40 Years of Excellence in Skeletal Biology and Regenerative Medicine - Laboratory for Mineralized Tissues (1986–2026) at the University of Zagreb School of Medicine

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Abstract

The Laboratory for Mineralized Tissues (LMT) was established in 1986 at the University of Zagreb School of Medicine within the Department of Anatomy "Drago Perović" and, over the past four decades, has developed into a leading center for bone biology and regenerative medicine. The Laboratory's research is primarily focused on bone morphogenetic proteins (BMPs), resulting in significant insights into their structure, function, and therapeutic potential. Among the most important discoveries are the identification of new members of the BMP family, elucidation of their roles in bone and systemic biology, and the discovery of BMP6 as a key regulator of iron metabolism. Of particular translational significance are the Laboratory's achievements that culminated in the development of OSTEOGROW—an innovative therapeutic solution for bone regeneration based on recombinant human BMP6 delivered within an autologous blood coagulum. LMT has coordinated numerous major national and international projects (e.g., FP7 OSTEOGROW, H2020 OSTEOproSPINE, EIC Accelerator OSTEOforUNION) and has trained more than 35 doctoral candidates, many of whom now hold prominent academic and clinical positions. The Laboratory has established an extensive international network of collaborations and played a leading role in organizing major international scientific conferences. The scientific excellence of LMT was further recognized in 2015 when it became the central research unit of the newly established Center of Excellence for Reproductive and Regenerative Medicine. This paper provides an overview of LMT's key scientific and professional contributions, its translational achievements, and its vision for future research directions and development.

Keywords: bone morphogenetic proteins, BMPs, TGF-β, bone regeneration, regenerative medicine, bone tissue engineering, mineralized tissues, translational research, OSTEOGROW

Sažetak

40 godina izvrsnosti u biologiji skeletnog sustava i regenerativnoj medicini – Laboratorij za mineralizirana tkiva (1986.–2026.) Medicinskog fakulteta Sveučilišta u Zagrebu

Laboratorij za mineralizirana tkiva (LMT) osnovan je 1986. godine na Medicinskom fakultetu Sveučilišta u Zagrebu, u sklopu Zavoda za anatomiju „Drago Perović", te se tijekom protekla četiri desetljeća razvio u vodeći centar za koštanu biologiju i regenerativnu medicinu. Istraživački rad Laboratorija primarno je usmjeren na koštane morfogenetske proteine (engl. Bone Morphogenetic Proteins, BMP), a rezultirao je važnim otkrićima o njihovoj strukturi, funkciji i terapijskom potencijalu. Među najznačajnijim doprinosima izdvajaju se identifikacija novih članova BMP obitelji, razjašnjenje njihovih uloga u koštanoj i sustavnoj biologiji te otkriće BMP6 kao ključnog regulatora metabolizma željeza. Poseban značaj imaju translacijska dostignuća Laboratorija koja su kulminirala razvojem lijeka OSTEOGROW – inovativnog terapijskog rješenja za regeneraciju kosti temeljenog na rekombinantnom humanom BMP6, apliciranom unutar autolognog krvnog ugruška. LMT je koordinirao niz značajnih nacionalnih i međunarodnih projekata (npr. FP7 OSTEOGROW, H2020 OSTEOproSPINE, EIC Accelerator OSTEOforUNION) te su djelatnici laboratorija mentorirali više od 35 doktoranada, od kojih mnogi danas zauzimaju istaknute akademske i kliničke pozicije. Laboratorij je uspostavio široku međunarodnu mrežu suradnji i imao vodeću ulogu u organizaciji međunarodnih znanstvenih skupova. Znanstvena izvrsnost LMT-a potvrđena je 2015. godine proglašenjem nacionalnog Znanstvenog centra izvrsnosti za reproduktivnu i regenerativnu medicinu. Ovaj rad pruža pregled ključnih znanstvenih i stručnih doprinosa LMT-a, njegovih translacijskih postignuća te vizije budućeg razvoja i istraživačkih smjerova.

Ključne riječi: koštani morfogenetski proteini, BMP-ovi, TGF-β, regeneracija kosti, regenerativna medicina, tkivno inženjerstvo kosti, mineralizirana tkiva, translacijska istraživanja, OSTEOGROW

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Introduction

The Laboratory for Mineralized Tissues (LMT) was established at the University of Zagreb School of Medicine in 1986. It is located within the Department of Anatomy "Drago Perović" and operates as an integral part of the Center for Translational and Clinical Research. Since its foundation, LMT has grown into a leading research unit, recognized both nationally and internationally for its contributions to skeletal biology and regenerative medicine (Figure 1).

