the proband and all family members carrying the likely pathogenic variant, ensuring comprehensive care and early intervention where necessary. This case underscores the significance of genetic testing in identifying at-risk individuals and guiding targeted interventions, ultimately paving the way for potential prevention of visual impairment among these patients.

Keywords: Stargardt disease, retinal dystrophy, ABCA4, whole genome sequencing, electroretinograph

FORENSIC GENETICS

FORENSIC AND COMPARATIVE GENETICS

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REVISITING THE MYSTERY OF THE CHIDLOW MAN IN WESTERN AUSTRALIA – STRATEGIES FOR DNA ANALYSIS OF 45-YEAR-OLD HUMAN SKELETAL REMAINS

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In August 1979, the remains of a man were found in a semi-rural area northeast of Perth. The male had a gunshot wound to the chest and had been deceased for approximately 30-50 days before being discovered. As DNA techniques were not available in 1979 to assist in identifying the remains, no samples were taken from the body specifically for DNA analysis at the time. Subsequent attempts at extracting DNA from the deceased clothes and bones from the body after exhumation were unsuccessful. Specialized techniques are needed to improve DNA profiles, especially when no other biological material is available due to the age of the remains or exposure to adverse environmental conditions. Despite bones and teeth being more resilient, they still undergo DNA degradation, aggravated by high mineral content hindering extraction and resulting in suboptimal outcomes. The DNA extraction method was optimized to withstand harsh conditions and soil compositions prevalent in the Western Australian region, guided by recent scientific advancements. Briefly, bone samples were ground, then either extracted using the PrepFiler Express BTATM method, or subjected to a full demineralization protocol followed by PrepFiler Express BTATM extraction. The standard PrepFiler Express BTATM method yielded lower-quality DNA extracts, with all PowerPlex® 21 loci falling below reportable thresholds. On the other hand, bone fragments processed using the PrepFiler Express BTATM full demineralisation method resulted in higher quality DNA and reportable PowerPlex® 21 profiles. The optimised full demineralisation method proved effective in this cold case, where despite significant degradation, a clavicle bone produced a good quality DNA sample that was suitable for Short Tandem Repeat (STR) and Single Nucleotide Polymorphism (SNP) analysis which enabled further investigative options including Familial searching and Forensic Genetic Genealogy for the unresolved murder inquiry.

Keywords: demineralisation, DNA bone extraction, human remains, DNA profiling, PrepFiler Express BTA

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NONINVASIVE PRENATAL PATERNITY TESTING: A NEW CONTRIBUTION FROM DIP-STR MARKERS

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Noninvasive prenatal paternity testing (NIPPT) plays an important role in forensic analysis, especially in cases of suspected post-rape pregnancy. It allows for the determination of fetal paternity within weeks of gestation. This project aims to contribute to the field of NIPPT for forensic applications by developing a novel and robust method. The goal is to leverage Next-Generation Sequencing (NGS) technology to analyze DIP-STR (Insertion/Deletion Polymorphism coupled with Short Tandem Repeat) markers. These genetic markers have demonstrated an enhanced ability to deconvolute mixtures of DNA from two contributors even under extreme DNA imbalances (up to 1000-fold). They have already shown promises for NIPPT up to 7 weeks of gestation using capillary electrophoresis analysis. To maximize their potential, a panel of 27 DIP-STRs has been optimized for NGS analysis. We will present promising preliminary results regarding the application of the multiplex to single-source profiles. Efforts are currently being dedicated to ensuring the results' reproducibility. The novel sequencing approach applied to DIP-STRs markers is expected to enhance sensitivity, specificity, and multiplexing capability, thus improving the performance of these markers in NIPPT. Upon completion of optimization, the panel of markers will be validated through the analysis of plasma samples collected from a cohort of 100 pregnant women at three different gestational intervals.

Keywords: NIPPT, NGS, DIP-STR markers, multiplex, forensic genetics

Presentation number: FG 03 Abstract number: ABS-73-ISABS-2024

IMPLEMENTING LIMITS OF DETECTION IN FORENSIC DNA ANALYSIS BY MASSIVELY PARALLEL SEQUENCING

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Goal was to define and characterize a sequence-aware approach to establishing lower limit of detection (LOD) thresholds based on positive control data. Compare and contrast the novel positive control-based method to the traditional negative control-based method. LODs were modeled from both negative and positive controls using a total of 53 negative controls and 100 positive controls analyzed using the OmniSTR (NimaGen) and ForenSeq DPMA (QIAGEN) reagent kits, and the MiSeq (QIAGEN) and NextSeq (Illumina) sequencing platforms. All analysis was performed using R (R Core Team) and MixtureAce forensic software (NicheVision Forensics). Statistical models were built on positive or negative control data analyzed without a threshold to assure observation of the complete distributions of noise reads. Noise models were built on contamination in negative controls according to published methods, and on artifacts in positive controls according to a novel approach. Briefly, artifacts other than back-one LUS (longest uninterrupted stretch) stutter were used to calculate thresholds in positive controls. Back-one LUS stutter can be considered informative signal, along with true alleles, in cases where back-one LUS stutter is included in probabilistic genotyping models. Models were also tested where back-one LUS stutter was included in the artifacts, and where back-one SLUS stutter was excluded. LODs determined from negative and positive controls ranged from 10-200 reads and 50-150 reads respectively. LODs based on negative controls were more variable due to the stochastic nature of contamination. Selected STR loci can generate significant back-one SLUS stutter which can exceed calculated thresholds. LODs based on negative controls can be set per sequencing run or transformed to dynamic thresholds when being used with samples having different levels of coverage.

Keywords: sequencing, LOD, STR, stutter, LUS

Presentation number: FG 04 Abstract number: ABS-175-ISABS-2024

EFFECT OF SURFACE ROUGHNESS ON THE DEVELOPMENT OF LATENT FINGERMARKS USING DIFFERENT FINGERPRINT POWDERS

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Aim was to investigate the effect of surface roughness on the effectiveness of latent fingerprint visualization using the two most commonly used fingerprint powders. For the experiment, we used a white polystyrene board, which we cut into four sections. Three sections were treated with sandpaper (grit sizes 60, 240, and 600), while one remained in its original state. We determined the mean roughness depth (Rz) for all surfaces using the Mitutoyo device (Mitutoyo, Japan). They were classified as very smooth (Rz = 0.0092 µm), smooth (Rz = 0.1493 µm), medium to smooth (Rz =2.1251), and of a medium roughness (Rz = 4.2839 µm). Each section was then separated into two halves, and eight participants left one thumb fingermark on each surface. To develop fingermarks, the first halves were treated with Jet-Black Special Powder (BVDA, The Netherlands) and the second with Magnetic Jet Black (BVDA, The Netherlands). The quality of developed fingermarks was scored on a scale of 0 – 4, where scores 3 and 4 were considered suitable for the identification. Fingerprints developed with black special powder were suitable for identification in 71.9% (23/32) cases, and those developed with magnetic powder were suitable in 96.9% (31/32). Fingermarks on very smooth and smooth surfaces were almost all suitable for identification, despite the powder used. On the medium to smooth surfaces, magnetic powder provided identifiable marks for all cases, while the efficiency of special powder dropped to 62.5%. On the surface of medium roughness, magnetic powder was efficient in 87.5 cases, while special powder could provide 37.5% of prints suitable for identification. The study findings imply that selecting fingering powder could be less important when dealing with very smooth and smooth surfaces. On the other hand, Magnetic powder could be more effective on rough surfaces than Special powder.

Keywords: surface roughness, fingermark development, identification, fingerprint powder, visualization

Presentation number: FG 05 Abstract number: ABS-76-ISABS-2024

EVALUATION OF AUTOSOMAL, X- AND Y-CHROMOSOME STR LOCI SEQUENCING PERFORMANCE WITH FORENSEQ® SIGNATURE PREP KIT ON MISEQ FGX® INSTRUMENT

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Massively parallel sequencing is steadily finding its place within routine forensic workflows, thus enabling extraction of more forensically relevant information from challenging samples. ForenSeq® DNA Signature Prep kit (Verogen), with its Primer Mix B, targets over 200 markers of different types, including 27 autosomal STR (aSTR), 7 X-STR and 24 Y-STR loci. In this study, we aimed to evaluate genotyping performance of 58 STR markers by testing sensitivity, repeatability, reproducibility and concordance, as part of internal validation. Genomic DNA was extracted according to our validated laboratory procedures, and samples of positive control 2800M were used as provided by the manufacturer (Verogen). Libraries were prepared, pooled and sequenced using ForenSeq® DNA Signature Prep kit (Verogen) on MiSeq FGx® (Illumina/ Verogen) sequencing platform, according to the manufacturer's instructions. Subsequent data analysis was performed in ForenSeq® Universal Analysis Software (Verogen) and Microsoft Excel. Sequencing quality parameters were within optimal range for all sequencing runs. Complete aSTR and Y- STR genotypes were obtained for DNA inputs down to 125 pg, while dropouts were observed at X-STRs already with 250 pg input. Results were repeatable and reproducible for all replicates and were 100% concordant with capillary electrophoresis results. When testing reference samples, concordance rate was 99% for aSTRs, 100% for X-STRs, and 98% for Y-STRs, due to allele dropouts observed in D22S1045 and ambiguous allele calls in DYS392 and DYS612. Stutters n-1 comprised most non-allelic signals (71%) and exceeded default stutter thresholds in 11/58 loci, while other stutters (n+1, n+2, n-2, n- 3) were also detected but with lower intensities (<10%). Overall, this study presents analysis thresholds and interpretation guidelines for sequencing 58 STR loci as part of in-house validation of ForenSeq® DNA Signature Prep kit.

Keywords: massively parallel sequencing, evaluation, ForenSeq, autosomal STRs, X- and Y-STRs

Presentation number: FG 06 Abstract number: ABS-87-ISABS-2024

ABOUT ETHYLENDIAMINETETRAACETIC ACID (EDTA) POSSIBILITY TO INCREASE THE SELECTIVITY OF COMBUR TEST E FOR FORENSIC BLOOD ANALYSIS

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Recently published method validation reported increased selectivity of tetramethyl-benzidine (TMB)-based presumptive tests, by adding 0.5M ethylendiaminetetraacetic acid (EDTA) to a reaction pad. Chelator EDTA binds positively charged metal ions and other substances preventing them to react with TMB in pad, i. e. eliminating possible false positives. Hence, the main goal of this study was to verify these data for subsequent upgrade of ours validated protocols. In addition, possible interference of the 0.5M EDTA on DNA analysis was evaluated. Twenty-one substances/surfaces were tested. Whole blood (known donor) was used as a positive control, and test strips moistened with ultrapure water as negative control. All testing was done in triplicates, with methods of EDTA application previously described. Presence/absence of colored reaction was recorded at 30s and 60s and interpreted as positive or negative after 60s. Rust, brass, brick, soil-1, tomato pureè/paste and saliva samples of known donor exhibited negative results for test strips moistened with water and 0.5M EDTA. Contrary to previously published, majority of tested samples including plant leaf, copper surface and bleach, showed false positives with 0.5M EDTA. Negative results with EDTA for wood branch, soil-2 and banana pointed out possible influence of EDTA on increased selectivity since positive results were obtained with water. Finally, all EDTA tested blood samples resulted in complete DNA profile using the GlobalFiler™ PCR Amplification Kit. Overall findings showed considerable discrepancy when compared with previously published, indicating that further study about influence of EDTA on selectivity of Combur3 Test® E are required. Sodium hypochlorite as a major compound of comercially available bleaches, remains important substance causing false positives. Nevertheless, Combur3 Test® E is distinguished as highly sensitive, cheap, easy to use and STRs analysis compatible presumptive test for blood.

Keywords: blood, Combur3 Test® E, selectivity, EDTA, STRs analysis

Presentation number: FG 07 Abstract number: ABS-84-ISABS-2024

IMPACT OF TREATED VS. UNTREATED HAIR SHAFTS AND CHEMICAL CLEANING APPROACHES ON THE YIELD OF MITOCHONDRIAL DNA

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In forensic science, traces such as hair are common pieces of evidence. Although nuclear DNA is known to be present in hair shafts, it's been found to be very fragmented. Mitochondria have been observed to be a common component of keratinizing hair shafts, therefore, providing a rich source for mitochondrial DNA (mtDNA). It has been shown that heating and chemical hair treatments can affect the physical structure of the hair shaft. For heating treatment, a critical temperature of 140C caused modifications that were irreversible. These modifications included a change in appearance of the cuticle and gradual disappearance of the scales of the cuticle. Chemical treatments can include lightening, dying, relaxers, and perms. These changes, particularly of the scales along the shaft, can lead to external biological material being trapped within the cuticle scales. The DNA of the trapped material will be extracted along with the DNA of the hair if the biological material cannot be adequately removed. A study demonstrated that 3% NaClO, bleach, worked very well to remove biological contaminants. However, this study didn't examine whether the NaClO damages the endogenous DNA. In addition, no studies have assessed whether this type of NaClO cleaning would be effective when conducting analysis on treated hairs. Since heat and chemical treatments affect the hair's physical characteristics, it is plausible that the entirety of the shaft of treated hairs might allow the NaClO to penetrate further into the hair, ultimately causing unwanted DNA damage and degradation. This research will be conducted in two phases. The first phase will assess whether there is an impact on mtDNA yield on treated vs. untreated hairs and the second phase will assess whether NaClO impacts mtDNA yield when compared to Terg-a-zyme, a cleaning detergent containing protease enzymes. A custom mtqPCR assay will be used for quantification. Significant differences between groups in both phases will be assessed.

Keywords: hair, mtDNA, treatment, cleaning, yield

Presentation number: FG 08 Abstract number: ABS-134-ISABS-2024

Y-HAPLOGROUP ANALYSIS OF MEDIEVAL BOSNIAN POPULATION: DISCOVERIES FROM ARCHAEOLOGICAL REMAINS

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Archaeological sites in modern Bosnia and Herzegovina provide evidence of continuous life during the Middle Ages. This study aimed to ascertain Y-haplotypes, predict Y-haplogroups, and assess their frequencies in a sample of the medieval Bosnian population. DNA samples were collected from 42 male remains across 12 archaeological sites dating to medieval Bosnia. DNA extraction was performed using phenol-chloroform extraction from bones and teeth, followed by Y-STR analysis using the PowerPlex® Y23 System. Y-haplogroups were predicted using online software. Statistical analysis was conducted using the 2 test with a significance level of $p<0.05$. The most frequently detected haplogroups were I2a, R1a, R1b, and J2a. The predominant haplogroup in both the medieval Bosnian and contemporary Bosnian and Herzegovinian populations was I2a. However, the European haplogroup E1B1b, present in 10% of the recent population, was absent in the medieval samples. This discrepancy may be attributed to factors such as limited successfully amplified Y-STR profiles, small sample size, and stochastic effects. The 2 test revealed no significant differences in haplogroup frequencies between the medieval and contemporary populations. Based on the obtained Y-haplotypes, Y-haplogroups were detected for the first time, and their frequency in a sample of the medieval Bosnian population was determined.

Keywords: ancient DNA, Y-STR markers, medieval Bosnia, archaeology

FORENSIC DNA DATABASES

Presentation number: FG 09 Abstract number: ABS-31-ISABS-2024

MITOGENOME SEQUENCING OF 5,000 POPULATION SAMPLES USING THE PACBIO SEQUEL II SYSTEM AND DEEP DIVE INTO THE DATA ANALYSIS

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In forensic investigations where nuclear DNA cannot be obtained for damaged or degraded samples, sequence analysis of mitochondrial (mt) DNA plays an important role. Large population databases of mitogenome sequences for forensic purposes are not yet available, reducing the value of a mtDNA profile match since statistical analysis is based on the size of the database. Laboratories around the world utilize the European DNA profiling group (EDNAP) forensic mtDNA population (EMPOP) database in their casework. The primary goal of our research is to produce 10,000 mitogenome sequences from blood samples to be included in the EMPOP database and used for forensic and population studies. Extraction of the mtDNA from blood samples is being performed using the Zymo Quick-DNA Miniprep Plus kit. The mitogenomes are amplified using primer sets targeting two, overlapping 8.5kb amplicons. SMRTbell adapters are added to the DNA amplicons prior to running them on the PacBio Sequel IIe instrument. The sequence files are analyzed using GeneMarker (GM) HTS software to produce mitotypes. The sequences are analyzed before being sent to EMPOP. GM HTS data analysis is performed with the help of Haplogrep to obtain a detailed analysis of the population data, addressing confirmation of haplotype information and haplogroup assignments, and addressing anomalies in sequence data related to misalignment and noise patterns or amplification errors. Analysis also includes confirmation of single nucleotide polymorphisms (SNPs), whether they are part of the sequence or noise generated within the sequenced mitogenomes. Finally, before uploading the samples to EMPOP they are interpreted for mitochondrial DNA sequence variation and checked for quality and error using the SAM2 algorithm. By obtaining the haplotypes of the samples and ensuring the sequenced mitogenomes meet the standards of the EMPOP database, the sample data is then incorporated into EMPOP to increase statistical power of mtDNA matches.

Keywords: mitogenome, PacBio Sequel IIe, mitochondrial DNA, haplotypes, EMPOP, next generation sequencing

Presentation number: FG 10 Abstract number: ABS-146-ISABS-2024

DEVELOPING FORENSIC DATABASES BY Y-CHROMOSOME HAPLOGROUPS FOR MEGALOPOLISES CONSIDERING MIGRATION

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The goal was to analyze migration influence on dynamics of Y-chromosome haplogroups in megalopolis populations and consider migration role for developing DNA forensic databases for megalopolises. In the samples from population of three megalopolises (Moscow, Novosibirsk and Sankt-Petersburg), Y-chromosome haplogroups were detected by means of Whit Athey's Haplogroup Predictor basing on 18 STR haplotypes. Simultaneously, questionnaire data for residents of megalopolises was collected, including data and place of birth, ethnic affiliation, and their ancestors in two previous generations. In three megalopolises, distribution of Y-chromosome haplogroups (R1a, N, I1, I2, E1b1b. R1b, J1 and J2) characteristic for the Russian population was revealed, heterogeneity of the frequency profiles was observed. In the previous years, intensive migration to megalopolises took place from Northern Caucasus and Middle Asia, that resulted in accumulation of the Southern origin haplogroups (C3, G2a, G2c, J1, J2, L, O2, O3, Q, R2 and T). During three generations of Moscow population, frequency of the Southern origin haplogroups increased from 11 to 21% with parallel decrease of frequencies for the most widely spread haplogroups (R1a and N). Molecular data obtained was in good agreement with the questionnaire data. Our results demonstrate necessity of developing DNA forensic databases by Y-chromosome for each megalopolis taking in consideration geographical position and genetic demographic processes, especially, migration. Individual affiliation to concrete generation should be considered, as different generations are under action of different migration flows. The DNA forensic databases for megalopolis should be updated considering migration processes.

