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

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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

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MESSENGER RNA TO INDUCE TISSUE HEALING

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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

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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

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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

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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

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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

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

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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

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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

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

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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

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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

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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)

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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

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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

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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 CELLULAT 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

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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

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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

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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 FPREVENTIVE 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

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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

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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

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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

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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