The central research focus of LMT is directed toward investigating the biology of bone morphogenetic proteins (BMPs) and their applications in regenerative medicine. Over the years, the Laboratory has made significant discoveries in elucidating the role and structure of members of the transforming growth factor-beta (TGF-β) superfamily, advancing knowledge in bone biology, as well as in the pathophysiology of diseases affecting the skeletal system. During the last two decades, the emphasis of LMT research has progressively shifted toward the development of innovative therapeutic approaches based on BMPs. A major achievement of this effort was the discovery of OSTEOGROW, an innovative medicinal product for bone regeneration composed of recombinant human bone morphogenetic protein 6 (rhBMP6) delivered within an autologous blood coagulum (ABC) (1). In collaboration with leading national and international institutions, scientists from LMT conducted the complete preclinical development of this medicinal product and coordinated Phase I/II clinical trials. This endeavor represents a unique example at the global level of a medicinal product being developed entirely within an academic institution, from the initial concept through preclinical testing to early-phase clinical evaluation.

The scientific excellence of LMT in basic, translational, and clinical research was formally acknowledged in 2015, when the Laboratory became the central research unit of the newly established Center of Excellence for Reproductive and Regenerative Medicine. In addition, LMT has successfully acquired and implemented a number of highly competitive national and international research projects. Among these, the FP7 project OSTEOGROW, the H2020 project OSTEOproSPINE, and the EIC Accelerator project OSTEOforUNION stand out for their scientific significance and complexity. Through the conduct of these projects, LMT has established extensive collaborations with leading Croatian and international scientific institutions, thereby further strengthening its role in the scientific community. Equally important, the Laboratory's staff remain strongly dedicated to the education and training of young scientists, as evidenced by the numerous doctoral dissertations, master's theses, and graduate theses completed within LMT.

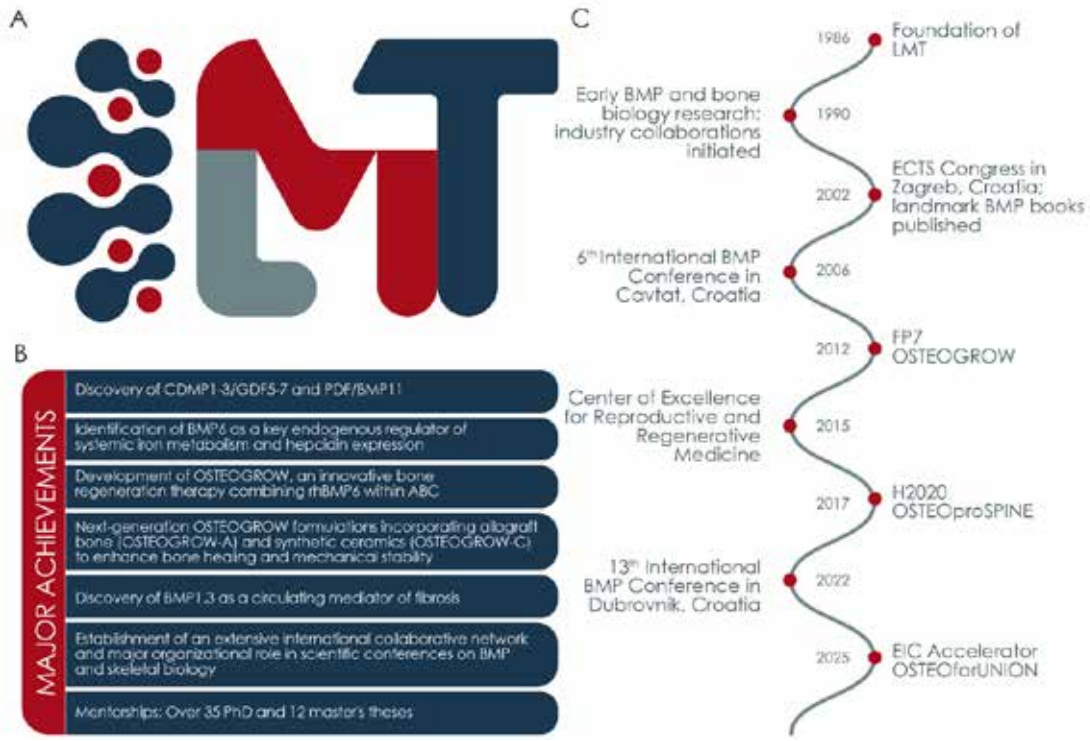


Figure 1. (A)A new logo of the Laboratory for Mineralized Tissues (LMT). (B) Overview of the major scientific discoveries, translational achievements, and academic contributions of the LMT, including the discovery of novel bone morphogenetic proteins and regulators of skeletal biology, as well as the development of innovative bone regeneration therapies (OSTEOGROW platform). (C) Timeline highlighting key milestones in the history of the LMT, including major research grants and projects, the organization of international scientific conferences, and the establishment of the Center of Excellence for Reproductive and Regenerative Medicine.