Keywords: megalopolis, migration, forensic databases, Y-chromosome haplogroups

Presentation number: FG 11 Abstract number: ABS-152-ISABS-2024

FORENSIC DNA ANALYSIS AND GENETIC PRIVACY IN CRIMINAL PROCEEDINGS: PERSPECTIVES FROM THE INNOCENCE PROJECT CROATIA ON WRONGFUL CONVICTIONS IN CROATIA

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The emergence of the Innocence Project in Croatia in 2015 has significantly highlighted the challenges and potential of post-conviction DNA examinations in addressing wrongful convictions. Established experimentally at the Faculty of Law in Zagreb in 2020 with support from the Croatian Science Foundation, this initiative plays a pivotal role in raising public awareness about miscarriages of justice and advocating for essential legal reforms to aid defendants in reopening their cases. Within the framework of the Innocence Project Croatia, several regional and national conferences and workshops have been organized, partnerships have been formed, and the prison population has been notified about this project and actively participates in it. Currently, there are 27 cases on the docket of the Innocence Project Croatia from prisoners who consider themselves innocent. These cases have raised significant issues regarding the treatment of DNA evidence and genetic privacy in criminal trials, underscoring the need for improved legal standards and practices in the handling of such sensitive information. This paper explores the handling of DNA evidence, focusing on its retention, use, and the challenges of ensuring genetic privacy in criminal investigations. Through a detailed analysis of the European Court of Human Rights jurisprudence, this paper evaluates how DNA data is managed in Croatian national criminal legislation and its implications for individual privacy and the presumption of innocence. Additionally, the paper discusses forensic errors and the significant risks they pose to justice, as well as received cases from inmates as part of the Innocence Project Croatia initiative. By incorporating theoretical, comparative, and case study methodologies, this article suggests potential legislative reforms to optimize the use, storage, and ramifications of DNA data in Croatia.

Keywords: DNA evidence, innocence project, wrongful convictions, genetic privacy, croatian legal reforms, European Court of Human Rights

FORENSIC DNA PHENOTYPING

Presentation number: FG 12 Abstract number: ABS-75-ISABS-2024

ASSESSMENT OF THE GENOTYPING AND PREDICTION PERFORMANCE OF PISNPS AND AISNPS USING FORENSEQ® DNA SIGNATURE PREP KIT

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The application of massivelly parallel sequencing (MPS) in forensic genetics has enabled the analysis of larger number and types of markers in a single multiplex assay. Development of single nucleotide polymorphisms (SNPs) genotyping technologies provided the prediction of externally visible characteristics and the inference of biogeographical ancestry based on genetic data that may be used as investigative lead. The ForenSeq® DNA Signature Prep Kit includes 24 phenotypic (piSNPs) and 54 ancestries informative (aiSNPs) with two markers common to both categories. The aim of this study was to assess the genotyping and prediction performance of piSNPs and aiSNPs using ForenSeq® DNA Signature Prep Kit (Verogen) with Primer Mix B on MiSeq® FGx Forensic Genomics System (Illumina). Genomic DNA was extracted from 83 buccal swabs according to the validated laboratory procedures. Libraries were prepared, pooled, and sequenced following the manufacturer's recommendations. Pooled libraries were quantified before sequencing using Qubit™ dsDNA HS Assay Kit and Qubit 3.0 Fluorometer (Thermo Fisher Scientific). Results were analyzed with ForenSeq Universal Analysis Software v.1.3 (UAS). Sequencing performance was assessed using UAS. Run metrics passed across all runs. The kit was able to produce complete piSNP and aiSNP genotypes using DNA inputs of positive control (PC2800M) from 1.0 ng down to 0.25 ng. As expected, SNP coverage imbalances became more significant with the reduction of the DNA input. Inter-replicate discordance was observed in terms of allele and locus drop-out. Reference- type samples showed a high call rate with the generally balanced heterozygous reads in piSNPs (0.85). However, sample-to-sample variation was observed for 9 piSNPs (<0.6) that may impact phenotype prediction. As a part of in-house validation, this study presents the application of piSNPs and aiSNPs genotyping and potential challenges in phenotype estimation.

Keywords: massively parallel sequencing, phenotype informative SNPs, ancestry informative SNPs, ForenSeq DNA Signature Prep kit, MiSeq FGx

Presentation number: FG 13 Abstract number: ABS-166-ISABS-2024

NEXT-GENERATION FORENSIC DNA TOOLS: A LEAP FORWARD IN CRIMINAL JUSTICE

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The field of forensic science is rapidly evolving, particularly in DNA phenotyping, which holds the promise of revolutionizing crime scene investigations. This technique allows for the prediction of a suspect's physical appearance based on associated genetic markers, thus providing a valuable tool when a DNA database for comparison is lacking. By integrating DNA evidence with crime methodologies, biogeographical ancestry, medical information, and familial genetic traits, DNA phenotyping can significantly aid criminal investigations. In Taiwan, there is a growing need for law enforcement agencies to become familiar with this technology. Through a comprehensive literature review, this paper discusses the intricacies of DNA phenotyping, its application alongside genetic technologies and databases, and the legal challenges that may arise in the future. The literature reveals that DNA phenotyping can construct predictive models of appearance, such as eye color, hair color, and skin tone, and refine these predictions with minor physiological features like eye spacing, nose width, earlobe formation, eyelid type, and thumb curvature. The accuracy of DNA phenotyping could be further enhanced by integrating it with national health care databases, which could narrow down investigation scopes, clarify case details, and greatly assist the criminal justice system in apprehending the true culprits or exonerating the wrongfully convicted. As this technology advances, it will be imperative to address the ethical and privacy concerns associated with accessing and utilizing personal genetic information.

Keywords: forensic science, DNA phenotyping, physical characteristics, genetic phenotypes, minor physiological features

GENETIC ANALYSIS OF FORENSIC NON-HUMAN MATERIAL

Presentation number: FG 14 Abstract number: ABS-26-ISABS-2024

WILDLIFE POISONING INVESTIGATION - THE IMPORTANCE OF USING MOLECULAR IDENTIFICATION METHODS IN THE INVESTIGATION PROCEDURES.

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The poisoning of wild animals continues to be one of the main methods of illegal killing. Recently, reports of poisoning by biological baits and poisoned carcasses of domestic animals have been increasing. This type of poisoning is mainly directed against predators such as foxes, jackals, and wolves, which cause damage to game in hunting areas, or against livestock kept outdoors, indirectly harming birds of prey that feed on poisoned carcasses. Investigating the facts and circumstances of such illegal killing is a complex investigation that necessarily requires the involvement of experts in the field of veterinary medicine and experts in the field of forensic investigation, research, and expertise, in addition to the action of the competent authorities. In addition to establishing the cause of death through the forensic veterinary examination and the presence of poison in the organs and tissues of the poisoned animal, the investigating authorities sometimes have an interest in determining the origin of the bait that served as the source of an excellent or individual identification. In the case that took place in January 2020, which the media called the case of Mazin poisoning, poisoning with carbofuran was confirmed in a fox (Vulpes vulpes) and a strictly protected species the wolf (Canis lupus) and the bald eagle (Aquila chrysaetos) in two separate incidents in different locations and in a time interval of 14 days. In both cases, cattle carcasses were used as bait, which was confirmed by molecular identification of stomach content samples from fox, wolf, and bald eagle by determining species-specific polymorphisms on the cytochrome b (cyt b) and cytochrome c oxidase subunit I (COI) genes. In addition, each individual was genotyped to determine a unique DNA profile assessment of the Thermo Scientific Bovine Genotypes Panel 3.1 Kit panel of 12 STRs to determine the calves possible connection to the cow and connection to the potential herd.

Keywords: wildlife poisoning, baits, carbofuran, DNA barcoding, ST

Presentation number: FG 15 Abstract number: ABS-88-ISABS-2024

A META-ANALYSIS OF DNA EXTRACTION METHODS IN FORENSIC SCIENCES

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This study presents the findings of a meta-analysis conducted in February 2024, focusing on DNA extraction methods from human and animal samples within the field of forensic sciences. Utilizing the Web of Science database, we systematically searched for papers using the keywords "DNA extraction" OR "DNA isolation" AND "forensic*" covering the period from 2013 through 2023. The analysis included 491 papers from 14 high-ranking journals in the field of Forensic Sciencesof, of which 313 articles met the requirements of our meta-analysis, the rest of the articles were excluded mainly because of missing or insufficiently described methodology, or because the article referred to the source of another article that was no longer available. We carefully examined and summarized the most frequently utilized extraction kits and methods. This comprehensive review offers valuable insights into the current landscape of DNA extraction practices, shedding light on the predominant approaches employed in forensic investigations. The results of this meta-analysis serve as a useful resource for forensic scientists, aiding in the selection of optimal DNA extraction techniques for a wide range of sample types.

Keywords: extraction kits, forensic samples, tissue, swabs

GENOME-BASED APPLICATIONS IN FORENSIC SCIENCE

Presentation number: FG 16

Abstract number: ABS-141-ISABS-2024

COMPARISON OF FST AND RST COEFFICIENT OF GENETIC DIFFERENTIATION IN THE ANALYSIS OF POPULATION SUB-STRUCTURE

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Coefficient of genetic differentiation, F_{ST}, is a measure of population differentiation due to genetic structure. The analog coefficient, R_{ST}, adapted to microsatellite data, is also used. The aim of this study was to perform a meta-analysis of synthesized data and investigate the influence of specific intrapopulation genetic structures on interpopulation relationships. Special focus was the influence of island population isolation on the substructuring of the Croatian population, and the influence of regional population groups on the substructuring of Southeast Europe. Autosomal STR loci of microsatelite DNA were analyzed in the sample of 590 non-related adult individuals of insular (Cres, Ugljan, Pašman and Dugi Otok) and continental populations of Croatia (Baranja) and Slovenia were integrated with the data on 952 individuals available at the Institute for Anthropological Research, and the data on 1335 individuals available from the database for South-Eastern Europe. The calculation of F_{ST} and R_{ST} coefficient of genetic differentiation was performed using the statistical package Arlequin version 3.5.1.2. software. Finally, we performed comparison of F_{ST} and R_{ST} coefficient of genetic differentiation at aforementioned levels. Based on two mentioned coefficients of genetic differentiation lower genetic differentiation was detected at the higher level of grouping of SE European populations (F_{ST}/R_{ST} = 0,002) than at the level of sub-populations of Croatia (F_{ST}/R_{ST} = 0,005), due to the decreased influence of endogamy. The comparison of F_{ST} and R_{ST} coefficient between different (sub)populations of Croatia and Southeast Europe indicates that the specific features of (sub)populations and certain rare alleles in their gene pool affects the values of this statistical parameters.

Keywords: STRs, genetic sub-structuring, coefficient of F_{ST}, R_{ST}, Croatia, Southeast Europe

ANTHROPOLOGICAL GENETICS

ANCIENT DNA

Presentation number: AG 01 Abstract number: ABS-49-ISABS-2024

DIMINISHED PREVALENCE OF THE CURRENTLY PREDOMINANT CROATIAN Y HAPLOGROUP IN THE EARLY MIDDLE AGES

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Y haplogroup I2a2-M423 is a Paleolithic European marker most abundant in modern-day Bosnia and Herzegovina (over 55%), Croatia, and Serbia (around 40%). It was initially suggested that the halogroup survived the last Ice Age in refugial areas in Southeastern Europe and the Balkan Peninsula. However, more recent research introduced the possibility that it might have arrived in this region during later medieval migrations associated with the influx of Slavs and other populations and that it became dominant more recently. The objective of this study was to test if the I2a2 haplogroup is present at the early medieval Jagodnjak site (6-9th century CE), located in present-day Croatia and to compare obtained results with a more extensive, publicly available aDNA database (samples spanning from 1st to 15th century CE). Laboratory work was performed at the Department of Evolutionary Anthropology, University of Vienna. Shotgun sequencing of 9 male individuals was performed on Illumina NextSeq500 platform, and Yleaf program was used to infer Y hgs based on ISOGG nomenclature. Paternal genetic diversity in the sample was high, but the sample lacked I2a2 individuals. Half of males were assigned to the typical, local E1b1 hg and second most prevalent hg was R1a1a (33%), previously associated with Slavic migrations in Southeastern Europe. The more extensive database encompassed only 3.9% I2a2 carriers, from which only one was dated to a period preceding 6th century CE, indicating almost complete absence of I2a2 individuals in older historic periods. This preliminary finding provides an additional overview on the history of the Croatian territory, which should be more comprehensively analyzed by examining additional archaeological skeletal remains (possibly from older historical periods) as imperative to make evidence- based conclusions on the I2a2 origin and diversity in this region.

Keywords: aDNA, Y chromosome, I2a2 haplogroup, Middle Ages

Presentation number: AG 02 Abstract number: ABS-39-ISABS-2024

ANCIENT DNA PATERNITY TESTING AND KINSHIP ANALYSIS REVEALED FATHER – SON RELATIONSHIP IN TWO CASES OF CONGENITAL BUTTERFLY VERTEBRAE ANOMALY IN THE LATE AVAR POPULATION

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Recent methodological advances in sequencing technologies and ancient DNA extraction protocols from skeletal remains opened a window for direct insight into the past of human populations. Here we present an archeogenetic analysis of 43 individuals from the late Avar population (8th century) in the Šarengrad Klopare site from Eastern Croatia. The aim was to compare bioarcheological analysis of human remains with genetic findings to gain deeper insight into their social organization, health and genetic history. Extraction of aDNA and library preparation were performed in dedicated clean aDNA facilities. Sequencing was performed on Illumina NextSeq500 platform. Haplogrep2 was used to assign mtDNA haplogroups, and Yleaf program to infer Y haplogroups. Kinship analysis up to the 4th degree of ancestry was estimated using the READ and TKGWV2 methods. Bioanthropological examination of this population showed an absence of intentional perimortem injuries. At the same time, kinship analysis revealed the presence of at least four families with up to four degrees of relatedness, both pointing to the continuation of living on this territory for a more extended period. Some burials suggested social stratification, particularly in several traditional horseman graves. One was an adult male (grave 25) with an interesting finding of a congenital anomaly called butterfly vertebra. The same anomaly was found in a young adolescent (grave 21). In both cases, the malformation was located on the 4th lumbar vertebrae. Kinship and Y chromosome analysis confirmed that these two individuals were father and son, belonging to the southern European Y haplogroup E1b1b1a1b1a. Their mitogenome analysis also revealed European haplogroups, T1a and H46, all pointing to mixing with local communities over a longer period. This finding emphasizes the importance of using ancient DNA analysis to shed light on ancient populations' genetic ancestry and health with little or no written historical record.

Keywords: ancient DNA, kinship analysis, Y chromosome, butterfly vertebrae, Avars

Presentation number: AG 03 Abstract number: ABS-92-ISABS-2024

THE ECHOES OF ANCIENT DNA: UNCOVERING CONNECTIONS TO MODERN SOCIETIES AND CULTURAL DESCENDANTS

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The goal of this study is to examine the relationship between ancient human remains, their genetic legacy, and the modern social groups claiming ancestral rights to these relics. It aims to trace genetic lineages across millennia, amidst substantial cultural shifts, to determine connections between ancient remains and contemporary (indigenous) communities. The study involves the critical examination of bioarchaeological research of ancient human remains and their DNA with a particular focus on the legal and ethical dimensions of such work. The research reveals that claims of autochthonous groups to ancient skeletal remains represent a contentious issue that intersects science, history, religion, ethics, and identity. It underscores the need for a balanced approach that respects both scientific inquiry and cultural heritage. The ethical and legal dimensions of researching ancient remains and DNA are scrutinized, emphasizing the sensitive nature of such research and the potential for misuse. Research on ancient DNA and ancient human remains underscores the need for a balanced approach that respects both scientific inquiry and cultural heritage, paving the way for more responsible and inclusive practices in exploring of our shared human past.

Keywords: human skeletal remains, bioarchaeology, ancient DNA, genealogical descendants, cultural descendants

MIGRATION HISTORY

Presentation number: AG 04 Abstract number: ABS-105-ISABS-2024

INVESTIGATING RUNS OF HOMOZYGOSITY IN NEAR OCEANIC POPULATIONS

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Populations from Oceania are underrepresented in genomic studies and many questions about their population-specific variation and demographic history remain unanswered. To fill this gap, we sequenced 177 new Near Oceanic genomes from 12 geographically diverse populations and used this data to examine population-specific patterns in runs of homozygosity (ROH) and characterize their physical distribution along the genome to identify ROH hot and cold spots. While ROH are found in all human populations, variation in the length distribution of ROH and patterns of non-uniform ROH distribution across the genome can provide insight on the demographic and evolutionary processes that result in differences in genome-wide genetic diversity among populations. Our results show that lengths and total sum of ROH segments differed greatly between Near Oceanic populations, suggesting a complex demographic history of population structure and corroborating previous findings of population bottlenecks within Near Oceania.

Keywords: Oceania, runs of homozygosity, human population genetics, genomics, population history

Presentation number: AG 05 Abstract number: ABS-145-ISABS-2024

MOLECULAR ANTHROPOLOGICAL STUDY OF THE INDIAN OCEAN LITTORAL, FROM AUSTRO ASIATIC TO AUSTRONESIAN DISPERSAL, ACROSS THE PACIFIC

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The Indian Ocean region is a critical route/corridor/barrier for the migration and settlement of people whose social, linguistic, and genetic ancestry is of interest to anthropologists worldwide. Varying from the 'little tradition' of small, isolated populations to the 'great tradition' of global and admixed heritage, in the field of collating evidence from culture, language and anthropological genetics this paper will examine the 'Austro Asiatic and Austronesian dispersal' within the boundaries of the Indian ocean sporadically sprinkled across Pacific islanders. Littoral or near shore settlements may have simply act as 'gateways' as would have been the case with pre-historic settlements somewhere near a fresh water source or riverbank. Physical environmental changes such as those driven by drastic ecological catastrophes including severe and acute adaptations to climatic and nutritional stressors can leave signatures providing vital clues for the dispersal of humankind. During the last two decades or more, a plethora of genomic information has surfaced tracing the genetic history of an archaic hominin group from ancient DNA. In the light of ensuing works by palaeoanthropologists and evolutionary biologists, the dispersal and migration of people, genes and languages studying human history either directly through their remains or indirectly through tools, pottery or other cultural items have provided concerns over interpretation of archaeological dates. Similarly assessing the reliability of linguistic data which may favor a close correlation between genes and languages, yet at times appear to conflict with genetic evidence. From single versus multiple dispersal models' molecular anthropologists have re-examined hypotheses about the colonization of the Pacific with different pliable approaches to understand population histories in the context of the 'Austronesian dispersal' across the Pacific. Is the Austro-Asiatic element be related in anyway via the south routes?

Keywords: Molecular anthropology, genetic, linguistic, archaeological, migration, dispersal, Austro- Asiatic, Austronesian, Indian Ocean, Pacific

Presentation number: AG 06 Abstract number: ABS-175-ISABS-2024

ACCURACY OF THE ANGLE OF THE GREATER SCIATIC NOTCH IN THE ESTIMATION OF SEX IN THE ALGERIAN POPULATION

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This study aims to evaluate the precision of sex estimation by the angle of the Greater Sciatic Notch (GES) on an Algerian adult sample. 123 "virtual" left iliac bones (62 men and 61 women, aged between 18 and 86 years), were included after agreement from the Scientific Council and anonymity of the sample. The bones were obtained from three-dimensional reconstructions of clinical abdominopelvic scans, carried out during 2018. The angle of the GES (the total angle) was quantified by referring to three metric landmarks. The results show that the GES angle is wider in women. The female mean was 76.6°±6.6 (62°-92°) and the male mean was 62.2°±6.8 (47°-81°). A significant metric difference was observed between the female and male sample ($p<0.001$). An overall correct sex classification rate of 87.8% was obtained by the metric method using one section point. Differences between populations emerge from the comparison of the results obtained in similar works. In conclusion, this study revealed a significant metric sexual dimorphism of GES in the Algerian population and offers specific standards that can be used in forensic cases. Other studies using larger samples will make it possible to refine the results obtained.