The present paper provides an overview of the most significant scientific discoveries originating from LMT, as well as the activities of its researchers in project implementation, education of young scientists, and the internationalization of research. Finally, it outlines the vision for the future development of LMT and the broader field of regenerative medicine.

1. Main Scientific Discoveries

Research on BMPs has profoundly transformed both experimental biology and clinical medicine. BMPs, members of the TGF-β superfamily, play a crucial role during embryonic development, regulating body axis formation and the development of multiple organs and organ systems, including the heart, lungs, kidneys, digestive tract, and nervous system (2-7). Clinically, BMPs are applied to accelerate and induce bone formation in patients undergoing spinal fusion, as well as in cases of segmental bone defects and non-unions (8-23). Their functional scope has further expanded through extensive studies on their role in the regeneration of bone, kidney, and articular cartilage. This line of research has become a central focus of the Laboratory, driving key scientific discoveries, patented innovations, and the development of novel therapeutic strategies for bone regeneration. The most significant scientific discoveries of LMT, which have resulted in the publication of more than 240 manuscripts in high-impact journals such as The New England Journal of Medicine, Cell, Nature Genetics, Bone, Nature Microbiology, Nature Communications, The Journal of Clinical Investigation, Proceedings of the National Academy of Sciences of the United States of America (PNAS), Biomaterials Research, Cancer Research, Gastroenterology, Circulation, Blood, Journal of Bone and Mineral Research, International Orthopaedics, and The Journal of Biological Chemistry, collectively cited over 16,600 times, are highlighted below (Figure 2A-C).



Figure 2. (A–C) Covers of high-impact international scientific journals (Cell, Nature Genetics, and Bone) featuring discoveries and research achievements of the Laboratory for Mineralized Tissues, including studies related to extracellular matrix biology, BMP6 regulation of iron metabolism, and bone regeneration. (D–G) Covers of landmark scientific books dedicated to the biology, regenerative potential, and clinical applications of bone morphogenetic proteins (BMPs), edited and published by members of the Laboratory for Mineralized Tissues. These volumes significantly contributed to the dissemination and advancement of BMP research in skeletal biology and regenerative medicine.

a) Discovery of Structure and Function of Genes and Proteins from the TGF-β Superfamily

Within this field, the Laboratory has been responsible for a number of seminal discoveries that have advanced the understanding of BMP biology and its clinical potential. Among the most significant is the discovery of cartilage-derived morphogenetic proteins (CDMP-1, -2, and -3; also known as GDF-5, -6, and -7 or BMP-12, -13, and -14), as well as prostate-derived factor (PDF; also known as BMP-11) (24-26). These findings provided the basis for further functional characterization of BMPs, including their purification and in vitro demonstration as potent inducers of osteoblast precursor cell differentiation into fully mature osteoblasts, and their ability to reverse the inhibitory effects of TGF-β on cell differentiation (27-31). This principle was later confirmed in collaborative studies with scientists from the Universities of Leiden and Bern as a key mechanism by which TGF-β induces epithelial-to-mesenchymal transition in prostate and breast cancer (32, 33). Additional advances include the characterization of tissues and organs producing BMPs at the mRNA and protein level during embryonic and postnatal development (29, 34, 35), as well as the discovery that BMP7 not only induces kidney mesenchyme formation during fetal development but also prevents ischemic and nephrotoxic acute and chronic renal failure (4, 36-38). Mechanistically, this renoprotective effect involves prevention of TGF-β–induced fibrogenesis and inflammation, as well as stimulation of epithelial regeneration through recapitulation of the embryonic developmental cascade mediated by specific BMP type II receptors (4). Another landmark achievement of the Laboratory, conducted in collaboration with Harvard Medical School, was the identification of BMP6 as a key endogenous regulator of hepcidin expression and systemic iron metabolism (39-41). We demonstrated that genetic ablation of BMP6 results in a hereditary hemochromatosis–like phenotype, characterized by reduced hepcidin expression and tissue iron overload, thereby establishing BMP6 as the physiological ligand for hemojuvelin in the maintenance of iron homeostasis (39). Furthermore, in collaboration with colleagues from the University of Oxford, we demonstrated that BMP/SMAD activity influences antiviral immunity and that BMP6 correspondingly regulates a gene repertoire reminiscent of type I interferon (IFN) signaling (42). These discoveries expanded the biological significance of BMPs beyond skeletal and developmental processes, directly linking BMP signaling to systemic metabolic regulation. Translational studies further demonstrated the effectiveness of local BMP7 application in children and adults (10, 19, 43-50) with delayed bone healing, and revealed its capacity, along with other recombinant BMPs, to stimulate articular cartilage regeneration and to facilitate the incorporation of reconstructed anterior cruciate ligaments in large animal models (48). Moreover, systemic administration of BMP6 has been shown to restore bone volume and microarchitecture in aged, ovariectomized rats by simultaneously stimulating bone formation and suppressing bone resorption, suggesting its potential use in osteoporosis therapy (51, 52).

b) Development of OSTEOGROW Family Innovative Therapeutic Solutions for Bone Regeneration

OSTEOGROW is a novel bone regeneration therapy developed in the Laboratory for Mineralized Tissues, consisting of rhBMP6 delivered within autologous blood coagulum (ABC) (1) (Figure 3). The rationale for this approach arose from the serendipitous discovery that ABC serves as a natural physiological carrier for BMPs, providing a biocompatible scaffold in which rhBMP6 binds tightly to plasma proteins within the fibrin meshwork (1, 53-55). Among osteoinductive BMPs, rhBMP6 was selected as the optimal candidate because it requires significantly lower doses than rhBMP2 or rhBMP7 (56, 57). Its superior potency was explained by resistance to noggin inhibition and by its dual role in bone remodeling (58). Extensive preclinical studies provided proof of concept for OSTEOGROW's efficacy and safety. In rat subcutaneous implant assays, rhBMP6/ABC induced robust endochondral ossification (1, 59), while in rabbit critical-size segmental defect models, OSTEOGROW achieved complete defect bridging and restoration of bone architecture in a dose-dependent manner (59). Furthermore, the safety and efficacy of OSTEOGROW have been demonstrated in Phase I/II clinical trials in patients undergoing high tibial osteotomy (HTO) (60) and in patients with distal radial fractures (DRF) (61) (Figure 3). To further expand clinical applications to spinal fusion and load-bearing sites, a compression-resistant matrix (CRM) was required to withstand mechanical forces. The first CRM-based formulation, OSTEOGROW-A, incorporated allograft bone particles within ABC (62, 63). In rabbit and sheep posterolateral spinal fusion (PLF) models, OSTEOGROW-A promoted uniform bone formation, creeping substitution of allograft particles, and mechanically competent fusion (62) (Figure 3). These promising results with OSTEOGROW-A led to Phase II clinical evaluation in patients undergoing posterior lumbar interbody fusion (PLIF), while the next-generation formulation, OSTEOGROW-B, combining rhBMP6 in ABC with autograft bone, was subsequently evaluated in a randomized, placebo-controlled Phase II study in patients undergoing transforaminal lumbar interbody fusion (TLIF) (64) (Figure 3). However, both allograft- and autograft-based approaches have inherent limitations, including limited availability and variability in graft quality for allograft, as well as donor-site morbidity associated with autograft harvesting, prompting the development of a next-generation formulation using synthetic ceramics (65-67).



Figure 3. Schematic overview of the Osteogrow family of products, including formulation components, biomaterial carriers, corresponding product variants (OSTEOGROW, OSTEOGROW-A, -B, -C, and -D), and their intended clinical indications in orthopedic and spinal applications. HTO – high tibial osteotomy; DRF – distal radius fracture; ARA – alveolar ridge augmentation; PLIF – posterior lumbar interbody fusion; TLIF – transforaminal lumbar interbody fusion; FNU – fracture non-union; CPT – congenital pseudarthrosis of the tibia.

OSTEOGROW-C combines rhBMP6/ABC with synthetic calcium phosphate ceramics, which serve as CRM and provide both mechanical stability and an osteoconductive environment (68-70) (Figure 4A). Preclinical studies systematically examined the influence of ceramic chemistry (tricalcium phosphate [TCP], hydroxyapatite [HA], and biphasic calcium phosphate [BCP]) and particle size on the quality and quantity of new bone (68, 71). These studies established that ceramic composition and morphology can be tailored to optimize osteogenesis and implant handling properties. The efficacy of OSTEOGROW-C was then validated in clinically relevant large-animal models (68, 72-76). In rabbits, OSTEOGROW-C promoted posterolateral spinal fusion (72, 77), with uniform osseointegration of new bone and superior biomechanical competence compared to allograft controls (62). In sheep, OSTEOGROW-C containing TCP/HA ceramics achieved consistent fusion between lumbar transverse processes within 9–14 weeks (78) (Figure 4B). OSTEOGROW-C also outperformed an FDA-approved formulation containing rhBMP2/ACS (Infuse) in rabbit ulnar segmental defect models, demonstrating faster and more reliable bridging with higher radiographic scores and confined bone formation (75, 79) (Figure 4C). Moreover, translational relevance was demonstrated in a veterinary case: a dog with a 3 cm multisegmented humeral defect, refractory to conventional fixation, was successfully treated with OSTEOGROW-C (80). Progressive bridging and cortical remodeling restored limb function, preventing amputation and underscoring OSTEOGROW's therapeutic potential in complex non-unions (81). Furthermore, long-term studies examined the durability of regenerated bone and demonstrated that local application of zoledronate, bound to ceramic particles within OSTEOGROW-C implants, sustained bone volume for over one year in rats (82). These findings suggest that bisphosphonate supplementation may help stabilize newly formed bone in challenging clinical conditions such as congenital pseudoarthrosis (85,86)(81, 83) (Figure 3).