Keywords: forensic anthropology, sex estimation, metric method, large sciatic notch

GENETIC ADAPTATION

Presentation number: AG 07 Abstract number: ABS-78-ISABS-2024

CORTISOL LEVELS IN PREGNANT WOMEN ON ISLANDS AND MAINLAND

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The term "stress" describing a state of emotional or physical tensions and exhaustion, is commonly encountered in contemporary discourse. It is a well-established fact that periods of stress lead to dysregulation of the hypothalamic- pituitary-adrenal (HPA) axis resulting in elevated levels of serum cortisol, often referred as the “stress hormone” which plays a pivotal role in various metabolic and immunomodulatory processes. The main goal of this study was to detect and compare cortisol levels in pregnant women in relation to place of living: mainland vs islands. The underlying assumption is that differences in adaptation related with place of living may influence stress hormone levels. The research was conducted using data collected during the implementation of the "Croatian Island's Birth Cohort Study (CRIBS)" project, aimed at elucidating factors related to metabolic syndrome, which increasingly affects a significant part of the population. The analyzed samples consisted of plasma specimens collected from healthy pregnant women residing in Split-Dalmatia County (Croatia). An analytical protocol for the determination of cortisol in human plasma by High-performance liquid chromatography (HPLC) was implemented. The study revealed that maternal cortisol levels were statistically higher in pregnant women residing on islands compared to those living on the mainland ($p=0,046$). Additionally, irrespective to the place of residence, in the CRIBS study, higher cortisol levels were observed in women who carried a female fetus. These differences in maternal cortisol levels show that place of residence influences stress levels, further research into the factors that induce this difference is needed.

Keywords: cortisol, stress, HPA, pregnancy, islands

Presentation number: AG 08 Abstract number: ABS-39-ISABS-2024

POLYMORPHISMS OF THE LACTASE PERSISTENCE VARIANT IN LCT GENE IN THE CROATIAN ROMA POPULATIONS

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One significant step in human adaptation that connects genetic evolution, and the evolution of dairying is the ability of some adults to digest milk. Enzyme lactase – responsible for breaking down the milk sugar lactose into glucose and galactose – declines after 5th year of age, leading to adults' lactose intolerance. However, in some human populations, lactase activity persists into adulthood. The frequency of lactase persistence (LP) variants globally varies greatly, ranging from 0% to almost 100%. Roma minority population in Croatia belong to two large groups: the Vlax/Bayash Roma, descendants of Roma who lived in captivity (mostly forced to work in mines) in Wallachia and Moravia (now Romania) from the 14th century until 1850, and the Balkan Roma, descendants of groups who traditionally lived as nomads. Since none of these lifestyles allowed for the basic care of livestock, just like the lifestyle of their ancestral population in India had not as well, these Roma groups are not expected to be under selective pressure for LP. Two genotypes associated with the LP phenotype, -13910C>T (rs4988235) and -13915C>T (rs41380347) in the lactase gene (LCT), were determined using KASP method in Vlax Roma living in Baranja and Međimurje (n =252) and in a group of Balkan Roma living in Zagreb (n=171). The results showed very low allele frequency for LP variant LCT-13910T and the absence of LCT-13915T variant in the Croatian Roma population. There were only two carriers of LCT-13910TT genotype, and T allele prevalence differed between the three Roma groups; there was significantly more T allele carriers in Međimurje (13.5%), than in Baranja (6.7%) or Zagreb Roma (4.1%) ($p<0.001$). Considering the average European frequencies of the LCT-13910T allele are as high as 63.5% (GnomAD database, n = 55,000), those found in the Croatian Roma populations are exceptionally low, indicating that Roma ancestors were not under selection pressure for the lactase persistence in adulthood.

Keywords: lactose intolerance, lactase persistence, LCT gene, rs4988235, Roma population

Presentation number: AG 09 Abstract number: ABS-89-ISABS-2024

HEFNER'S ANCESTRY-SPECIFIC TRAITS ON THE EASTERN ADRIATIC COAST POPULATIONS: FROM MIDDLE AGES TO CONTEMPORARY PERIOD

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To compare frequencies of Hefner's morphological cranial traits for ancestry estimation in the medieval and modern population sample from the Eastern Adriatic coast. The sample consisted of 140 medieval dry skulls from two archaeological sites, Velim Velištak and Radašinovci (7th – 9th century), housed in the Croatian Academy of Sciences and Arts and 195 multi-sliced computed tomography (MSCT) scans collected from the University Hospital Center in Split. Dry skulls and MSCT scans were scored for nasal overgrowth (absent or present), anterior inferior nasal spine (score 1 – 3), post bregmatic depression (absent or present), interorbital breadth (score 1 – 3), nasal breadth (score 1 – 3), shape of the zygomaxillary suture (score 1 – 3), and malar tubercle (score 1 – 3). We calculated and compared frequencies between samples using a Chi-squared test with a statistical significance level set at $P \leq 0.05$. Frequencies of all traits showed statistically significant differences ($P < 0.05$), except for the nasal breadth ($\chi^2 = 0.308$, $P = 0.857$). The study results demonstrated significant differences between populations from the Eastern Adriatic coast that could arise from the possible secular changes and population dynamics through the millennium timespan. However, further studies should examine the genetic admixtures through the centuries, as well as expand the sample to in-between periods to detect the time frame when these changes first occurred.

Keywords: Hefner's morphological traits, population differences, early medieval period, modern population, Eastern Adriatic coast

ABSTRACTS OF THE 9TH CROATIAN HUMAN GENETICS CONFERENCE & 2ND CROATIAN PERSONALIZED AND PRECISION MEDICINE CONFERENCE

ORAL PRESENTATIONS

Presentation number: CSHG TM-1 Abstract number: ABS-14-ISABS-2024

SPECTRUM OF GENETIC VARIANTS IN 306 PATIENTS WITH NON- SYNDROMIC HEARING LOSS FROM CROATIA

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A major challenge in the study of congenital non-syndromic hearing loss (NSHL) is extreme genetic heterogeneity, whereby the same or very similar clinical phenotype is the result of pathogenic variants in a significant number of genes. Next-generation sequencing strategies, such as clinical exome sequencing (CES), have significantly contributed to the diagnosis of genetically and clinically heterogeneous conditions, including hereditary hearing loss (HL). Aim: To report the spectrum and frequency of disease- causing variants detected in 306 unrelated patients with childhood-onset mild to profound NSHL referred to Children's Hospital Zagreb for genetic testing in the period between March 2006 and October 2023. Methods: Multiplex ligation–dependent probe amplification method and Sanger sequencing of the coding region of the GJB2 gene were used for the analysis of the GJB2 variants in all subjects. CES was performed in 21 patients negative for GJB2 biallelic variants. Results: Among 234 disease associated GJB2 alleles detected, there were 19 different clinically relevant GJB2 variants, of which 18 were reported as pathogenic/likely pathogenic. The c.35delG was by far the most common variant, accounting for 73.5% of mutated alleles. More than half of the patients (64/110, 58,2%) with biallelic GJB2 variants were 35delG homozygotes. Seventeen non-GJB2 variants were found in 10 genes (TECTA, NOG, SLC26A4, PCDH15, TMPRSS3, USH2A, GATA3, MYO15A, SOX10, COL2A1) in 11 subjects, and five variants (in TECTA, NOG, PCDH15 and SOX10) were novel (29,4%). Conclusion: By targeted GJB2 molecular screening and CES analysis, we were able to elucidate the genetic cause of HL in 121 patients, resulting in an overall diagnostic rate of 39.5%. CES allowed us to distinguish NSHL from the syndromic form of HL in cases where the phenotype was unclear or where symptoms were absent from an early age.

Keywords: Non-syndromic hearing loss, NSHL, GJB2, Clinical exome sequencing, syndromic HL

Presentation number: CSHG TM-2 Abstract number: ABS-87-ISABS-2024

THE DIAGNOSTIC JOURNEY OF CHROMATIN REMODELING DISORDERS

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Advances in genome sequencing technologies led to discovering of more than a thousand new genes and variants involved in NDDs (neurodevelopmental disorders) pathogenesis. Chromatin dynamics play key role in various developmental processes and their dysregulation is often linked to abnormal neurodevelopment causing chromatin remodeling disorders (CRDs). Due to their overlapping clinical features, and lack of molecular genetic data knowledge they present significant diagnostic challenge in routine clinical practice. For this study, we analyzed 29 patients from our cohort of NDD-s patients whose initial clinical features and molecular genetic testing results were suggestive on CRDs. Initial diagnostic evaluation included family tree analysis, description of clinical features, routine laboratory and radiological evaluation, hearing, vision, and developmental assessment. Phenotype abnormalities were annotated to specific HPO (Human Phenotype Ontology) terms. Clinical exome sequencing has been performed using Illumina TruSight One Kit. Data interpretation performed according to databases: USC Genome Browser, Decipher, PubMed, ClinVar, Varsome, OMIM. Initial exome sequencing results confirmed pathogenic variants in 12 patients: Charge syndrome (2), Kabuki (2), Coffin-Siris (4), Snijders Blok-Campeau (1), Kleefstra (1) and CHD8 -related disorder (2). In the remaining patients additional evaluation included: parental genetic testing, reanalysis of previously sequencing data, repeated clinical evaluation, reverse phenotyping and additional genetic testing (arrayCGH) confirmed CRDs in three patients: Kabuki (1), Cornelia de Lange (1), and KMT5B (1) related CRDs. Our approach emphasizes the importance of comprehensive approach to the diagnostics of CRDs patients combining clinical and molecular genetic approach. Unsolved patients require additional analysis: epigenetic signature and whole genome sequencing studies and specific expertise from collaborative rare disease studies.

Keywords: chromatin remodelling disorders, neurodevelopmental disorders, comprehensive approach, rare disease studies

Presentation number: CSHG TM-3 Abstract number: ABS-130-ISABS-2024

THREE CASES OF FIBRO-DYSPLASIA OSSIFICANS PROGRESSIVE WITH EXTRA LONG-TERM FOLLOW-UP

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Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare and severely disabling genetic disorder. The worldwide prevalence is approximately 1 per 2 million. Heterozygous mutations in ACVR1/ALK2 gene exist in all sporadic and familial cases of FOP. The primary aim of this study is to describe the clinic and management of three children suffering from FOP and followed for nineteen, twenty-three and forty years, respectively. Secondary aim is to provide clinical advice on how to diagnose the condition with special reference to the great toes malformation and give current best therapeutic approaches, including controversial issue of surgery. The three cases characterized with malformed great toes initially followed by progressive loss of mobility for a period from nineteen to forty years. Two of three patients presented here had surgical intervention according to specific indication. Additional attention is given to the natural history of the great toe malformation and stepwise decrease of patients' mobility status. Conventional radiology indicates the diagnosis and RNA/DNA test confirm it. Short and valgus deformity of the great toe combined with progressive heterotopic ossifications in the soft tissue is "almost" pathognomonic for FOP, but the RNA/DNA testing of the ACVR1 gene is strongly recommended to confirm diagnosis. Long-term natural history and the fate of the great toe malformation shows influence on mobility status in patients with FOP. Maintaining of the best possible mobility status is of utmost important goal of conservative supporting treatment and even in selected cases surgical intervention. However, prevention of any trauma, of soft tissue including intramuscular injection is recommended.

Keywords: *Fibrodysplasia ossificans progressiva*, FOP, great toe, surgery, case report

Presentation number: CSHG TM-4 Abstract number: ABS-120-ISABS-2024

A RETROSPECTIVE STUDY OF DIAGNOSTIC NEXT GENERATION SEQUENCING AT THE UNIVERSITY OF RIJEKA, FACULTY OF MEDICINE, CROATIA FROM 2018 TO 2023

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Next generation sequencing (NGS) is becoming increasingly implemented in various medical specialties for the purpose of diagnostic genetic testing. Considering the complexity and time-consuming efforts of this method, identifying patients with appropriate indications is an imperative. Therefore, the aim of this study was to determine the number, indications, and results of diagnostic NGS testing performed at the University of Rijeka, Faculty of Medicine, since its implementation. A retrospective study was conducted from years 2018 to 2023 to analyse the indications for patient referral for diagnostic NGS testing from the Clinical Hospital Centre Rijeka to the Faculty of Medicine in Rijeka, as well as subsequent test reports. All NGS tests were performed in collaboration with the Clinical Institute for Genomic Medicine in Ljubljana using Illumina NovaSeq 6000 (Illumina Inc). From April 2018 to December 2023, 355 diagnostic NGS tests were performed, with 15.5 times increase in the number of ordered tests. The most common specialists who referred patients for diagnostic NGS were paediatricians (55%), neurologists (29%), internists (7%), ophthalmologists (3%), gynaecologists (2%), and others (4%). Referral diagnoses were confirmed in 110/355 (31%) of cases, in whom likely pathogenic 34/110 (31%) or pathogenic sequence variants 76/110 (69%) were detected. Variants of uncertain significance were identified in 36/355 (10%) cases. Genetic counselling was provided to 21% of patients with class 3-5 sequence variants (30/146, 21%). Our results show an increase in the number of diagnostic NGS tests from 2018 to 2023, reflecting the raised awareness of clinicians for the need of genomic testing in clinical practice. The prevalence of confirmed referral diagnoses and numbers of genetic counselling might additionally be increased by implementing further efforts in genetic education of clinicians.

Keywords: diagnostic genetic testing, genetic education, genomics, next generation sequencing

Presentation number: CSHG TM-5 Abstract number: ABS-119-ISABS-2024

PHARMACOGENOMICS: CHALLENGES AND OPPORTUNITIES

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In the era of precision medicine, pharmacogenomics (PGx), among other "omic" disciplines, has an inevitable role. It helps predict drugs' efficacy, tolerability, and safety and should guide clinical decision- making to optimize therapy outcomes. The genes affecting a drug pharmacologic profile, i.e., those encoding metabolizing enzymes and transporters, as well as drug targets and some proteins associated with safety, are the most often analyzed. According to the highest level of clinical evidence, genotype- guided therapeutic recommendations for various drugs from different therapeutic classes are incorporated into the clinical guidelines, like those published by the Clinical Pharmacogenetics Implementation Consortium. However, a classical approach based on the genotyping pre-defined panel of selected functionally characterized gene variants does not completely predict the inter-individual variability in the drug pharmacokinetics and pharmacodynamics, i.e., its efficacy and safety. Therefore, broader approaches such as next-generation sequencing are needed to identify rare gene variants. It is also time to look into the entire human genome to detect genetic variants in coding and non-coding regions and structurally complex variants. These novel comprehensive tools implementation into the clinical practice is a key to diagnostic and therapeutic outcomes improvement. Another challenge represents understanding and applicability of large amounts of generated information. Artificial intelligence is a potent tool for "big data" analysis because it helps understand the heterogeneity in processes that contribute to the individualized genetic-tailored therapeutics approach, leading to better quality and more cost-effective healthcare. However, these goals are achievable only with continuous education of all those involved in providing patient care to keep pace with the rapidly evolving field of pharmacogenomics.

Keywords: pharmacogenomics, gene polymorphisms, drug-gene interactions, precision medicine

Presentation number: CSHG TM-6 Abstract number: ABS-127-ISABS-2024

GENOTYPE AND PHENOTYPE VARIABILITY OF SEVEN PATIENTS WITH GLUCOSE TRANSPORTER TYPE 1 DEFICIENCY SYNDROME

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Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare neurometabolic disease caused by pathogenic mutations in the SLC2A1 gene, resulting in impaired glucose delivery through the blood-brain barrier and insufficient brain energy production. The disease presents with a phenotypic continuum that includes various types of early-onset seizures and complex movement disorders. This retrospective case study included seven patients with GLUT1-DS followed at the Department of Pediatrics, University Hospital Centre Zagreb. The onset of the first symptoms started between 2 months and 5 years of age, with a median of 13 months. Four patients had seizures, one had episodic eye-head movements, and two had paroxysmal dyskinesia as the presenting signs. Two patients with epilepsy later developed dyskinesias. Clinical suspicion of GLUT1-DS was raised in three patients in whom the diagnosis was made after a hypoglycorrhachia finding and confirmed by gene testing subsequently. Four patients were diagnosed through next-generation sequencing (NGS). The delay in diagnosis from the first symptom was 0.5 to 15 years, with a median of 6 years. A ketogenic diet was commenced in all the patients to provide an alternative energy source for the brain, which alleviated symptoms and improved EEG in most of them. At the follow-up, five patients had mild cognitive problems. The best outcome was in two patients diagnosed and treated earlier, which may be biased due to shorter follow-up. GLUT1-DS should be suspected in patients with complex movement disorders, early-onset seizures, and drug-resistant epilepsies. Hypoglycorrhachia is a biochemical hallmark. The diagnosis is made or confirmed by gene testing. More patients are diagnosed through NGS, yet a significant diagnostic delay remains. The ketogenic diet is the only disease-specific treatment that improves patient outcomes.

Keywords: Glucose transporter type 1 deficiency syndrome, epilepsy, paroxysmal dyskinesia, hypoglycorrhachia, next-generation sequencing, ketogenic diet

Presentation number: CSHG TM-7 Abstract number: ABS-123-ISABS-2024

INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES FOR PRECISION MEDICINE IN PATIENTS AFFECTED BY INHERITED CARDIAC CHANNELOPATHIES

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Precision Medicine (PM) is an innovative approach that, by relying on large population datasets, patient genetics and characteristics, and advanced technologies, aims at improving risk stratification and at identifying patient-specific management through targeted diagnostic and therapeutic strategies. Cardiac channelopathies are being progressively involved in the evolution brought by PM and some of them are benefiting from these novel approaches, especially the long QT syndrome. We will explore the main layers that should be considered when developing a PM approach for cardiac channelopathies, with a focus on modern in vitro strategies based on patient-specific human-induced pluripotent stem cells. PM is where scientists and clinicians must meet and integrate their expertise to improve medical care innovatively but without losing common sense. In my talk, I will provide the cardiologist's point of view by comparing state- of-the-art techniques and approaches, including revolutionary discoveries, to current practice. This point matters because the new approaches may, or may not, exceed the efficacy and safety of established therapies. Thus, our eagerness to implement the most recent translational strategies must be tempered by an objective assessment to verify whether the PM approaches are indeed making a difference for the patients. PM may shape the diagnosis and treatment of cardiac channelopathies for years to come. Nonetheless, its potential superiority over standard therapies should be constantly monitored and assessed before translating intellectually rewarding new discoveries into clinical practice.

Keywords: Induced pluripotent stem cells, cardiomyocytes, precision medicine, inherited cardiac channelopathies, personalized therapies

Presentation number: CSHG TM-8 Abstract number: ABS-171-ISABS-2024

IMPLEMENTING WHOLE GENOME SEQUENCING (WGS) IN CLINICAL PRACTICE

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The integration of whole genome sequencing (WGS) into clinical practice represents a transformative shift in personalized medicine. Unlike the analysis of individual genes, gene panels, and whole exome sequencing (WES), WGS enables the detection of variants in deep intronic and non-coding regions of the genome that have an essential role as regulatory regions of the genome. Additionally, WGS allows for the simultaneous detection of not only SNPs and InDels but also structural variants (SVs) and copy number variants (CNVs). Thus, WGS is becoming the test of choice in diagnosing rare diseases, predicting treatment responses, and guiding therapeutic decisions in clinical practice. The value of WGS lies in its ability to provide not only diagnostic but also pharmacogenetic and nutrigenetic analyses, enabling evidence-based drug dosing and the issuance of nutritional guidance based on the nutrigenetic profile of each patient to prevent the most common multifactorial diseases of today, including obesity, diabetes, and cardiovascular diseases. Moreover, WGS facilitates the identification of novel disease-associated genes involved in the development of cancer, enabling more precise treatment, genetic counseling, and family planning in the case of hereditary cancer syndromes. The implementation of machine learning methods in the clinical interpretation of variants of uncertain significance (VUS) and for molecular classification of specific tumor types now enables personalized and precise oncological treatment that improves the prognosis of patients with cancer. Looking ahead, advancements in WGS technologies, coupled with enhanced data analysis techniques and machine learning models, promise to further optimize its clinical utility, and broaden its accessibility, ultimately revolutionizing the field of modern medicine.