Taken together, these preclinical studies consistently demonstrate that OSTEOGROW and its formulations (OSTEOGROW-A and OSTEOGROW-C) provide safe, potent, and spatially controlled bone regeneration at low rhBMP6 doses. OSTEOGROW-C, in particular, combines the biological efficacy of rhBMP6/ABC with the mechanical advantages of synthetic ceramics, achieving reliable spinal fusion and large defect repair in multiple animal models. Compared to existing BMP-based devices, OSTEOGROW avoids complications of ectopic ossification, inflammation, and osteolysis, while producing biomechanically competent, histologically mature bone. These findings establish OSTEOGROW-C as a promising therapeutic solution for bone regeneration and spinal fusion, currently advancing toward Phase III clinical evaluation.

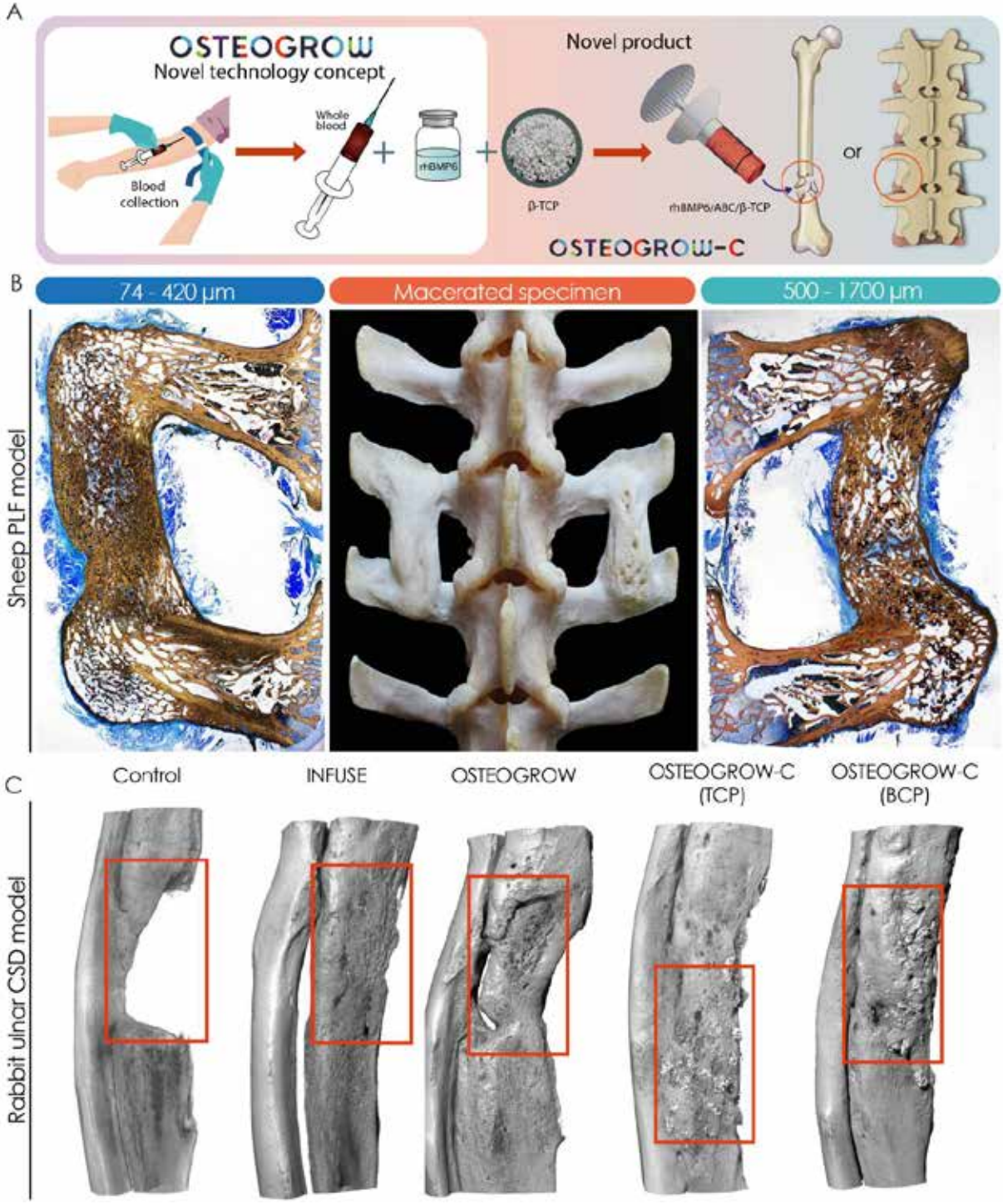


Figure 4. (A) Schematic illustration of the preparation of the Osteogrow-C implant, comprising rhBMP6 incorporated into an autologous blood coagulum and combined with synthetic ceramic for applications in bone regeneration and spinal fusion procedures. (B) Successful spinal fusion was achieved using Osteogrow-C implants containing small (74–420 µm) and medium-sized (500–1700 µm) ceramic particles in a sheep posterolateral spinal fusion (PLF) model. Effective bone formation and osseointegration are demonstrated in both histological sections and macerated specimens. Modified from Ivanjko et al., Scientific Reports, 2023. (C) Successful healing of a rabbit ulnar segmental defect following treatment with Osteogrow-C implants containing TCP and BCP ceramic particles, compared with control samples, as well as Infuse and Osteogrow implants. Modified from Stokovic et al., Biomaterials Research, 2025.

c) BMP1.3 Inhibition in Fibrotic Diseases: From Mechanisms to Therapy

We have identified BMP1.3 as a circulating factor that drives fibrosis across multiple organs. Detected in plasma from both healthy individuals and patients with chronic kidney disease, BMP1.3 acts as an active enzyme contributing to tissue scarring (84). In animal models, recombinant BMP1.3 worsened kidney fibrosis and reduced survival, whereas neutralizing antibodies against BMP1.3 preserved renal function, limited extracellular matrix accumulation, and improved outcomes (84). Mechanistically, BMP1.3 enhances profibrotic gene expression, including collagen I, Tgfb1, and β-catenin, while suppressing antifibrotic molecules like decorin, via an integrin β1–dependent pathway independent of canonical BMP or Wnt signaling (84). Beyond the kidney, BMP1.3 promotes fibrosis in the liver, heart, and skeletal muscle (85-87). We have further demonstrated that in liver injury, inhibition of BMP1.3 reduces collagen deposition and TGFβ1 activation (85). Similarly, after myocardial infarction, we have demonstrated that neutralization of BMP1.3 diminishes fibrosis, supports cardiomyocyte survival, and improves cardiac function (86, 88). Furthermore, our preliminary data revealed that in the MDC1A mouse model of congenital muscular dystrophy, BMP1.3 was strongly upregulated, suggesting that its blockade could protect muscle tissue by reducing pathological matrix accumulation (87). Among all Bmp1 splice variants, BMP1.3 uniquely circulates in plasma and correlates with disease severity (89). Taken together, our findings establish BMP1.3 as a central systemic mediator of fibrosis and underscore antibody-based inhibition as a promising therapeutic strategy for a range of chronic fibrotic diseases.

d) Beyond BMP Biology

Beyond BMP biology, the Laboratory has contributed to the identification and characterization of several other molecular mechanisms relevant to skeletal and renal regeneration. Novel small molecules specifically targeting prostaglandin E2 (PGE2) and PGE4 receptors were discovered through high-throughput screening, demonstrating efficacy in regenerating critical bone defects, accelerating fracture healing, and stimulating renal repair following acute and chronic renal failure (24, 90, 91). In addition, the discovery of the FRZB protein (secreted frizzled-related protein 3; sFRP3), a novel regulator of Wnt signaling with essential roles in early development and bone and joint formation, provided a new perspective on morphogenetic signaling pathways (92). The Laboratory also demonstrated that osteoblasts interact with discrete domains of laminin and type IV collagen within basement membranes, thereby suggesting that the smallest blood vessels regulate bone growth and repair by stimulating cell receptors and delivering growth factors bound to extracellular matrix proteins (93). Furthermore, intermittent administration of thyroid-stimulating hormone (TSH) at low concentrations was shown to exert an anabolic effect on bone without altering thyroid gland function, providing the first evidence for a direct TSH–bone axis (94). Parallel investigations introduced the concept of inflammation-induced osteoporosis, showing that granulomatosis in rats leads to bone loss through impaired osteoblast function and systemic inflammatory mediators, while leaving osteoclast function unaffected (94, 95). Additionally, studies into aluminum-induced rickets and osteomalacia in uremia revealed that the primary pathogenic mechanism is decreased serum levels of the active vitamin D3 metabolite, $1,25(OH)_2D_3$, rather than direct aluminum toxicity (96). Importantly, supplementation with $1,25(OH)_2D_3$ was able to prevent the development of rickets in uremic animal models, offering a therapeutic rationale for patients undergoing dialysis (97). Collectively, these discoveries have provided fundamental insights into bone and kidney biology while establishing a translational framework that bridges basic science and clinical application. Finally, researchers from the LMT made significant contributions to the study of cranial anatomy through research conducted on the Zagreb Skull Collection housed at the Department of Anatomy "Drago Perović" (98-100).