Keywords: whole genome sequencing, personalized medicine, artificial intelligence, machine learning, oncogenomics

Presentation number: CSHG TM-9 Abstract number: ABS-175-ISABS-2024

INSIGHTS IN OSTEOSARCOMA EVOLUTION BY SINGLE-CELL RNA SEQUENCING

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Tumor evolution and intratumor cell heterogeneity are deeply intertwined. Each time a tumor cell divides, new alterations of the genome are acquired resulting in tumor heterogeneity. That is a prerequisite for the selection of the fittest cell clones driving the evolution of the tumor resulting in treatment resistance, tumor relapse and development of metastases. To follow tumor evolution, we implemented single cell sequencing and analyzed transcriptome data from 3 osteosarcoma cell culture samples derived from the same patient at the stage of diagnosis, post-chemotherapy and relapse. The 18-year-old male was diagnosed with chondrobastic osteosarcoma (G3) of the femur. After 7 cycles of preoperative chemotherapy according to the EURAMOS protocol, the tumor was resected. This was followed by 12 cycles of postoperative chemotherapy. Due to the recurrence, an additional resection was performed. Tissue samples were seeded in the cell culture dish and passage 3 cells were processed using 10x Genomics technology. Processing raw reads with the Cell Ranger pipeline resulted in more than 92% of reads confidently mapped to the human genome (GRCh38). After quality control with the Seurat package, the cells were annotated using reference-based annotation methods which revealed distinct populations of mesenchymal stromal cells and stromal cells like fibroblasts. At the time of diagnosis, both fibroblast and mesenchymal stromal populations showed higher metabolic activity. Immediately after post-chemotherapy, they induced strong inflammatory, self-renewal pathways, and even apoptotic pathways. After relapse, cells induced self-renewal, hypoxia, epithelial-mesenchymal transition (EMT) signaling but also proliferation pathways.

Keywords: osteosarcoma, single-cell sequencing, tumor heterogeneity, tumor evolution, chemotherapy

Presentation number: CSHG TM-10 Abstract number: ABS-108-ISABS-2024

EXPRESSION PATTERN OF PDE4B, PDE4D AND SFRP5 MARKERS IN THE COLORECTAL CANCER

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Colorectal cancer (CRC) is the most frequently diagnosed malignant disease of the gastrointestinal system and new diagnostic and prognostic markers are needed to elucidate complete tumor profile. We used CRC tumor tissues (Dukes A-D) and adjacent noncancerous tissues of 43 patients. Immunohistochemistry was used to examine the expression of PDE4B, PDE4D and SFRP5 markers. In CRC stages, the distribution of PDE4B positive cells varied, with differing percentages between epithelium and lamina propria. Statistically significant differences were found in the number of PDE4B positive epithelial cells between healthy controls and all CRC stages, as well as between different CRC stages. Similarly, significant differences were observed in the number of PDE4B positive cells in the lamina propria between healthy controls and all CRC stages, as well as between different CRC stages. CRC stage Dukes' C exhibited a significantly higher number of PDE4B positive cells in the lamina propria compared to CRC stage Dukes' B. Significant differences were noted in the number of PDE4D positive epithelial cells between healthy controls and CRC stages Dukes' A, B, and D, as well as between CRC stage Dukes' C and stages A, B, and D. CRC stage Dukes' A had significantly more PDE4D positive cells in the lamina propria compared to stage D. Significant differences were also observed in the number of SFRP5 positive cells in the lamina propria between healthy controls and all CRC stages, as well as between CRC stages Dukes' A and D. While the expression of PDE4D varied across CRC stages, the expression of SFRP5 remained consistently strong in both epithelium and lamina propria, with significant differences noted mainly in the lamina propria. These findings suggest alterations in PDE4B, PDE4D and SFRP5 expression during CRC progression, as well as between different stages of CRC with potential implications for understanding the molecular mechanisms involved in CRC development and progression.

Keywords: colorectal cancer, PDE4B, PDE4D, SFRP5

Presentation number: CSHG FG-1 Abstract number: ABS-35-ISABS-2024

IDENTIFICATION OF SKELETAL REMAINS IN CROATIA AND BOSNIA & HERZEGOVINA, INCLUDING THE HOMELAND WAR – A 30-YEAR REVIEW

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Over the past 30 years, forensic experts from Croatia and Bosnia and Herzegovina have embraced advanced technologies and innovations to enable great efficacy and proficiency in the identification of war victims. The wartime events in the countries of former Yugoslavia greatly influenced the application of the selection of DNA analyses as routine tools for the identification of skeletal remains, especially those from mass graves. Initially, the work was challenging because of the sheer magnitude of the events, the technical aspects, and the political aspects. Collaboration with reputable foreign forensic experts helped tremendously in the efforts to start applying DNA analysis routinely, our deep involvement significantly contributed to the further improvement of DNA analysis methods, making DNA identifications increasingly successful. We strove to improve through collaboration and experiences gained, and most importantly being driven by the numerous missing persons' families that had high expectations of us. While the work we did was published in scientific journals, the invaluable information and experience we attained are still significant today. Therefore, in this abstract, we wanted to provide a brief overview of the history and the most significant achievements related to the application of DNA analysis in identifying skeletal remains in situations where standard identification methods were insufficient.

Keywords: DNA identification, skeletal remains, Homeland War, Croatia, Bosnia & Herzegovina

Presentation number: CSHG AG-1 Abstract number: ABS-10-ISABS-2024

THE GENETIC SCENARIO OF HISTORICAL HUMAN MIGRATIONS IN SOUTH-EASTERN EUROPE – THREE DECADES OF CROATIAN GENETIC HERITAGE STORY

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The presentation will provide an overview of scientific data on the Croatian genetic heritage accumulated over the past three decades. Studies of of mitochondrial DNA (mtDNA), Y chromosome, and Short Tandem Repeats (STRs) within South-Eastern European populations, with a special focus on Croatia, suggest that the genetic history of these populations fits within the broader genetic landscape of Europe and Eurasia, with high observed levels of genetic diversity. This is a consequence of the region's geographical location, which has positioned it as an ancient crossroads for numerous migrations, different cultures, populations, tribes, and religions over millennia. Many of these elements have contributed segments of their genetic heritage to the contemporary genetic pool of Croatia and the surrounding region. However, certain signals in the genetic landscape of Southeastern Europe are more dominant and several such signals will be mentioned in more detail in the lecture (Neolithisation, Slavic introgression). It is also important to highlight Croatian island populations, where evolutionary forces such as genetic drift and bottleneck effect have significantly influenced the specific patterns of their genetic diversity, placing them in the focus of anthropogenetic research in Croatia.

Keywords: human migrations, genetic heritage, Croatia, Southeastern Europe

POSTER PRESENTATIONS

Presentation number: CSHG P-TM-1 Abstract number: ABS-22-ISABS-2024

AN ASSOCIATION BETWEEN COX-2 POLYMORPHISM AND INCREASED PLASMA HDL CHOLESTEROL LEVELS AFTER CLOZAPINE TREATMENT

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Patients with schizophrenia frequently exhibit abnormal neurotransmitter signaling, attenuated skin flush response to niacin (a water-soluble B vitamin), and are more likely to experience weight gain, lipid disturbances, and glucose dysregulation. Several studies have shown antipsychotic effects of the selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib. We previously found an intriguing interaction between functional rs689466 polymorphism (A/G polymorphism) of the COX-2 gene and smoking status on schizophrenia onset. We also found that COX-2 polymorphism influenced skin flush response to niacin, among patients under antipsychotic treatment. Here, we investigated whether antipsychotic treatment was influenced by the COX-2 polymorphism. A total of 186 antipsychotic- naïve first-episode psychosis patients or nonadherent chronic psychosis individuals were genotyped by polymerase chain reaction analysis/restriction fragment length polymorphism. At baseline, and after 8 weeks of antipsychotic treatment, we assessed patients' Positive and Negative Syndrome Scale (PANSS) scores and factors, and metabolic syndrome-related parameters (fasting plasma lipid and glucose levels, and body mass index). In the total patient group, COX-2 polymorphism did not affect PANSS psychopathology or metabolic parameters ($P > 0.05$). However, patients with clozapine treatment positive for the COX-2-G allele (COX-2-GG homozygous and COX-2-AG heterozygous), compared to COX-2-AA homozygous, exhibited significantly higher increases of HDL cholesterol levels ($P < 0.05$). The COX-2 polymorphism accounted for ~9.6% of the HDL cholesterol levels variability. Our results suggest a relatively weak contribution of COX-2 polymorphism to HDL cholesterol level variations within a subgroup of patients with clozapine treatment. Antipsychotic-specific differences in the effect of COX-2 polymorphism may be due to inflammatory properties of clozapine.

Keywords: antipsychotic agents, cyclooxygenase-2, gene, polymorphism, psychosis

Presentation number: CSHG P-TM-2 Abstract number: ABS-23-ISABS-2024

PLA2G4C GENE POLYMORPHISM AND NICOTINE DEPENDENCE AMONG SCHIZOPHRENIA PATIENTS

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By playing a role in signal transduction and membrane phospholipid homeostasis, phospholipases (PLA2s) may influence conditions that are associated with altered dopamine action, such as substance use disorders and schizophrenia. We previously found that rs1549637 polymorphism of the PLA2G4C gene in interaction with polymorphism of the PLA2G6 gene, predicts an elevated schizophrenia risk. We also found that PLA2G4C gene polymorphism influences the clinical expression of schizophrenia, as measured by the Positive and Negative Syndrome Scale (PANSS), in the male patients. Here, we investigated the relationship between the PLA2G4C gene polymorphism and the risk of nicotine dependence in Croatian schizophrenia patients. We also addressed whether interaction between PLA2G4C gene polymorphism and smoking might influence schizophrenia onset and PANSS psychopathology. Genotyping was performed in 260 chronic patients (males/females: 134/126) by polymerase chain reaction analysis/restriction fragment length polymorphism. There were no significant differences in the distribution of PLA2G4C genotypes and alleles according to smoking status and no PLA2G4C genotype-smoking interaction on disease onset ($P > 0.05$). However, we revealed a significant PLA2G4C genotype-smoking interaction that predicted positive symptom severity among female patients ($P < 0.05$). A trend toward lower PANSS positive symptom scores observed among female smokers positive for the PLA2G4C-T allele (PLA2G4C-TT homozygous and PLA2G4C-AT heterozygous) compared to non-smoking females positive for the PLA2G4C-T allele mostly influenced this finding. Our results indicate no PLA2G4C gene polymorphism's effect on the risk of nicotine dependence, but they suggest that PLA2G4C genotype-smoking interaction might be of relevance in clinical psychopathology, in a gender-specific fashion.

Keywords: gene, phospholipase A2, polymorphism, schizophrenia, smoking

Presentation number: CSHG P-TM-3 Abstract number: ABS-24-ISABS-2024

ASSOCIATION BETWEEN THE ACE I/D POLYMORPHISM AND OBESITY AMONG PATIENTS WITH LUNG CANCER

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High body mass index (BMI) has been linked with both a reduced risk of lung cancer and better overall outcome of lung cancer patients. Recent studies have demonstrated a probable association between a functional insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene and obesity risk in the general population. In our previous study in lung cancer patients from a Croatian population, the ACE I/D polymorphism was shown to be associated with squamous cell carcinoma risk. In the present study, we investigated whether the ACE I/D polymorphism influenced obesity risk among patients with lung cancer. Genotyping was performed in 305 patients using polymerase chain reaction analysis. Patients were classified as obese with BMI ≥ 30, overweight (BMI: 25 – 29.9) or of normal body weight (BMI: 18.5 – 24.9). No significant differences were observed in the genotype and allele distributions of ACE polymorphism between different BMI categories in the total patient group or in the subgroup of patients with different types of lung cancer ($P > 0.05$). In subgroup of patients with squamous cell carcinoma, we found significantly different distributions of ACE-I allele carriers (ACE-II homozygous and ID heterozygous) and ACE-I allele non-carriers (ACE-DD homozygous) between BMI categories ($P < 0.05$). An increase in the ACE I allele carriers compared to ACE-I allele non-carriers among overweight (39.4% vs. 21.3%, respectively) and a decrease in the ACE I allele carriers compared to ACE-I allele non-carriers among obese (6.0% vs. 19.1%, respectively) contributed mostly to this finding. Overall BMI values were not significantly associated with ACE polymorphism either in the total patient group or in the subgroup of patients with different types of lung cancer ($P > 0.05$). ACE-I/D polymorphism might be of relevance in determining obesity risk in the subgroup of patients with squamous cell carcinoma.

Keywords: angiotensin converting enzyme, gene, lung cancer, obesity, polymorphism

Presentation number: CSHG P-TM-4 Abstract number: ABS-39-ISABS-2024

ROLE OF IL-6, IL-10 AND TNFα GENE VARIANTS IN PRETERM BIRTH

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The association of gene variants for interleukin 6 (IL-6) (rs1800796), interleukin 10 (IL-10) (rs1800896) and tumor necrosis factor-α (TNFα (rs1800629) with the occurrence of spontaneous preterm birth (PTB) was investigated to determine whether these genetic variants are a risk factor. 199 blood samples from pregnant women who had given birth prematurely and 200 control blood samples (samples from pregnant women with term delivery) were analyzed to determine single nucleotide polymorphisms (SNPs) for IL-6 (rs1800796), IL-10 (rs1800896), and TNFα (rs1800629). DNA extraction was performed on mini-spin columns according to the manufacturer's protocol. The quality and purity of the isolated DNA were tested using a Qubit 3 fluorometer. Genotyping was performed with an ABI PRISM 7500 SDS using TaqMan SNP genotyping assays. The genotypes obtained were analyzed using the 7500 Software v2.3 package. Carriers of the A/A genotype for the rs1800629 of the TNFα gene have 4.81 times greater chance of late- onset PTB compared to carriers of the G/G and A/G genotypes in the recessive inheritance model. The presence of the G/G genotype in the recessive inheritance model compared with the G/A and A/A genotypes for the rs1800896 of the IL-10 gene represents a potentially protective factor, with mothers in the term-birth group having an almost 2-fold lower odds of PTB in general and an almost 10-fold lower odds of early PTB. On the other hand, carriers of the A/G genotype of rs1800896 have a 1.54-fold higher chance of preterm birth in general and a 1.6-fold higher chance of late preterm birth in the super dominant inheritance model compared to the A/A and G/G genotypes in the group of mothers with PTB. In this study, no association was found between PTB and rs1800796 of the IL-6 gene. rs1800629 in mothers was associated with PTB. rs1800896 shows a potentially protective effect for the occurrence of PTB in this study. No association was found between PTB and rs1800796.

Keywords: premature birth, single nucleotide polymorphisms, inflammation, cytokines, interleukins

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MATERNAL ENDOGENOUS AND EXOGENOUS FACTORS AS RISK FACTORS FOR CONGENITAL HEART DEFECTS IN CHILDREN WITH DOWN SYNDROME

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Animal models have shown that maternal DNA methyltransferases (DNMT) are associated with birth defects, including different type of congenital heart defects (CHD). Approximately 50% of patients with Down syndrome (DS) have CHD. This study investigated the influence of maternal DNMT polymorphisms (DNMT1 (rs2228611), DNMT3A (rs1550117), DNMT3B (rs1569686) and DNMT3B (rs2424913)) and exogenous maternal factors (cigarette smoking, alcohol consumption, medication use) on the occurrence of CHD in children with DS. The study included 154 mothers of children with DS, 49% (75/154) mothers had a child with DS and CHD (DS-CHD+ mothers) and 51% (79/154) mothers had child with DS without CHD (DS-CHD- mothers). Atrial septal defect was present in 37%, ventricular septal defects 23%, atrio-ventricular defect in 23% and others CHD in 17%. All participants provided written informed consent prior to participation in the study. Information about CHD was obtained from each child's medical records. Before the sampling, the mothers were asked to complete a questionnaire that asked about demographic data, cigarette smoking, alcohol intake and medication use. Genomic DNA was extracted from peripheral blood leukocytes according to standard protocol. Genotyping was performed by PCR-RFLP. Maternal DNMT polymorphisms were not found to be a risk factor for CHD in DS ($P > 0.05$). Slightly more than half of participants 64% (99/154) completed the questionnaire. The results showed that DS-CHD+ mothers smoked more frequently before pregnancy than mothers with DS child but without CHD ($P = 0.0022$). No correlation was found between the polymorphisms and the other exogenous factor ($P > 0.05$). We found no association of maternal DNMT polymorphisms with CHD in children with DS. However, we found a significant association between cigarette smoking in DS-CHD+ mothers. These results emphasize the need for a multifactorial approach that could resolve in uter

Keywords: Down syndrome, DNMT, cardiac heart defects, maternal polymorphisms, exogenous factors

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THE ROLE OF ACE GENE POLYMORPHISM IN PRETERM BIRTH: INSIGHTS FROM A META-ANALYSIS AND A CASE-CONTROL STUDY IN THE CROATIAN POPULATION

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The ACE gene, encoding the angiotensin-converting enzyme (ACE), plays a crucial role in the regulation of placental circulation and angiogenesis. Impaired ACE activity has been linked to adverse pregnancy outcomes, including preterm birth (PTB). Despite extensive research, the exact cause of PTB remains unclear. Previous studies have suggested a connection between the insertion/deletion (I/D) polymorphism of the ACE gene and PTB, but results have been inconsistent across different populations. Therefore, we conducted a case-control study on the association between the ACE I/D polymorphism and PTB in the Croatian population. Moreover, we conducted a meta-analysis to systematically evaluate the results of previous studies on the association between ACE I/D polymorphism and PTB. In a case-control study, genotyping was performed on a total of 206 subjects, consisting of 121 individuals with PTB and 85 controls with full-term pregnancies. For meta-analysis, PubMed, Scopus and Google Scholar databases were systematically searched using a combination of keywords including "ACE", "angiotensin-converting enzyme", "ACE I/D polymorphism", "preterm birth" and "preterm delivery." The results of the case-control study did not indicate significant differences in the genotype and allele distributions, nor in different genetic models between PTB and control group. Meta-analysis was performed on 6 studies (including our case-control study) involving 601 cases and 787 controls. The significant difference was observed only when comparing II vs DD genotype (P = 0.050; OR = 0.178; 95%CI = 0.516-1.000). The present results suggest that the ACE I/D polymorphism does not emerge as a significant risk factor for PTB. Nevertheless, the observed modest association among homozygous genotypes emphasizes the need for further research to clarify the exact involvement of ACE in the pathogenesis of PTB.

Keywords: angiotensin-converting enzyme; ACE I/D polymorphism; case-control study; meta-analysis; preterm birth

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PAEDIATRIC CASE OF ACERULOPLASMINEMIA: 10.5-YEAR-OLD BOY WITH PERSISTENT MICROCYTIC ANAEMIA AND BIALLELIC LOSS-OF- FUNCTION VARIANTS IN CP GENE

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Aceruloplasminemia (ACP) is a rare adult-onset disorder in which iron accumulates in the brain and other organs, resulting in microcytic anemia, diabetes, retinopathy, liver disease, and progressive neurological symptoms. Cause are biallelic pathogenic variants in CP gene, encoding ceruloplasmin, a metalloprotein involved in maintaining iron homeostasis. Here we present a pediatric case of ACP. A 10.5-year-old boy was referred to us with persistent microcytic anemia since the age of 7 months, elevated liver transaminases, low iron and copper values, and elevated ferritin values. The extensive diagnostic work-up all came back negative. A clinical exome sequencing of proband and his parents was performed using TruSight One Sequencing panel (Illumina, USA). Two compound heterozygous variants in the CP gene were found. The first one is a novel likely pathogenic frameshift indel p.Asp48ThrfsTer37 inherited from his father. The second one is a known pathogenic nonsense variant p.Arg215Ter inherited from his mother. Both detected variants presumably cause nonsense-mediated decay and loss-of function (LOF). Biallelic LOF variants in CP gene are known mechanism of the disease. According to these genetic findings and clinical presentation, our patient is diagnosed with ACP. ACP generally presents in adulthood, from age 25 years to older than 70 years. The most common first symptom is sideropenic anemia, which occurs before the age of 20 years in 80% of patients. Early presentation of the disease, such as in this case, is extremely rare. To our knowledge, there is only one boy whose symptoms started at the age of eight (PMID: 36308763). Prompt diagnosis and therapy are crucial to prevent neurological complications since, once established, they are usually irreversible. Thereby, ACP should be considered if persistent microcytic anemia without apparent cause is present from a very young age.

Keywords: Aceruloplasminemia, ACP, Microcytic anemia, CP gene, Ceruloplasmin

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TNFRSF10A GENE POLYMORPHISM AND INTERFERON- TREATMENT RESPONSE IN MULTIPLE SCLEROSIS PATIENTS

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Interferon-beta (IFN-β) is widely used as a first-line disease-modifying treatment for multiple sclerosis (MS), although 30–50% of MS patients do not respond to this therapy. Identification of genetic variants that predict response to IFN-β may be useful for treatment prognosis. The TNFRSF10A gene encodes a protein that triggers apoptosis and is involved in T cell-mediated autoimmune diseases. The aim of this study was to investigate the influence of TNFRSF10A (rs20576) gene polymorphism on the response to IFN-β treatment in Croatian and Slovenian MS patients. A total of 274 IFN-β–treated MS patients (221 female; 63 male) were genotyped for TNFRSF10A (rs20576) gene polymorphisms using real-time polymerase chain reaction. Patients were diagnosed with relapse-onset MS according to the revised McDonald criteria. Based on the clinical criteria for MS treatment efficacy, they were classified as responders, Rs (N=165) and non-responders, NRs (N=119). Overall, no significant differences were found in the distribution of genotypes or allele frequencies of TNFRSF10A (rs20576) polymorphisms between Rs and NRs patients. However, the frequency of TNFRSF10A GG genotype was statistically significantly higher (p=0.039; OR=0.31; 95%CI 0.11-0.97) in male NRs (72.0%) compared to NRs (47.5%) patients. In addition, we observed a trend towards a higher prevalence of TNFRSF10A heterozygotes in NRs (38.1%) compared to Rs (27.1%) among female patients (p=0.066). Our results suggest that the presence of the TNFRSF10A (rs20576) gene variant may be associated with response to IFN-β treatment in a sex-specific association in MS patients, but further studies with a larger number of patients are needed.

Keywords: TNFRSF10A, gene polymorphism, multiple sclerosis, IFN-β treatment response

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SECOND CASE OF GONADAL MOSAICISM AND A NOVEL NONSENSE NR2F1 GENE VARIANT AS THE CAUSE OF BOSCH-BOONSTRA- SCHAAF OPTIC ATROPHY SYNDROME

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Bosch-Boonstra-Schaaf syndrome is a rare autosomal dominant disease characterized by developmental delay, intellectual disability, and optic atrophy, caused by the loss of function of the NR2F1 gene. To date, approximately a hundred cases have been reported with significant diversity in the remaining clinical features and, although precise genotype-phenotype correlation has not been completely elucidated, milder phenotypes appear to be associated with nonsense mutations. The goal of this report is to present two sisters with Bosch-Boonstra-Schaaf Optic Atrophy Syndrome with a novel nonsense mutation in the NR2F1 gene and gonadal mosaicism as the cause, making it the second such case described in the literature. A 32-year-old female patient (sister I) and her 30-year-old sister (sister II) were referred to the general ophthalmology clinic due to visual impairment. Sister, I have had visual impairment since early school years and sister II since birth. In addition, both sisters exhibited nystagmus, decreased visual acuity, pale optic discs, visual field defects, reduced vitamin levels, and thin optic nerves on MRI. Both sisters reported having intellectual difficulties during primary and secondary school. Whole exome sequencing in both sisters revealed a novel heterozygous nonsense pathogenic variant in the NR2F1 gene (c.169C>T) leading to early truncation of the NR2F1 protein. The variant was not found in the parents, suggesting gonadal mosaicism as the potential cause of Bosch-Boonstra-Schaaf Optic Atrophy Syndrome in both sisters. The novel nonsense NR2F1 gene variant described in two sisters in this case report contributes to the knowledge about genotype-phenotype correlation in Bosch-Boonstra-Schaaf Optic Atrophy Syndrome, supporting the previous findings which associate mild phenotypes with nonsense mutations. In addition, our findings further support gonadal mosaicism as a potential cause of this rare disease.

Keywords: Bosch-Boonstra-Schaaf Optic Atrophy Syndrome, genotype-phenotype correlation, genetic testing, gonadal mosaicism, next-generation sequencing

Presentation number: CSHG P-TM-10 Abstract number: ABS-111-ISABS-2024

SEMAGLUTIDE DIRECTLY AFFECTS VIABILITY OF HEPATOCYTES, STEATOSIS EXTENT AND KEY PROTEINS INVOLVED IN LIPID METABOLISM IN AN IN VITRO MODEL OF MASLD

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health issue with complex pathophysiology. Peroxisome proliferator-activated receptor gamma and alpha (PPARγ, PPARα) and microsomal triglyceride transfer protein (MTTP) play an important role in lipid metabolism. GLP-1 receptor agonists (GLP-1RAs), such as semaglutide, have demonsted a potential as a therapeutic option. In our research we aim to investigate effects of semaglutide in a cell culture model of MASLD. Cell culture model of MASLD was established by incubating Huh-7 cell line with 1 mM oleic acid (OA) for 24 hours. Cells were cotreated with 2 nM, 5 nM and 10 nM of semaglutide. Cell viability was measured using MTS assay. Steatosis was assessed by Oil-Red-O staining and colorimetric quantification. Concentrations of proteins were determined by ELISA kits. Fetal bovine serum and ethanol mixture was used as a solvent and served as a negative control. Cell viability in MASLD model was significantly reduced by 41.58% ($p<0.001$) compared to the negative control. 2 nM, 5 nM, and 10 nM of semaglutide increased cell viability compared to MASLD model by 20.51% ($p<0.03$), 14.42% and 18.45%, respectively. Oil-Red-O showed that 2 nM, 5 nM, and 10 nM of semaglutide reduced lipid content compared to the MASLD model by 6.64% ($p<0,001$), 12.36% ($p<0,001$), and 32.41% ($p<0,001$), respectively. MASLD model showed significantly higher concentrations of PPAR compared to the negative control ($p<0.001$). Compared to the MASLD model, the 2 nM group showed a statistically significant decrease of PPARγ by 29% ($p = 0.04$). An increase of PPARα compared to the negative control was statistically significant in all groups, while only 10 nM group showed a statistically significant decrease ($p = 0.002$). Semaglutide has beneficial cell injury and lipid accumulation reducing properties in an in vitro model of MASLD, as well as complex effects on PPARγ, PPARα, and MTTP.

Keywords: MASLD, GLP1, SEMAGLUTIDE, PPAR, HUH-7

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KETOGENIC DIET CAUSE SEX-SPECIFIC MOLECULAR CHANGE IN SKELETAL MUSCLE

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The ketogenic diet has emerged as a compelling dietary strategy for diverse health conditions, including weight management and metabolic disorders. Emerging evidence suggests that the efficacy and outcomes of the ketogenic diet may vary between sex, prompting a deeper investigation into the complex interplay between sex and metabolic response. In this study, effect of ketogenic diet on sex- specific differences in skeletal muscle metabolic profiles were analyzed. Twelve weeks old, male, and female C57Bl/6N mice were assigned to standard (SD) or ketogenic diet (KD) for 12 weeks. Mice were randomized in four groups (two control groups: male SD (10) and female SD (10) and two experimental groups: male KD (9) and female KD (7). Skeletal muscles sections were placed onto Indium-Tin-Oxide slides and analyzed by MALDI-TOF-MSI using positive mode and 300-700 m/z ratio. Based on principal component analysis (PCA) ketogenic diet had a significant effect on males but not on females who resisted gaining weight. PC1 component explained 44.8 % of variations and PC2 13.7 % of variations between groups. Hydroxyheptadecanoic acid, a long-chain fatty acid, was increased, while 7-methylguanosine 5-triphosphate (m7GTP), a key molecule in mRNA translation, was decreased in experimental males. Those results indicate sex-specific effect of ketogenic diet on mice metabolic profiles and mechanism of protein synthesis. This study was funded by the Faculty of Medicine Osijek, projects: MEFOS-2023-IP11 and MEFOS-2024-IP6, and European Union through the European Regional Development Fund grant agreement No. KK.01.1.1.02.0015, "Research and diagnostics of malignant, infectious and rare metabolic diseases based on MALDI TOF technology.

Keywords: ketogenic diet, sex-specific differences, obesity, skeletal muscle, MALDI-TOF-MSI

Presentation number: CSHG P-TM-12 Abstract number: ABS-175-ISABS-2024

A PATIENT WITH SHAAF-YANG SYNDROME – CASE REPORT

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Schaaf-Yang syndrome (SYS) is a rare neurodevelopmental disorder, affects many parts of the body and is similar to Prader-Willi syndrome. It is usually manifests at birth with muscular hypotonia and distal joint contractures in affected individuals. SYS is inherited in an autosomal dominant, maternally imprinted manner (paternally derived MAGEL2 allele). Case: Patient was born by C-section because of breech position. After birth, dysmorphic face, multiple joint contractures, hypotonia and feeding problems were noticed. Some type of seizures began in infancy and severe developmental delay was noticed. In the age of 17months he had severe complication after cardiac resuscitation due to infective myocarditis. After that, we detected sleep apneas and non-invasive ventilation support was started. In the age of 3 years, growth hormone therapy was started due to short statue, but therapy was stopped after 6 months because of scoliosis progression. Now, he is 4 years old boy and development delay, intellectual disability and autistic disorder is detected. During early infancy we started with genetic evaluation (molecular karyotype, SMA, MD type I and „Arthrogryposis Panel "), initial tests were normal. Finally, clinical exome sequencing detected pathogenic heterozygous mutation in MAGEL2 gene (NM_019066.4) and diagnosis of SYS was established. It is important to consider mutations in the MAGEL2 gene in the evaluation in patients with Prader-Willi-like disease that manifests as developmental delay/intellectual disability, hypotonia, feeding difficulties, and autism spectrum disorder. SYS has some unique features, such as arthrogryposis, which can help discriminate this syndrome from PWS.

Keywords: Schaaf-Yang syndrome, MAGEL2 gene, joint contractures, hypotonia, neurodevelopmental disorder

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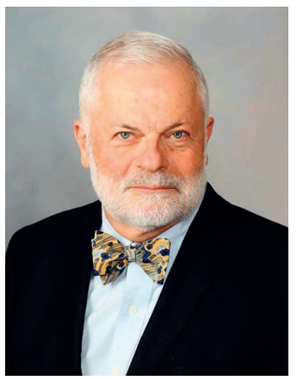
Dragan Primorac, M.D., Ph.D., is a pediatrician, forensic expert and geneticist. He is the first recipient of the title "Global Penn State University Ambassador" and currently he serves as the Chair of the International Affairs Committee of the American Academy of Forensic Sciences. He is professor at Eberly College of Science, The Pennsylvania State University, and Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, in the United States and as professor at Medical Schools in Split, Osijek and Rijeka as well as at Department of Biotechnology, University of Rijeka, in Croatia. In October of 2016. he was appointed as a visiting professor at the College of Medicine and Forensics, Xi'an Jiaotong University, People's Republic of China. Dr. Primorac is one of the pioneers in DNA identification of skeletal human remains from mass graves. Currently, he has particular interest in metabolic bone and cartilage disorders, pain treatment, sports medicine as well as in personalized and regenerative medicine. Dr. Primorac was invited speaker at more than 150 conferences all around the world. His work was published in most cited journals including Science and Nature and his papers have been cited more than 4300 times (Google Scholar) while h-index is 29. Currently, he is a team leader of the Croatian partner in the international consortium within EU FP7 project entitled "Multi-dimensional OMICS approach to stratification of patients with low back pain", worth 7.6 million euros. He is the cofounder and the President of the International Society of Applied Biological Sciences (www.isabs.hr). In 2017. he was elected president of The Croatian Society for Human Genetics. Dr. Primorac received 21 domestic and international awards. From 2003 to 2009 he served as Minister of Science, Education and Sports of the Republic of Croatia.



Stanimir Vuk-Pavlović, Ph.D., is Professor Emeritus of Biochemistry and Molecular Biology at the Mayo Clinic College of Medicine and Science, as well as Director Emeritus of the Stem Cell Laboratory, Mayo Clinic Comprehensive Cancer Center in Rochester, Minnesota. He is a native of Zagreb where he graduated from the School of Science, University of Zagreb. He obtained his Ph.D. in biophysics from the same University and received his postdoctoral training at the Weizmann Institute of Science, Rehovot, Israel. After a stint at the Institute of Immunology in Zagreb, he joined the Mayo Clinic, where he has remained for the rest of his career. For his contribution to the Croatian war of independence, he was awarded two presidential medals. Prof. Vuk-Pavlović is the corresponding (foreign) member of the Croatian Academy of Science and Arts. He has been involved with ISABS from the very beginning, joining Dragan Primorac and the late Moses Schanfield in organizing ISABS conferences. He initiated the collaboration of ISABS with the Mayo Clinic and has served as program director for several past conferences, including the current one.

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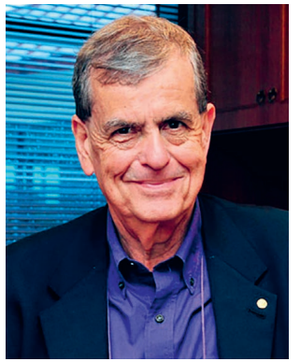


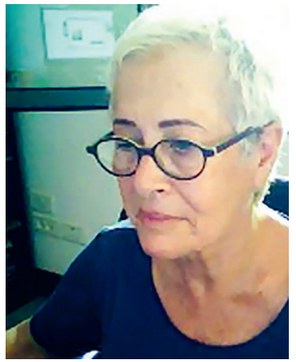
Aaron Ciechanover, M.D., Ph.D., was born in Haifa, Israel in 1947. He is currently a Distinguished Research Professor in the Faculty of medicine at the Technion – Israel Institute of Technology in Haifa, Israel. He received his M.Sc. (1971) and M.D. (1973) from the Hebrew University in Jerusalem. He then completed his national service (1973-1976) as military physician and continued his studies to obtain a doctorate in biological sciences in the Faculty of Medicine in the Technion (D.Sc.; 1982). There, as a graduate student with Dr. Avram Hershko and in collaboration with Dr. Irwin A. Rose from the Fox Chase Cancer Center in Philadelphia, USA, they discovered that covalent attachment of ubiquitin to a target protein signals it for degradation. They deciphered the mechanism of conjugation, described the general proteolytic functions of the system, and proposed a model according to which this modification serves as a recognition signal for a specific downstream protease. As a post- doctoral fellow with Dr. Harvey Lodish at the M.I.T., he continued his studies on the ubiquitin system and made additional important discoveries. Along the years it has become clear that ubiquitin-mediated proteolysis plays major roles in numerous cellular processes, and aberrations in the system underlie the pathogenetic mechanisms of many diseases, among them certain malignancies and neurodegenerative disorders. Consequently, the system has become an important platform for drug development. Among the numerous prizes Ciechanover received are the 2000 Albert Lasker Award, the 2002 EMET Prize, the 2003 Israel Prize, and the 2004 Nobel Prize (Chemistry; shared with Drs. Hershko and Rose). Among many academies, Ciechanover is member of the Israeli National Academy of Sciences and Humanities, The European Molecular Biology Organization (EMBO), the American Academy of Arts and Sciences (Foreign Fellow), the American Philosophical Society, the National Academies of Sciences (NAS) and Medicine (NAM) of the USA (Foreign Associate), the Pontifical Academy of Sciences at the Vatican, the Chinese Academy of Sciences (CAS; Foreign Member), the Russian Academy of Sciences (Foreign Member), and the German Academy of Sciences (Leopoldina).

Richard J. Roberts, Ph.D., is the Chief Scientific Officer at New England Biolabs. He was educated in England, attending St. Stephen's School and the City of Bath Boys' School in Bath before moving to the University of Sheffield where he obtained a B.Sc. in Chemistry in 1965 and a Ph.D. in Organic Chemistry in 1968. His postdoctoral research was carried out in Professor J.L. Strominger's laboratory at Harvard, where he studied the tRNAs that are involved in the biosynthesis of bacterial cell walls. From 1972 to 1992, he worked at Cold Spring Harbor Laboratory, reaching the position of Assistant Director for Research under Dr. J.D. Watson. He began work on the newly discovered Type II restriction enzymes in 1972 and in the next few years more than 100 such enzymes were discovered and characterized in Dr. Roberts' laboratory. His laboratory has cloned the genes for several restriction enzymes and their cognate methylases and studies of these enzymes have been a major research theme. Dr. Roberts has also been involved in studies of Adenovirus-2 beginning with studies of transcription that led to the discovery of split genes and mRNA splicing in 1977. This was followed by efforts to deduce the DNA sequence of the Adenovirus-2 genome and a complete sequence of 35,937 nucleotides was obtained. This latter project required the extensive use of computer methods, both for the assembly of the sequence and its subsequent analysis. His laboratory pioneered the application of computers in this area and the further development of computer methods of protein and nucleic acid sequence analysis continues to be a major research focus. The field of DNA methyltransferases is also an area of active research interest and crystal structures for the *Hha*I methyltransferase both alone and in complex with DNA have been obtained in collaboration with Dr. X. Cheng. The latter complex is quite remarkable as the protein causes the target cytosine base to flip completely out of the helix so that it is accessible for chemical reaction. This extreme, but elegant, distortion of the double helix had not been seen previously. A major interest at present is the semi-automatic identification of restriction enzyme and methylase genes within the GenBank database and the development of rapid methods to assay function. Already several new specificities have been found and there are many more restriction enzyme genes in Nature than had been previously suspected. Most recently, Sir Roberts is one of the leaders of the COMBREX project that is concerned with the functional annotation of prokaryotic genomes.

Svante Pääbo, Ph.D., has developed techniques that allow DNA sequences from archaeological and paleontological remains to be determined. His research group has determined high quality genome sequences from Neanderthals and discovered Denisovans, a previously unknown hominin group in Asia. They have shown that both Neanderthals and Denisovans contributed DNA to present-day humans and that these contributions have physiological and medical consequences today. Professor Pääbo is a Director at the Max-Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and an Adjunct Professor at the Okinawa Institute of Science and Technology, Japan.

Gregg L. Semenza M.D., Ph.D., received his B.S. degree in genetics from Harvard University and the M.D. and Ph.D. degrees from the University of Pennsylvania. He completed an internship and a residency in pediatrics at Duke University, and postdoctoral studies in medical genetics at Johns Hopkins University. He joined the Johns Hopkins faculty where he established his own laboratory. He later served as director of the Vascular Program at the Johns Hopkins Institute for Cell Engineering. Dr. Semenza is known for his investigations of how cells use and regulate oxygen and for his discovery of hypoxia-inducible factor (HIF), a molecule that is activated by reduced oxygen availability in cells and that plays a critical role in enabling cells to survive in certain disease states. Semenza's research opened a door for the investigation and development of novel treatments for diseases such as cancer and ischemic cardiovascular disease, in which reduced oxygen availability is a major feature of disease. Dr. Semenza was recognized for his work with multiple awards throughout his career. He shared the 2010 Canada Gairdner International Award and the 2016 Albert Lasker Basic Medical Research Award with the American William G. Kaelin, Jr., and the British Sir Peter J. Ratcliffe. He is a member of the National Academy of Sciences and the National Academy of Medicine. For his discoveries he was awarded the 2019 Nobel Prize for Physiology or Medicine (shared with Kaelin and Ratcliffe).