2. Major Scientific Projects

Over the past 40 years, the Laboratory has carried out a wide range of research and development projects that have shaped its reputation and visibility within both the national and international scientific community. Since its establishment, more than 20 projects totaling approximately 30 million euros have been implemented in the Laboratory. The research focus has consistently encompassed bone biology, tissue regeneration, and the translational application of novel therapeutic strategies. Over time, projects have evolved from fundamental studies investigating the mechanisms of growth factor activity to the development of advanced biological drugs and implants designed for clinical application.

The first projects in the 1990s focused on the roles of the BMPs and the extracellular matrix in the morphogenesis of cartilage and bone. These investigations later expanded through collaborations with the pharmaceutical and biotechnology industry (e.g., Pfizer, Stryker Biotech, PLIVA, Genzyme). With Croatia's integration into the European research area, the Laboratory assumed leadership of several major international projects. Among them, the project "OSTEOGROW – Novel Bone Morphogenetic Protein 6 Biocompatible Carrier Device for Bone Regeneration" (2012–2017, FP7 HEALTH; €5,683,000) marked a significant milestone by enabling the development of an innovative system for bone regeneration based on rhBMP6 delivered within an autologous blood coagulum. Building on these results, the subsequent project "OSTEOproSPINE: Novel Bone Regeneration Drug 'OSTEOGROW': Therapeutic Solution for Lumbar Back Pain" (2017–2023, Horizon 2020; €6,000,000) explored the therapeutic potential of OSTEOGROW in the treatment of degen-

erative intervertebral disc disease. The most recent project, 'Drug Solution for Bone Fracture Nonunions – OSTEOforUNION' (2025–2029; EIC Accelerator: research component €2,500,000 and investment component €5,800,000), led by Genera Research with participation from the University of Zagreb School of Medicine, represents a pivotal translational advance in the management of fracture nonunions through a global Phase III clinical trial. Collectively, these endeavors illustrate the Laboratory's trajectory from fundamental biological research to the development of advanced therapeutic solutions with tangible potential for clinical application.

At the national level, the Laboratory has successfully implemented competitive projects funded by the Croatian Science Foundation. Noteworthy examples include the project "New targeted anabolic therapy for osteoporosis: BONE6-BIS consortium" and the project "BMP6Fe3 – Development of novel antibodies (biological drug) selectively inhibiting hepatic hepcidin expression for the treatment of anemia of chronic disease." These initiatives opened entirely new directions of research, not only in the field of anabolic therapy for osteoporosis but also in the development of biological drugs aimed at addressing anemia of chronic disease.

The scientific excellence of the Laboratory for Mineralized Tissues was formally acknowledged in 2015, when it was designated as the national Centre of Excellence for Reproductive and Regenerative Medicine (CERRM), with the Laboratory serving as one of its central research units (Figure 5). The implementation of the CERRM projects "Reproductive and regenerative medicine – exploring new platforms and potentials" (2017–2023; €5,043,465.84) and "Development of innovations and translational research in reproductive and regenerative medicine"(2024-2026; €1,498,241.71) secured state-of-the-art research infrastructure and provided a robust framework for long-term translational investigations (101). This achievement not only reinforced the Laboratory's capacity for cutting-edge research but also positioned it as a key contributor to the advancement of regenerative medicine in Croatia and beyond.