ISABS 2024
ABOUT INVITED SPEAKERS



Prof. Zvia Agur, Ph.D., President of the Institute for Medical BioMathematics (IMBM) As the senior scientist and President of IMBM, she is responsible for the innovative aspects and the scientific soundness of developed scientific concepts and methodologies. She acquired the appropriate background and training experience for this role in more than four decades of scientific research in mathematical biomedicine and over twenty years of experience in leading technology development in the Healthcare domain. During these years she made major contributions to the theory of disease dynamics, chemotherapy optimization and vaccination policies. Her scientific work was published in ca. 150 peer-reviewed papers in mathematical, medical, biological, and interdisciplinary professional journals and books, and successfully applied pre-clinically and clinically. Over the last twenty-five years, she initiated and led collaborative interdisciplinary projects with clinicians from leading medical centers in the United States, Europe, and Israel. She is the Founder and President of the Scientific Research Institute for Medical BioMathematics (IMBM). As Founder & Chairperson of a company pioneering the development of tools for individualization of cancer treatment (closed), she led innovative development and was initiator and co-author of 13 granted USA, European and international patents. She has also been Co-Founder & President of the Israeli Society of Theoretical and Mathematical Biology and Co-Founder & Member of the Board of Directors of the European Society of Mathematical and Theoretical Biology (ESMTB). A 2016 finalist for the EU Prize for Women Innovators and was elected to the rank of 2022 Fellow of the American Association for the Advancement of Science for "developing computational models of diseases and incorporating these into medical software devices to facilitate drug development and personalized patient treatment."

Julie Allickson, Ph.D., is the Michael S. and Mary Sue Shannon director of Mayo Clinic's Center for Regenerative Biotherapeutics and the Otto Bremer Trust director, Biomanufacturing and Product Development, Center for Regenerative Biotherapeutics and Associate Professor of Regenerative Medicine. Dr. Allickson is leading the next phase of development of the Center for Regenerative Biotherapeutics as it delivers on innovations that Cure, Connect and Transform patient care in alignment with Mayo Clinic's 2030 vision. She directs the enterprise-wide biomanufacturing strategy that aspires to introduce new regenerative therapeutics into the practice and establish Mayo Clinic as a category of one in regenerative medicine for rare and complex conditions. Dr. Allickson provides strategic leadership for all center activities and operations across the Mayo Clinic Enterprise. The Center for Regenerative Biotherapeutics has over 25 clinical trials in cell & gene therapy underway. With more than 25 years of experience in clinical translation of cellular therapies and regenerative medicine products, Dr. Allickson has expertise in business management,

regulatory affairs, strategic planning, project management and team building. She has been in industry and academic healthcare facilities. She has served as an executive officer of a publicly traded company that builds services for cellular banking, including licensure of technology with international affiliates. Mayo Clinic, Center for Regenerative Biotherapeutics across the enterprise including Minnesota, Arizona, and Florida. We are building a team of industry experienced leaders to frame a successful structure for Biomanufacturing including cellular therapies, gene and viral therapies, and tissue engineering and bioprinting technology.

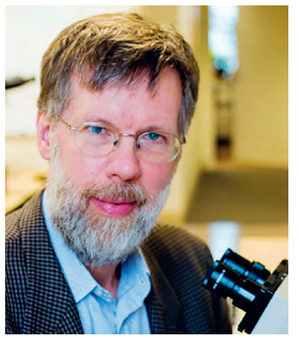
Elizabeth Rosado Balmayor is currently a University Professor for Experimental Orthopaedics and Trauma Surgery at the RWTH Aachen University Hospital (Germany). She is the head of research at the Department of Orthopaedic, Trauma, and Reconstructive Surgery, and the director of the research institute for Experimental Orthopaedics and Trauma Surgery. She was trained as a Chemist and earned an M.Sc. in Materials Science and Technology at the University of Havana (Cuba). She received a Marie Curie scholarship in the area of Biomaterials and completed her Ph.D. in 2009 with Prof. Rui Reis at the 3B's research group (Portugal). Elizabeth obtained her assistant professorship in Experimental Trauma Surgery from TUM (Germany) in 2017. Thereafter, she moved to the MERLN Institute for Technology-Inspired Regenerative Medicine at the Maastricht University (the Netherlands) where she was the Principal Investigator of the research group "Molecular Transfer and Therapy" until early 2022. She is an associate researcher with Prof. Chris Evans at the Mayo Clinic (USA). She holds visiting professorships at the Peruvian University Cayetano Heredia and the UNESCO Biomaterials chair of the University of Havana. Her achievements have been recognized with awards and grants; she has secured over 4.5 million euros from competitive grants for her research. Prof. Dr. Balmayor focuses on mRNA therapeutics for musculoskeletal tissue and tissue interface healing. A powerful breakthrough in her research is the development of a chemically modified mRNA encoding BMP-2 as an alternative to traditional gene therapy for bone healing. She holds a patent on this discovery, and her research has been widely published. She has made unique contributions to mRNA therapeutics applied to tissue engineering and the regenerative medicine field.

Atta Behfar, Ph.D., is the Russ and Kathy Van Cleve Professor of Regenerative Medicine at Mayo Clinic. His clinical area of focus is heart transplant and hemodynamic mechanical support devices. His research focus has been in regenerative medicine for the last 25 years with emphasis on stem cell and exosome innovation, translation, and clinical trial application.

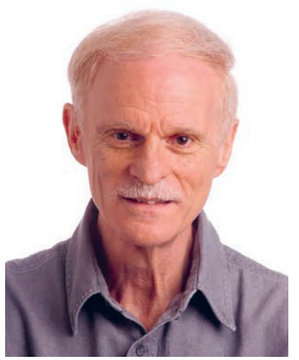
Zwi N. Berneman, M.D. Ph.D. FRCP is Emeritus Professor of Hematology at the University of Antwerp, Antwerp, Belgium and previously Head of the Division of Hematology at the Antwerp University Hospital. His basic and clinical research is focused on vaccination with immunogenic dendritic cells in cancer and with tolerogenic dendritic cells in multiple sclerosis; and on retargeting T-lymphocytes against cancer with T-cell receptors directed against the tumor-associated Wilms' tumor protein (WT1). The Laboratory of Experimental Hematology, which he previously led, has pioneered mRNA electroporation as a clinically safe gene transfer methodology and has applied it to the fields of dendritic cells and T-lymphocytes. He has been conducting clinical trials with cultured dendritic cells electroporated with mRNA since 2005 and can thus be considered as an early pioneer of the use of mRNA in medicine. To make clinical dendritic cell vaccination possible, he established the Center for Cell Therapy and Regenerative Medicine (CCRG) of which he is the Medical Director, at the Antwerp University Hospital and for which he obtained a Good Manufacturing Practices (GMP) Certification and Production License from the (Belgian) Federal Agency for Medicines and Health Products. He is a Fellow of the Royal College of Physicians, London, UK. He is the author or co-author of more than 340 peer-reviewed publications and his ISI h-index is 58.

Dr. Kapil Bharti obtained his Ph.D. from J.W. Goethe University, Frankfurt, Germany, graduating summa cum laude. His Ph.D. work involved research in the areas of molecular chaperones and epigenetics. He did his postdoc at the National Institutes of Health, where he published numerous papers in the areas of transcription regulation, pigment cell biology, and developmental biology of the eye. His lab at the National Eye Institute recently received started the first U.S. phase I/IIa trial to test autologous iPSC-derived RPE patch in AMD patients. Currently, he is co-developing a dual RPE/photoreceptor cell therapy with Opsis Therapeutics. He has given several keynote lectures, won several awards

including the NIH Director's award, NEI Directors Dr. Karl Kupfer Visionary award, and Sayer Vision Research lecture at NEI, and over two dozen keynote/award lectures for his revolutionary work on developing ocular cell-therapies. He serves on the advisory board (pro bono) of several stem cell therapies-based companies and patient-advocacy groups. His current work as a Senior Investigator at NEI involves understanding mechanism of retinal degenerative diseases using induced pluripotent stem cell derived eye cells and tissues and developing cell-based and drug-based therapies for such diseases. He is also the Director of the NEI Intramural Research Program where he oversees 21 research labs and 6 core facilities.



Prof. Frederick R. Bieber is a member of the Faculty of Medicine at Harvard University. He serves as Senior Medical Geneticist in the Center for Advanced Molecular Diagnostics, providing diagnostic laboratory genetic testing to patients and their families served by the MassGeneral/Brigham Hospital network in Boston. He has directed the undergraduate genetics course at Harvard for the past 40 years. Bieber's academic work focuses on medical genetics and the laboratory and statistical aspects of DNA-based human identification, with a focus on kinship analysis in forensic and humanitarian applications and its attendant legal, ethical, and public policy implications. He has testified in scores of civil and criminal cases in state, federal, and military courts in the U.S. and abroad. Professor Bieber was a member of the FBI DNA Advisory Board (DAB) and was appointed to the first-ever National Commission on Forensic Science during the Obama administration. As a commissioned officer in the U.S. Army Reserve, he served at the U.S. Army Criminal Investigation Laboratory (USACIL) and the Armed Forces DNA Identification Laboratory (AFDIL). Bieber currently serves on the Advisory Committee of the National DNA Databank of Canada, the DNA Subcommittee of the New York State Forensic Commission, and the U.S. Forensic Sciences Standards Board (FSSB).



Dr. Bruce Budowle received a PhD in Genetics in 1979 from Virginia Polytechnic Institute and State University. From 1979-1982, Dr. Budowle was a postdoctoral fellow at the University of Alabama at Birmingham. Working under a National Cancer Institute fellowship, he carried out research predominately on genetic risk factors for diseases such as insulin dependent diabetes mellitus, melanoma, and acute lymphocytic leukemia. From 1983-2009, Dr. Budowle worked at the FBI's Laboratory Division to carry out research, development, and validation of methods for forensic biological analyses. He has published more than 700 articles, made more than 800 presentations, and testified in well over 300 criminal cases in the areas of molecular biology, popula-

tion genetics, statistics, quality assurance, and forensic biology. In addition, he has authored or co-authored books on molecular biology techniques, electrophoresis, protein detection, forensic genetics, and microbial forensics. Dr. Budowle recently retired as Director of the Center for Human Identification and Regents Professor at the University of North Texas Health Science Center at Fort Worth, Texas where his efforts focused on the areas of human forensic identification, microbial forensics, and emerging infectious disease with substantial emphasis in genomics and next generation sequencing. He continues to research and work in the areas of forensic genomics and contributes to supporting humanitarian efforts via human identification. He currently is a visiting professor in the Department of Forensic Medicine at the University of Helsinki and an adjunct professor in the Forensic Science Institute at Radford University.

Prof. Jung Kyoon Choi's research has primarily focused on cancer genomics. More recently, he leveraged the power of data science and artificial intelligence (AI) in emerging fields such as cancer immunotherapy, cancer detection, and single-cell genomics. In the realm of cancer immunotherapy, he utilized machine learning and single-cell genomics data to develop novel methods for neoantigen-based cancer vaccines and CAR-T cell therapies. Additionally, prof. Choi developed AI algorithms to predict clinical responses to cancer immunotherapy and to analyze cell-free DNA for early detection of multiple cancers.

Dr. Henry Erlich's laboratory has been involved for over 40 years in the development and application of molecular genetic technology such as PCR and DNA-based HLA typing for the analysis of infectious diseases and autoimmune diseases. They have also focused on the development of diagnostic tests for monogenic disease, such as cystic fibrosis and the hemoglobinopathies, as well as the application of PCR in forensic genetics. His lab performed the first forensic DNA case in the US in 1986 (Penn. Vs. Pestinikas) and the first post-conviction review. They were also being applying HLA typing system to the analysis of type 1 diabetes, inflammatory bowel disease, and many other autoimmune diseases. They have pioneered the application of next generation sequencing (NGS) to the analysis of the highly polymorphic HLA class I and class II genes as well as to the analysis of mitochondrial DNA for forensic analyses. They applied HLA NGS systems to the analysis of cell free DNA in plasma for detecting donor DNA in recipient plasma for early detection of graft rejection. Recently, they are using a probe capture/NGS strategy to analyze fetal DNA in the maternal plasma to develop a non-invasive prenatal test (NIPT) for the beta-hemoglobinopathies.

Prof. Christopher Evans, Ph.D., is the John and Posy Krehbiel Professor of Orthopedics and Professor in the Departments of PM&R and Molecular Medicine at the Mayo Clinic. Dr. Evans serves as director of the Rehabilitation Medicine Research Center and is also the Maurice Müller Professor of Orthopaedic Surgery Emeritus at Harvard Medical School. Dr. Evans earned his B.Sc. in genetics and microbiology and his Ph.D. in biochemistry at the University of Wales, U.K. He completed a postdoctoral fellowship in molecular biology at Free University of Brussels, Belgium. From there he took a junior faculty position in the Department of Orthopaedic Surgery at the University of Pittsburgh, working his way through the ranks to become the inaugural Henry Mankin Professor of Orthopaedic Surgery and Professor of Molecular Genetics and Biochemistry. While at the University of Pittsburgh he earned a Master's in the History and Philosophy of Science. He was subsequently awarded a D.Sc. degree by the University of Wales and an honorary M.A. from Harvard University. Dr. Evans studies clinical problems involving bones and joints, with an emphasis on developing novel biological therapies that can be translated into early phase clinical trials. His research has two main areas of focus: arthritis and regenerative orthopaedics. He has developed a gene therapy for osteoarthritis that recently completed a Phase I human, clinical trial at Mayo Clinic and is now the subject of a Phase Ib trial. Research in regenerative orthopaedics focuses on the use of gene delivery to promote the healing of bone, cartilage, tendon, and the intervertebral disc. Dr. Evans is a Fellow of the Learned Society of Wales, the Royal Society of Chemistry and the Royal College of Pathologists; an honorary Fellow of Swansea University and an inaugural Fellow of International Orthopaedic Research and the Orthopaedic Research Society, where he served as President. He is an honorary member of the Croatian Orthopaedic Society.

Dr. Robert L. Ferris, M.D., Ph.D., is Hillman Professor of Oncology and Director at UPMC Hillman Cancer Center, Director, UPMC Hillman Cancer Center, and Hillman Professor of Oncology, and UPMC Senior Vice President for Oncology Programs, and Associate Senior Vice Chancellor for Cancer Research, University Pittsburgh School of Medicine. As a head and neck surgical oncologist and translational tumor immunologist, his lab performs neoadjuvant "window" trials developing novel immune-oncology agents, combinations and biomarkers. His group is uniquely positioned to investigate mechanisms of anti-tumor immunity in the tumor microenvironment (TME), as well as tumor cell escape. Dr. Ferris's NIH-funded laboratory is focused on reversal of immune escape and immunotherapy using monoclonal antibodies and vaccines, leading to the first randomized phase II-III trials of head and cancer immunotherapy in the world. He was founding director of the Hillman Tumor Microenvironment Center. He is a Principal Investigator of the University of Pittsburgh Specialized Program of Research Excellence (SPORE) grant for translational head and neck research and a R01 grant focused on T cell receptor dynamics and immune phenotypes regulating response to immunotherapy.

Dr. Arezou Ghazani, Ph.D. is a faculty member at Harvard Medical School, and the Director of Clinical Genomics at Brigham Genomic Medicine at Brigham and Women's Hospital. She is a board-certified medical geneticist (ABMGG) and clinical scientist with 10 years of experience in clinical genomics and precision oncology. She is well-versed in CLIA/CAP genetic testing regulations across academia and industry. Dr. Ghazani's leadership role in clinical genomics involves the development and implementation of novel programs, platforms, and methods for the clinical interpretation of the genome, and investigation of complex genome structures. Dr. Ghazani is the Founder and the Chair of the multi-institutional INT^{2}GRATE | Oncology Consortium and Director of several large-scale genome programs at Brigham and Women's Hospital, including CroSeq Genome Program. Dr. Ghazani's research activities are focused on using an integrated approach in the evaluation of somatic (tumor) and germline (constitutional) genomic data to aid interpretation of germline variants and assessment of their clinical utility in cancer. Her passion for bridging scientific advances with current clinical needs led to the development of INT^{2}GRATE. Implemented in a multi-institutional cancer consortium, INT^{2}GRATE incorporates tumor-derived signature profiles and clinical genetic information to identify clinically actionable germline alterations in cancer patients.

Dr. Massimiliano Gnecchi is an Associate Professor of Cardiology at the University of Pavia (Italy. He is a faculty member of the PhD program in Translational Medicine and of the Fellowship Programs in Cardiology, Internal Medicine and Respiratory Diseases. Prof. Gnecchi is also the Director of the "Translational Cardiology Centre" at the IRCCS San Matteo Hospital in Pavia, Italy. His research interests include discovering new cell and molecular therapies for cardiovascular disease. In particular, he studied for several years the mechanisms of action through which MSCs heal infarcted hearts and the results of his research demonstrated for the first time that MSC act mainly through paracrine actions mediated by their secretome. His discovery paved the way for a new field of research based on stem cell-derived secretomes and microvesicles to treat tissue repair. In addition, Prof. Gnecchi leads an iPSC-based program for precision medicine strategies and drug discovery. Prof. Gnecchi also does clinical research on acute myocardial infarction, secondary prevention in post-AMI and cardiac sudden death. Prof. Gnecchi is the Chair of the Cardiovascular Committee and the 2021-23 regional Vice President Europe of the International Society of Cell Therapy. Recently, he was elected Chair of the Working Group on Cardiac Regeneration (CARE) of the European Society of Cardiology.

Dr. Mateja Hajdinjak (Dr. rer. nat.) is a Croatian molecular biologist using ancient DNA to study human evolutionary history. She is currently a Max Planck Research Group Leader of the Hominin Palaeogenomics group (HOPE) at the Max Planck Institute for Evolutionary Anthropology (MPI EVA) in Leipzig, Germany. She completed her PhD at the MPI EVA under the supervision of Dr. Matthias Meyer and Prof. Dr. Svante Pääbo, recovering and analysing genome-wide data of some of the last Neandertals and some of the earliest modern humans in Eurasia. As a Marie Skłodowska Curie Individual Fellow she then went to the Ancient Genomics Laboratory of Dr. Pontus Skoglund at the Francis Crick Institute in London, United Kingdom, where she continued working on human evolutionary genomics and tracing origins of modern human ancestry using ancient DNA.

Dr. Robert J. Hariri, M.D., Ph.D. pioneered the use of stem cells to treat a range of life-threatening human diseases and continues today to make transformative contributions in the fields of immuno-oncology and cell therapeutics along with tissue engineering and functional regeneration. He is widely acknowledged for his discovery of pluripotent stem cells derived from the human placenta, and as a member of the team that discovered the physiological activities of tumor necrosis factor (TNF). He holds over 200 issued and pending patents for discoveries including placenta- derived stem cells, which Nature recognized as one of the ten most important patent estates in the field. He has authored over 200 published chapters, articles, and abstracts. Dr. Hariri was the founder and CEO of Anthrogenesis Corporation, and after its acquisition by Celgene Corporation, served as CEO of Celgene Cellular Therapeutics which was spun-out in 2017 to form Celularity. Dr. Hariri also co-founded the genomic-based health intelligence company, Human Longevity, Inc. and serves on numerous public boards including Cryoport (NASDAQ:CYRX). Dr. Hariri is an Adjunct Professor of Neurosurgery and member of the Board of Fellows of the Weill Cornell Medical College and a former member of the board of visitors of the Columbia University School of Engineering and Applied Sciences, and the Science & Technology Council of the College of Physicians and Surgeons. He is the recipient of numerous awards for his scientific contributions including The Thomas Edison Award, The Pontifical Medal for Innovation and The Fred Epstein Lifetime Achievement Award in Neurosurgery. Dr. Hariri completed his undergraduate education at Columbia University School of Engineering and Applied Sciences and Columbia College. He received his M.D. and Ph.D. degrees from Cornell University, where he was the recipient of both the Julian R. Rachele Award and the Doctoral Dissertation Award. He was a surgical resident and fellow in neurosurgery at The New York Hospital- Cornell Medical Center and served as an Assistant Professor of Neurosurgery and Associate Research Professor of Surgery at Cornell University Medical College.

Mitchell Holland, Ph.D., is a Fellow in the American Academy of Forensic Sciences, has served as an associate professorial lecturer and adjunct faculty member at various colleges and universities. Dr. Holland has been on the Editorial Board of the Journal of Forensic Sciences and a member of the Advisory Board of the International Journal of Legal Medicine. Prior to being asked in early 2005 to help develop the Forensic Science Program at Penn State, Dr. Holland was the Senior Vice President of Operations and Laboratory Director of The Bode Technology Group. At Bode, Dr. Holland led the efforts to produce DNA profiles from victim remains recovered from Ground Zero (World Trade Centers) following the terrorist attacks of 9/11. His group is currently leveraging the power of massively parallel sequencing (MPS) to measure rates of mtDNA heteroplasmy in different population groups; evaluate the transmission of heteroplasmic variants between maternal relatives and tissue types; assess the impact of damage on the interpretation of low-level heteroplasmic variants; and develop best practices for the application of MPS approaches in forensic casework. In addition, members of Dr. Holland's group are exploring ways to extract small fragments of DNA from highly degraded skeletal material for STR and SNP analysis on an MPS platform.

Dr. Tae Hyun Hwang, Ph.D., is a distinguished researcher in machine learning and AI applications in cancer therapy, holding the Florida Department of Health Cancer Chair at Mayo Clinic. With a focus on immuno-oncology cell therapy and precision oncology, he leverages advanced technologies to explore treatment resistance within tumor immune microenvironments. At Mayo Clinic, he leads innovative research integrating computational techniques with biological insights to enhance precision oncology care. His efforts include developing novel therapeutic targets and biomarkers for CAR T/NK cell therapy. Dr. Hwang's work is globally recognized, making significant impacts on cancer research and patient care.

Prof. John P.A. Ioannidis was born in New York City and raised in Athens, Greece. He was Valedictorian at Athens College; received the National Award of the Greek Mathematical Society; and received his MD (top rank of medical school class) from the National University of Athens. He also received DSc in biopathology from the same institution. Trained at Harvard and Tufts (internal medicine, infectious diseases), then held positions at NIH, Johns Hopkins, Tufts, Harvard, Imperial College, and University of Ioannina. Moved to Stanford in 2010, initially as Director/C.F. Rehnborg Chair/Director at Stanford Prevention Research Center, then diversified with appointments in 4 departments and membership in 8 centers/institutes at Stanford. He launched the PhD program in Epidemiology & Clinical Research and the MS program in Community Health & Prevention Research at Stanford, as well as the Meta-Research Innovation Center at Stanford (METRICS). He has served as President of the Society for Research Synthesis Methodology and of the Association of American Physicians, as editorial board member of many leading journals and as Editor-in-Chief of the European Journal of Clinical Investigation. He has been elected to many honorific academies around the world and has received five honorary doctoral degrees and many awards. He is the author of nine literary books, three of them shortlisted for best book of the year Anagnostis awards in Greece. His work aims to improve research methods and practices and to enhance approaches to integrating information and generating reliable evidence. Full CV available at https://profiles.stanford.edu/john-ioannidis

Prof. Manfred Kayser is a molecular biologists and geneticists with a broad interest in human variation. Since 2004, he is (full) Professor of Forensic Molecular Biology at Erasmus MC University Medical Center Rotterdam, where he chairs the Department of Genetic Identification. His scientific interested is in understanding human (epi)genetic and (epi)genomic variation and applying it to address forensic, anthropological, and medical questions. During the last 20 years, his ground-breaking fundamental and applied research has innovated the field of forensic genetics in several subfields such as forensic DNA phenotyping, forensic Y-chromosome analysis, forensic tissue identification, forensic time estimation and he additionally published on forensic epigenetics, forensic microbiome analysis, and forensic massively parallel sequencing. He published over 300 articles in peer-reviewed scientific journals. He is the most cited scientist worldwide in the field of forensic genetics and second most cited in forensic medicine 1960-2022. He received several research awards such as from the International Society for Forensic Genetics (ISFG). Since 2023, he is elected member of the European Molecular Biology Organisation (EMBO).

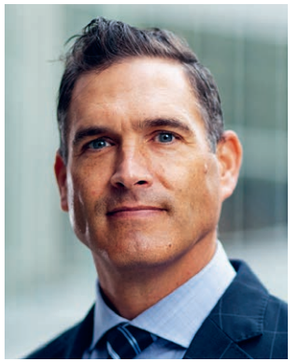
Dr. Saad J. Kenderian, M.B., Ch.B., is a consultant in the Division of Hematology and Bone Marrow Transplantation, Department of Internal Medicine, at Mayo Clinic in Rochester, Minnesota, with joint appointments in the Department of Immunology and Department of Molecular Medicine. Dr. Kenderian serves as director of the T-Cell Engineering Laboratory Program, a federally funded laboratory focused on immunotherapy. He co-leads the Cancer Immunology Immunotherapy program within the Mayo Clinic Comprehensive Cancer Center and leads the cellular therapy and gene and viral therapy domains within the Center for Regenerative Therapeutics. He holds the academic rank of assistant professor of immunology, medicine and oncology, Mayo Clinic College of Medicine and Science. Dr. Kenderian earned his M.B., Ch.B. at the University of Baghdad School of Medicine in Baghdad, Iraq. He completed a residency in internal medicine at McLaren Regional Medical Center at Michigan State University, where he served as chief medical resident. He further completed a fellowship in hematology and medical oncology, serving as chief fellow, at Mayo Clinic School of Graduate Medical Education. He continued his training in immunotherapy and chimeric antigen receptor T-cell therapy as a Mayo Clinic Scholar at the University of Pennsylvania School of Medicine. Dr. Kenderian's research focuses on the development, application, and optimization of novel next generation engineered T-cell therapies for the treatment of cancer and non-cancer applications. He and his research colleagues hold more than 150 patent applications covering 30 technologies and have published more than 100 manuscripts. Dr. Kenderian has given presentations on his research both nationally and internationally and has authored numerous journal articles and abstracts. He also holds reviewer and editorial responsibilities for prominent scientific publications.

Prof. Toomas Kivisild graduated as a Biologist and received his PhD in Genetics, from University of Tartu, Estonia, in 2000. Since then he has worked as a postdoctoral research fellow in the School of Medicine, at Stanford University (2002-3), Estonian Biocentre (since 2003), as the Professor and Head of the Department of Evolutionary Biology, University of Tartu (2005-6), and as a Lecturer and Reader in Human Evolutionary Genetics in the Department of Archaeology and Anthropology at the University of Cambridge (2006-2018). From 2018 he is a professor in the Department of Human Genetics at KU Leuven. His research interests include human evolution and evolutionary population genetics in the broadest sense. His recent work has focused on questions relating population structure with evolutionary processes such as selection, drift, migrations and admixture. He is a co-author of the 2nd edition of 'Human Evolutionary Genetics' textbook and has led and co-authored in more than 100 peer reviewed papers on human population genetics.

Prof. Guido Kroemer is currently Professor at the Faculty of Medicine of the University of Paris-Cité, Director of the research team "Metabolism, Cancer and Immunity" of the French Medical Research Council (INSERM), Director of the Metabolomics and Cell Biology platforms of the Gustave Roussy Comprehensive Cancer Center, and Hospital Practitioner at the Hôpital Européen George Pompidou, Paris, France. His work focuses on the pathophysiological implications of cell stress and death in the context of aging, cancer and inflammation. He discovered the ignition of regulated cell death pathways by mitochondrial membrane permeabilization, the cytoprotective and antiaging effects of macroautophagy, as well as the decisive role of immunogenic cell death in anticancer treatments. With over 1600 articles including 63 papers in the 'CNS' Journals Cell (13 papers), Nature (5), Nature Medicine (21), Science (18) and Science Translational Medicine (6) and an h-index of 290, he is worldwide most cited researcher in Biology and Biochemistry. Kroemer is the founding Editor-in-Chief of five journals: Cell Death & Disease, Cell Stress, OncoImmunology, Microbial Cell, and Molecular & Cellular Oncology. He is the Editor-in-Chief of Seminars in Immunology and a member of the Academia Europaea, Austrian Academy of Sciences, Chinese Academy of Engineering, European Academy of Cancer Sciences (EACS), European Academy of Sciences (EAS), European Academy of Sciences and Arts (EASA), European Molecular Biology Organization (EMBO), German Academy of Sciences (Leopoldina), Institut Universitaire de France (IUF) and Royal Spanish Academy of Sciences. He is the Founding President of the European Academy of Tumor Immunology (EATI). His contributions have been recognized with multiple awards including the most prestigious cancer research prizes from Belgium (Baillet-Latour Health Prize), France (Prix Duquesne, Prix Léopold Griffuel, Grand Prix Ruban Rose) and Switzerland (Brupbacher Prize), the European Union-sponsored Descartes Prize, and the most important Italian science prize (Lombardia & Ricerca Prize).

Prof. Gordan Lauc, Ph.D., is a Professor of Biochemistry and Molecular Biology at the University of Zagreb, Director of the National Centre of Scientific Excellence in Personalised Healthcare, Honorary professor at the Kings College London and member of the Johns Hopkins Society of Scholars. He graduated Molecular Biology in 1992 and got PhD in Biochemistry in 1995 at the University of Zagreb. In 2017 he initiated the launch of the Human Glycome project and is one of its two co-directors. His research team is pioneering high throughput glycomic analysis and the application of glycan biomarkers in the field of precision medicine. By combining glycomic data with extensive genetic, epigenetic, biochemical, and physiological data on over 200,000 individual they are trying to understand the role of glycans in normal physiology and disease. Professor Lauc co-authored over 300 research articles that are cited over 15,000 times in

Google Scholar. In 2007 he founded Genos, a biotech company that is currently global leader in high throughput glycomics. Research in Genos led to the development of the GlycanAge test of biological age.

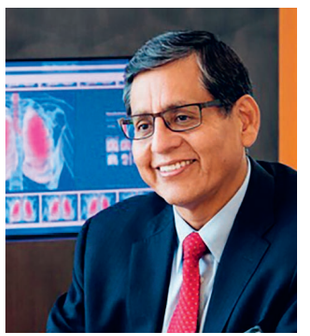


Dr. Nathan LeBrasseur, P.T., Ph.D., is a Professor in the Department of Physical Medicine and Rehabilitation and has a joint appointment in the Department of Physiology and Biomedical Engineering at Mayo Clinic. Dr. LeBrasseur is the Director of the Robert and Arlene Kogod Center on Aging, the Co-Director of the Paul F. Glenn Center for Biology of Aging Research, and Scientific Director of the Office of Translation to Practice at Mayo Clinic. He is the recent chair of the NIH Cellular Mechanisms in Aging and Development Study Section. Dr. LeBrasseur's research team conducts translational "bench-to-bedside" research on strategies to improve physical function, metabolism, and resilience in the face of aging and disease. His latest work has centered on cellular senescence, a fundamental mechanism of aging, and interventions to counter this process to extend health span. Dr. LeBrasseur has received the Glenn Award for Research in Biological Mechanisms of Aging, the Nathan W. Shock Award Lecture from the National Institute on Aging, and the Vincent Cristofalo Rising Star Award in Aging Research from the American Federation for Aging Research. He is a Fellow of the Gerontological Society of America.

Prof. Dr. Henry C. Lee is one of the world's foremost forensic scientists. Dr. Lee's work has made him a landmark in modern-day criminal investigations. He has been a prominent player in many of the most challenging cases of the last 50 years. Dr. Lee has worked with law enforcement agencies in helping to solve more than 8000 cases. In recent years, his travels have taken him to England, Bosnia, Canada, China, Brunei, Bermuda, Germany, Singapore, Thailand, Middle East, South America, and other locations around the world. Dr. Lee's testimony figured prominently in the O. J. Simpson, Jason Williams, Peterson, and Kennedy Smith Trials; and in convictions of the "Woodchipper" murderer as well as thousands of other murder cases. Dr. Lee has assisted local and state police in their investigations of other famous crimes, such as the murder of Jon Benet Ramsey in Boulder, Colorado, the 1993 suicide of White House Counsel Vincent Foster, the death of Chandra Levy, the kidnapping of Elizabeth Smart, and the reinvestigation of the Kennedy assassination. He was a consultant for more than 800 law enforcement agencies. Dr. Lee is currently a Distinguished Emeritus Professor in Forensic Science, Vice President of Institute of Forensic Science and the director of Forensic Research and Training Center of University of New Haven. He was the Chief Emeritus for the Connecticut State Police during 2000-2010 and was the Commissioner of Public Safety for

the State of Connecticut during 1998 to 2000 and has served as the state's Chief Criminalist from 1978 to 2000. Dr. Lee was the driving force in establishing a modern state police communication system, Community based police services sex offender and DNA databank, major crime investigation concepts and advanced forensic science services in Connecticut. In 1975, Dr. Lee joined the University of New Haven, where he created the school's Forensic Sciences program. He has also taught as a professor at more than a dozen universities, law schools.

Dr. David G. Lott, M.D. holds the academic rank of Professor of Otolaryngology at Mayo Clinic College of Medicine and Science. He serves as the Chair of the Department of Otolaryngology – Head and Neck Surgery/Audiology at Mayo Clinic Arizona. His practice includes voice and swallowing restoration, laryngeal cancer, and laryngotracheal reconstruction. Dr. Lott received his M.D. degree at the University of Iowa Carver College of Medicine and completed a residency in Otolaryngology/Head and Neck Surgery at the Cleveland Clinic Head and Neck Institute. He received further fellowship training in Laryngeal Surgery and Professional Voice at Harvard Medical School/Massachusetts General Hospital. Dr. Lott is the Associate Director of the Mayo Clinic Center for Regenerative Biotherapeutics on the Arizona Campus. He is faculty for both the Clinical & Translational Science and Regenerative Sciences tracks within the Mayo Clinic Graduate School of Biomedical Sciences. In addition, he is the Director of the Head and Neck Regenerative Medicine and Transplantation Program at Mayo Clinic. The primary goal of the NIH-funded lab is to establish safe and effective clinical translation of regenerative medicine technology. The lab is initiating a FDA-approved human clinical trial to evaluate the efficacy of the tissue-engineered technologies. Additionally, the efforts of this program have established the world's first UNOS-approved laryngeal transplantation human clinical trial. Dr. Lott has received many awards and honors, including the Transform the Practice Award, Mayo Clinic Teacher of the Year Award, and the Mayo Clinic Distinguished Clinician Award.



Dr. Jorge M Mallea, M.D. is a consultant in the Department of Critical Care Medicine and the Center for Regenerative Biotherapeutics at Mayo Clinic Florida. He holds a joint appointment in the Department of Transplantation. He serves as the medical director for Lung Bioengineering Jacksonville (LB-JAX) a joint project between Mayo Clinic and Lung Biothechnology (a subsidiary of United Therapeutics). He is the chair for the Center for Regenerative Biotherapeutics' equity, inclusion and diversity committee and the Director for CRB's Seminar Series. Dr. Mallea received his M.D. degree at the Universidad Nacional de San Agustin. He completed a residency in Internal Medicine at New York

Medical College in New York. He received further fellowship training in Pulmonary, Critical Care and Sleep Medicine at Saint Louis University, Missouri. He joined the lung transplant team at Mayo Clinic Florida in 2011. Dr. Mallea's research interests include lung repair and regeneration, and organ preservation. He is conducting a FDA-approved clinical trial to evaluate the safety of mesenchymal stem cells in patients with advanced Chronic Obstructive Pulmonary Disease. He has served as principal investigator in industry sponsored clinical trials involving endobronchial valves to treat emphysema and centralized ex vivo lung perfusion facilities. Dr. Mallea serves as the chair for the American Society of Transplant Recovery and Preservation Community of Practice. He is a fellow of the American College of Chest Physicians and the American Academy of Sleep Medicine.

Dr. Shai Meretzki received his B.S. degree in biology and chemical engineering, and his M.S. and Ph.D. degrees in biotechnology, all from Technion–Israel Institute of Technology. After a brief stint in teaching, he joined Israeli biotechnology companies in different leadership positions. Together with Prof. Avinoam Kaduri, Dr. Meretzki founded the Bonus BioGroup, a Haifa-based biotechnology company of which he has served as CEO. Bonus BioGroup has revolutionized bone healing by having developed a unique technology for manufacturing viable human bone grafts as the world's first facility of its kind. Among Dr. Meretzki's achievement is the Bonus BioGroup's breakthrough technology. Their laboratory-grown bones promise to transform bone healing, offering hope to patients worldwide. Dr. Meretzki also founded Pluristem, where he served as both CEO and CTO. Pluristem is a biotech company specializing in cell therapies and regenerative medicine. In addition, Dr. Meretzki held leadership positions at Biological Industries (BI), Polyol Biotech, and Polyheal Ltd. His expertise spans various facets of the life sciences industry.

Dr. Ir. Eskeatnaf Mulugeta is an assistant professor at Erasmus University Medical Center Rotterdam (Erasmus MC) in The Netherlands. He has a multidisciplinary educational background with a Bachelor's degree in Pharmacy, followed by three Master's degrees in Biotechnology, Bioinformatics, and Molecular Medicine. He performed his PhD research at Erasmus MC in the lab of Prof. Dr. Joost Gribnau, where he investigated the evolution of mammalian sex chromosomes (X&Y) during evolution and development. He then moved to the Institut Curie (Paris, France) for his postdoctoral research (with Prof. Edith Heard), focusing on cancer genomics and epigenomics, and also adapting Naked mole rats as model animals for aging and cancer research. After completing his postdoctoral research, he started his research group at Erasmus MC in the Department of Cell Biology. Eskeatnaf's current research focus includes deciphering and understanding gene regulatory networks that orchestrate normal and diseased development, understanding the role of the non-coding genome, developing novel single-cell omics techniques and analysis methods, and understanding the molecular mechanisms of longevity and cancer resistance in Naked mole rats. Additionally, in collaboration with Prof. Dr. Manfred Kayser (Department of Genetic Identification, Erasmus MC), he adapts single-cell omics

techniques and analysis methods for forensic applications. Eskeatnaf is also a coordinator of the genetics and genomics course at a graduate school and a lecturer in computational biology.

Prof. Giuseppe Orlando, M.D., Ph.D., Marie Curie Fellow, is a surgeon scientist at the Wake Forest School of Medicine in Winston Salem, North Carolina, US. He specializes in the transplantation, bioengineering and regeneration of the kidney and endocrine pancreas at Atrium Health Wake Forest Baptist Medical Center and the Wake Forest Institute for Regenerative Medicine. He received his MD, general surgery and PhD degrees from the University of Rome, Italy, and specialized in abdominal organ transplantation, transplant immunology, regenerative medicine, and tissue engineering in Paris (France), Brussels (Belgium), Oxford (England) and Winston Salem. He is the President Elect and Chair of the Education Committee of the Cell Transplant and Regenerative Medicine Society (CTRMS), the Co-Chair of the Regenerative Medicine Advisory Council of the American Society of Transplantation and the Editor in Chief of a the Regenerative and Transplant Medicine new book series published by Elsevier-Academic press. He chairs the AST-Tissue Engineering and Regenerative Medicine International Society (TERMIS)-International Society of Cell and Gene Therapy (ISCT) cosponsored webinar series. The overarching goal of his scholarly activity is to bring the fields of transplant and regenerative medicine together to join forces and build their mutual future. As of March 11th, 2024, his h-index is 56 and has 10,351 citations

Prof. Walther Parson, Ph.D., holds an associate professorship at the Institute of Legal Medicine, Medical University of Innsbruck, Austria and an adjunct professorship at the PennState University, PA, USA. Together with his colleagues he set up the Austrian National DNA Database Laboratory in 1997 in Innsbruck, where he currently supervises the High Through-put DNA Database Laboratory and the research group Forensic Genomics. His research focuses on various fields of genetics and genomics, including forensic, medical and population genetics and he entertains collaborations with other fields of research such as anthropology, archaeology, ethics, history and mathematics. His group was repeatedly consigned to handle international requests on Forensic DNA fingerprinting of victims of mass fatalities (e.g., the 2004 Tsunami, the 1973 victims Chile, the 2014 Missing Mexican students), international human identification cases (e.g., the Russian Tsar family Romanov) and identification of individuals of historic interest (e.g., Friedrich von Schiller, Wolfgang Amadeus Mozart). WP is representing Austria in international boards including the European Network of Forensic Science

Institutes (ENFSI) DNA Working Group and the European DNA Profiling Group (EDNAP) and he is an elected active member of the National Academy of Sciences Leopoldina. He served as President of the International Society for Forensic Genetics (ISFG) from 2015-2019 and is currently Vice-President. He received the Scientific award of the German Society of Legal Medicine (DGRM) in 2004 and the Scientific award of the International Society for Forensic Genetics (ISFG) in 2005. WP has co-authored >480 peer-reviewed publications with an h-index of 90 (Google Scholar, Feb 2024).

Dragan Primorac, M.D., Ph.D., is a pediatrician, forensic expert and geneticist. He is the first recipient of the title "Global Penn State University Ambassador" and currently he serves as the Chair of the International Affairs Committee of the American Academy of Forensic Sciences. He is professor at Eberly College of Science, The Pennsylvania State University, and Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, in the United States and as professor at Medical Schools in Split, Osijek and Rijeka as well as at Department of Biotechnology, University of Rijeka, in Croatia. In October of 2016. he was appointed as a visiting professor at the College of Medicine and Forensics, Xi'an Jiaotong University, People's Republic of China. Dr. Primorac is one of the pioneers in DNA identification of skeletal human remains from mass graves. Currently, he has particular interest in metabolic bone and cartilage disorders, pain treatment, sports medicine as well as in personalized and regenerative medicine. Dr. Primorac was invited speaker at more than 150 conferences all around the world. His work was published in most cited journals including Science and Nature and his papers have been cited more than 4300 times (Google Scholar) while h-index is 29. Currently, he is a team leader of the Croatian partner in the international consortium within EU FP7 project entitled "Multi-dimensional OMICS approach to stratification of patients with low back pain", worth 7.6 million euros. He is the cofounder and the President of the International Society of Applied Biological Sciences (www.isabs.hr). In 2017. he was elected president of The Croatian Society for Human Genetics. Dr. Primorac received 21 domestic and international awards. From 2003 to 2009 he served as Minister of Science, Education and Sports of the Republic of Croatia.

Prof. Antti Sajantila, M.D., Ph.D., works as a professor of forensic medicine in the Department of Forensic Medicine, at the University of Helsinki, and as a senior medical examiner in the Forensic Medicine Unit at the Finnish Institute of Health and Welfare. He is an Honorary Professor of Pontificia Universidad Católica del Perú in Lima. He received the ISFG Scientific Prize in 1997. Professor Sajantila is a member of the executive board of European Council of Legal Medicine and the Steering Committee of the Independent Forensic Expert Team hosted by the International Rehabilitation Council for Torture Victims. He has served in the Advisory Board for the United Nations Human Rights Special Rapporteur for the Minnesota Protocol on the Investigation of Potentially Unlawful Death. Professor Sajantila has participated in many international medico-legal investigations, implemented on the requests of various international communities. Professor Sajantila has published over 230 articles in peer-reviewed scientific journals and co-authored books in forensic genetics, pathology, and pharmacogenetics. His current research interests are ancient DNA, archeaovirology, forensic genetics and forensic pathology.

Dr. Thomas Salinas, Ph.D., is Professor and Chair of Dental Specialties at the Mayo Clinic, where his time is dedicated to rehabilitation of patients with complex care needs. He has authored 95 publications related to prosthodontics and interdisciplinary care. His research interests are biomaterial behavior and clinical outcome studies. He is Board Certified in Prosthodontics and serves as an examiner for the American Board of Prosthodontics. He is a fellow of the American College of Prosthodontists, The Academy of Prosthodontics, and Past President of American Academy of Maxillofacial Prosthetics. A native of New Orleans, Louisiana he was educated at Louisiana State University Health Science Center and MD Anderson Cancer Center.

Dr. Nidhi Shah, M.D., is a pediatrician-medical geneticist and physician-scientist, with a research interest in implementation science, studying precision genomic medicine as well as novel applications of genetic tools and technologies. She completed fellowship training in clinical genetics at the Harvard Medical School Genetics Training Program. She serves as a Clinical Geneticist at Dartmouth Health Children's and Assistant Director of Center for Clinical Genomics and Advanced Technology (CGAT) in the Department of Pathology at Dartmouth Health and is part of the core scientific team working on the NIH funded Babyseq2

project. She is the Lead for Data and Analytics within the International Consortium of Newborn Sequencing (ICoNS).

Dr. Nikolaos Skartsis, M.D., Ph.D., is a transplant nephrologist, who is active in both clinical practice and research investigation. Dr. Skartsis is a physician/scientist with an overarching goal to promote the discovery of novel biologic drugs and cell therapies. His research focus is on the molecular pathways that lead to organ rejection and autoimmunity. Dr. Skartsis is an inventor of a novel method of ex-vivo Treg cell manufacturing that can be used in transplantation and autoimmune diseases. Dr. Skartsis has authored multiple scientific manuscripts and has given national and international invited lectures.

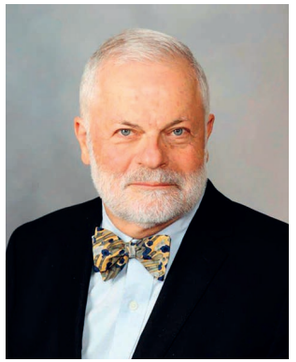
Dr. Doris Taylor, Ph.D., is CEO of Organamet Bio Inc. a biotech company committed to bioengineering personalized human hearts on demand. Taylor, a pioneer in cardiovascular regenerative medicine, led the first stem cell therapy in heart in the 1990s. She founded a company that went public in 2022 and was purchased by United Therapeutics in 2023. She is a fellow of the European Society of Cardiology, the American College of Cardiology, the American Heart Association and the American Institute of Biological and Medical Engineering. She is a senior member of the National Academy of Inventors.

Prof. Serena Tucci, Ph.D., is Assistant Professor of Anthropology, Ecology and Evolutionary Biology and Principal Investigator of the Human Evolutionary Genomics Laboratory at Yale University. Dr. Tucci's research addresses fundamental questions in human evolution and population history using DNA from present-day and ancient humans. Her interdisciplinary approach combines expertise from anthropology, population genetics, and computational biology, to reconstruct past demographic events and disentangle the genetic basis of human adaptation and disease. By integrating field work, laboratory work and cutting-edge computational methods, her work sheds light on mechanisms of evolutionary change, and on the genetic legacy that extinct humans - such as Neandertals

and the enigmatic Denisovans - left in the genomes of human wehlingpopulations in Island Southeast Asia and Oceania. Prior to joining Yale, she conducted postdoctoral research at the Department of Genome Sciences at the University of Washington and the Lewis-Sigler Institute for Integrative Genomics at Princeton University. She was awarded the Maximizing Investigators' Research Award by the National Institute of General Medical Sciences, and her work has been supported by the Lewis and Clark Fund for Exploration and Field Research from the American Philosophical Society. Tucci received her Ph.D. in Evolutionary and Environmental Biology from the University of Ferrara in Italy, where she was awarded the Young Investigator Fellowship in 2013 and 2015.

Prof. Dr. Ron H.N. van Schaik, Ph.D./FACB, is a European Specialist Laboratory Medicine and Full Professor Pharmacogenetics (2013) and of Clinical Chemistry (2023). He is head of the Dept. Clinical Chemistry at Erasmus MC - University Medical Center Rotterdam and Director of the International (IFCC) Expert-Center for Pharmacogenetics. Main interest is implementation of pharmacogenetics in clinical practice. He published >350 peer reviewed articles (h-index 81; Google Scholar). Specific research topics include pharmacogenetics in oncology, cardiology, psychiatry, and pain medication, as well as ctDNA/liquid biopsy analyses and genetics behind opioid use disorder. Prof. van Schaik participates in national (DPWG) and international groups on pharmacogenetics (ESPT, PGRN, CPIC, PharmVar, AMP, EMA) and is chair of the Dutch Network Clinical Pharmacogenetics. He is recipient of the Ortho Clinical Diagnostics Award for Outstanding Research (2001), the AACC Outstanding Speaker Award (2009) and the AACC/Mol Pathology Award for Outstanding Scientific Research (2010).

Dr. Samuel Volchenboum, Ph.D., is a professor of pediatrics and the associate chief research informatics officer for the Division of Biological Sciences at the University of Chicago. He is the Dean of Masters Programs, and he designed and launched the UChicago Master's in Biomedical Informatics. His clinical specialty is pediatric hematology / oncology, caring for kids with cancer and blood diseases. His research group includes the University of Chicago's Data for the Common Good (D4CG), dedicated to building communities, platforms, and ecosystems that maximize the potential of data to drive discovery and improve human health. D4CG's flagship project, the Pediatric Cancer Data Commons is dedicated to liberating and democratizing international data for pediatric malignancies. He is the director of the Informatics Core for the Clinical and Translational Science Award (CTSA), and he is director of the UChicago Clinical Informatics fellowship program.



Prof. Stanimir Vuk-Pavlović, Ph.D., is Professor Emeritus of Biochemistry and Molecular Biology at the Mayo Clinic College of Medicine and Science, as well as Director Emeritus of the Stem Cell Laboratory, Mayo Clinic Comprehensive Cancer Center in Rochester, Minnesota. He is a native of Zagreb where he graduated from the School of Science, University of Zagreb. He obtained his Ph.D. in biophysics from the same University and received his postdoctoral training at the Weizmann Institute of Science, Rehovot, Israel. After a stint at the Institute of Immunology in Zagreb, he joined the Mayo Clinic, where he has remained for the rest of his career. For his contribution to the Croatian war of independence, he was awarded two presidential medals. Prof. Vuk-Pavlović is the corresponding (foreign) member of the Croatian Academy of Science and Arts. He has been involved with ISABS from the very beginning, joining Dragan Primorac and the late Moses Schanfield in organizing ISABS conferences. He initiated the collaboration of ISABS with the Mayo Clinic and has served as program director for several past conferences, including the current one.

Prof. Susan Walsh, Ph.D., received her BSc. In Biochemistry from University College Cork, Ireland, an MSc. in DNA profiling from the University of Central Lancashire, UK, and a Ph.D. in Forensic Genetics from Erasmus University in the Netherlands. She was a Research Assistant at the University of Sydney, Australia, and a Postdoctoral Research Associate in Anthropology at Yale University, CT, USA. She is now an Associate Professor of Biology at Indiana University Indianapolis (IUI), IN, USA, where her laboratory focuses on understanding the genetics of human physical appearance, from pigment to facial structure, and its prediction from DNA. She has published over 40 peer-reviewed articles in the last 10 years spanning the fields of genetics, forensics and bioinformatics. Her research has been funded by the US NIJ, DOD and NIH.

Prof. Peter Wehling, Ph.D., is a specialist for orthopedics, sports medicine and pain management from Düsseldorf, Germany. Dr. Wehling invented and established the Regenokine® Program. Together with a team of international experts, Dr. Wehling has significantly shaped the growing field of molecular orthopedics through pioneering that many orthopedic diseases are not merely wear and tear. Rather, they are linked to biomolecular changes, such as inflammation, oxidative stress and regenerative deficiency. Peter Wehling's expertise focuses on non-surgical, targeted approaches engaging the abilities of the patients' immune system. This way, the overarching goal is to restore natural balance and healthy conditions in diseased tissue in a sustainable as well as gentle manner.

Prof. Laurence Zitvogel, M.D. (Clinical Oncology), Ph.D. (Tumor Immunology), full professor at the University Paris Saclay, graduated in Medical Oncology in 1992. Scientific career first at the University of Pittsburgh, US. Became Research Director at Institut National de la Santé et Recherche Médicale U1015, and Scientific Director of the Clinicobiome program at Gustave Roussy, the largest cancer Center in Europe in 1998. Actively contributed to the field of cancer immunology and immunotherapy. Pionner of the concepts of immunogenic cell death and gut microbiota in cancer immunosurveillance and therapies. Recipient of many awards: Translation Research INSERM Prize, the ASCO-SITC, Brupbacher Awards 2017, ESMO Immuno-Oncology Award 2017, Baillet Latour Prize 2019, the Griffuel Prize 2019, the Duquesne Ligue Prize, and ITOC9 german award. Knighted Officer of Légion d'Honneur by French Ministery of Health 2019 and elected member of the National Academy of Medicine 2021. Her H-factor is 145, with >500 publications on PubMed, 108 265 citations in Clarivate analytics (highly cited researchers 2021, 2020, 2019, 2018, 2017, 2016).

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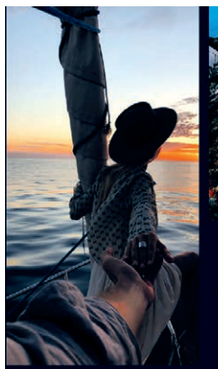

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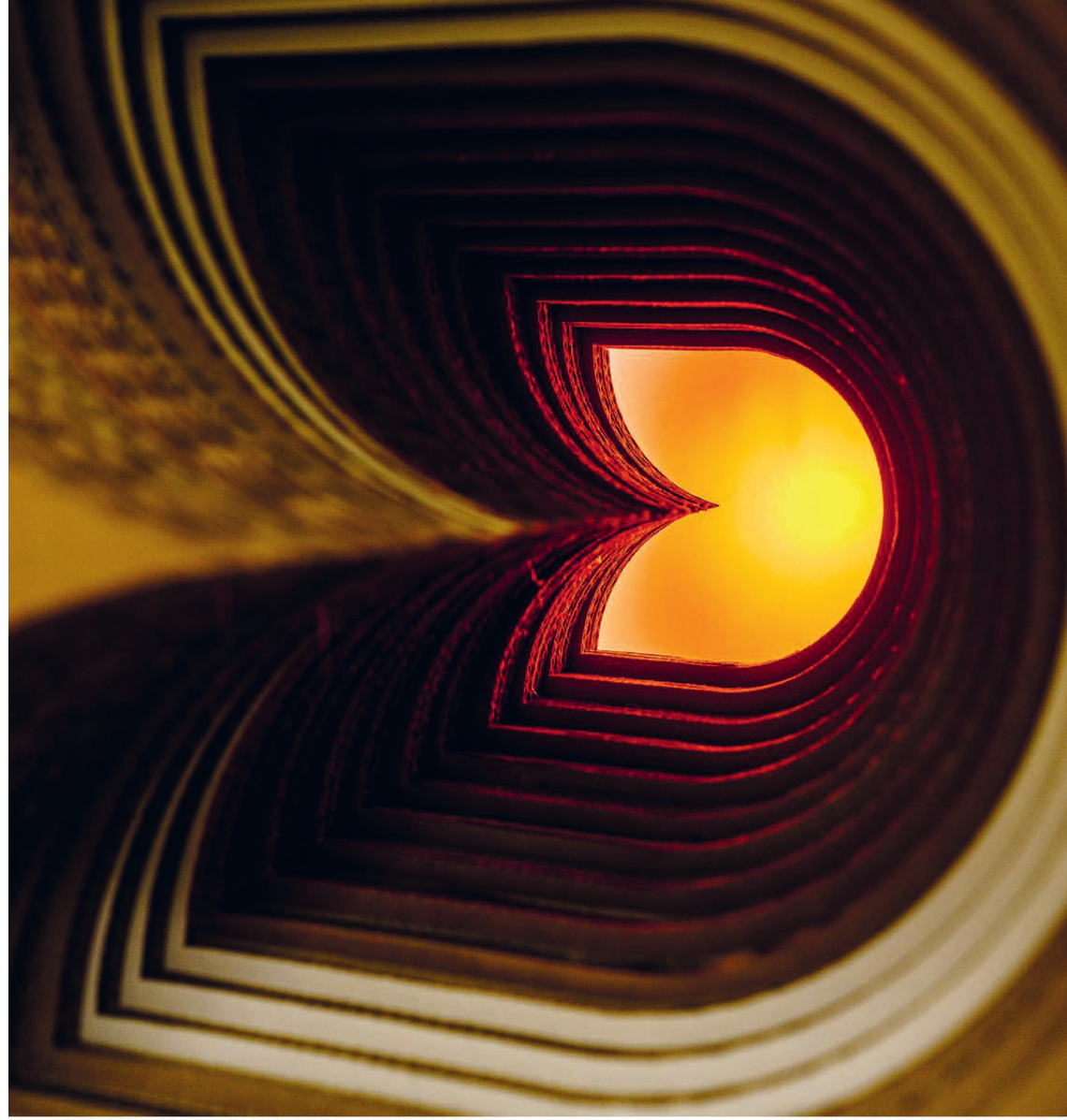

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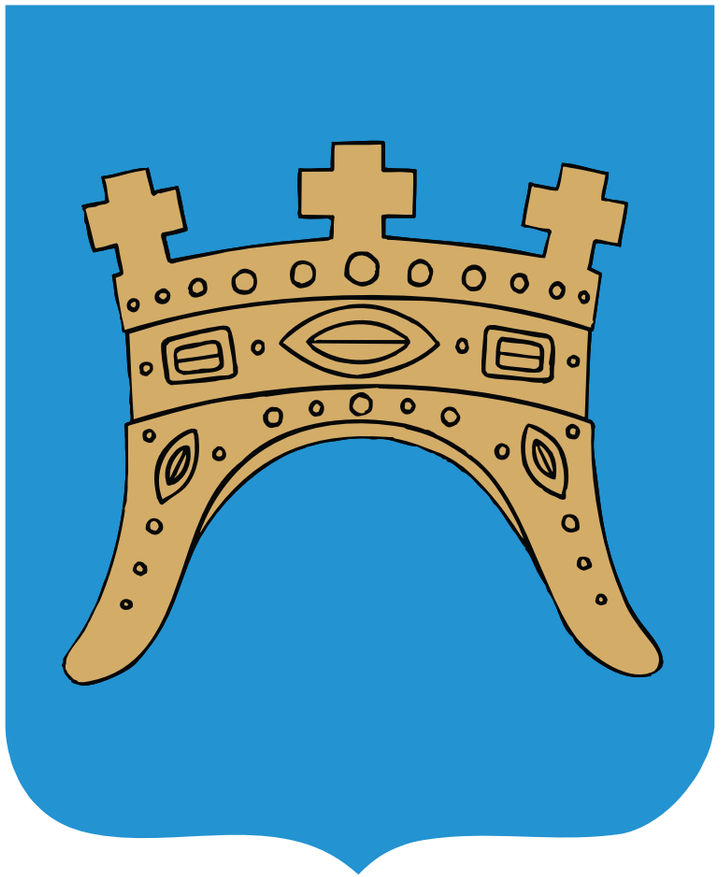

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