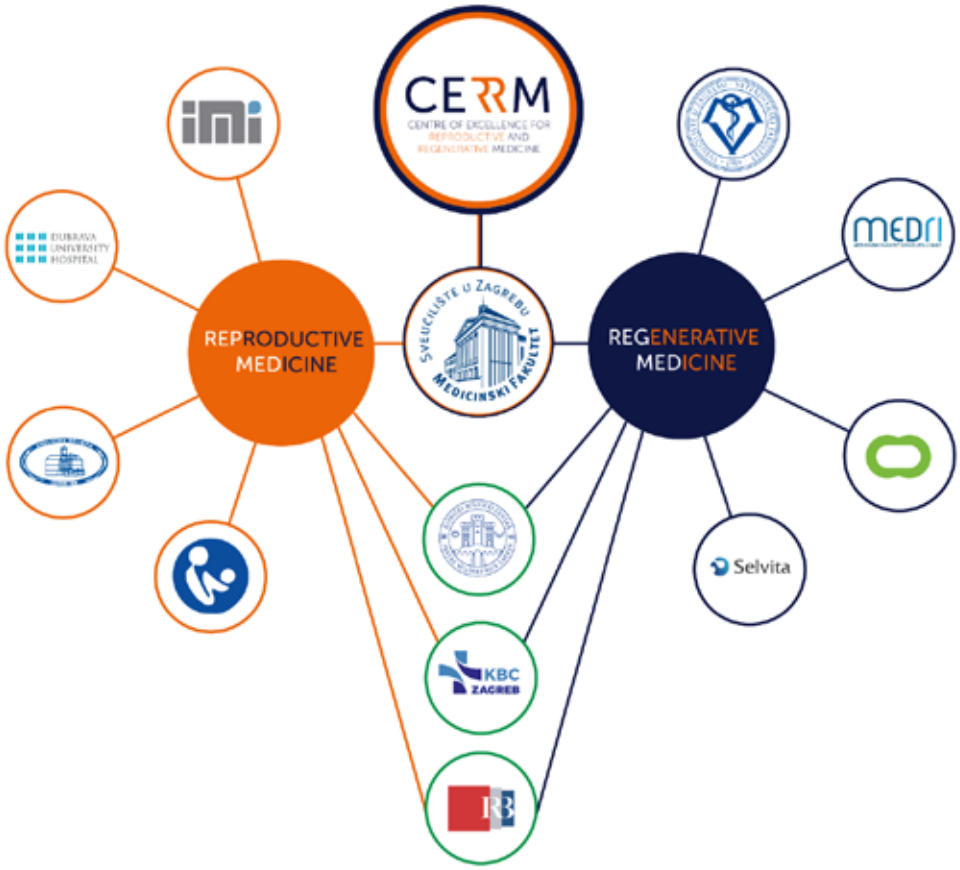


Figure 5. Schematic overview of the Center of Excellence for Reproductive and Regenerative Medicine (CERRM). The Center comprises two research units—the Regenerative Medicine Unit and the Reproductive Medicine Unit—and consists of the University of Zagreb School of Medicine as the coordinating institution, together with 11 academic, clinical, and industrial partners, including the University of Zagreb Faculty of Veterinary Medicine (UZFVM), University of Rijeka School of Medicine (MEDRI), University Hospital Centre Zagreb (UHCZ), University Hospital Centre Sestre milosrdnice (UHCSM), Ruđer Bošković Institute (RBI), Genera Research (GEN), Selvita (formerly Fidelta), Clinical Hospital Sveti Duh (CHSD), University Hospital Dubrava (UHD), Children's Hospital Zagreb (CHZ), and the Institute for Medical Research and Occupational Health (IMROH).

3. Mentorship and Education of Young Scientists

From its inception, the education and mentorship of young scientists and students have been recognized as among the most vital activities of the LMT. Rapidly establishing itself as a center of scientific excellence, the Laboratory has attracted numerous talented early-career researchers eager to pursue their doctoral dissertations within the Laboratory. To date, 35 doctoral dissertations and 12 master's theses have been successfully completed under its auspices. It is a source of considerable pride that several LMT doctoral candidates have been honored with awards for scientific excellence and productivity during the course of their dissertation research. Equally noteworthy is the fact that former LMT doctoral students now hold key positions in leading clinical hospitals, academic departments, and research institutions. The scope of the completed doctoral research has closely mirrored the Laboratory's principal scientific endeavors and projects. Topics have spanned diverse aspects of bone biology, the biological functions of bone morphogenetic proteins, and translational research in regenerative medicine. This alignment underscores the Laboratory's commitment to integrating fundamental research with clinically relevant applications. Throughout its history, the Laboratory has actively engaged students not only from the School of Medicine but also from related faculties, including the Faculty of Pharmacy and Biochemistry and the Faculty of Veterinary Medicine. To date, student research projects have received multiple Rector's and Dean's Awards. The education of young researchers continues to constitute a central pillar of the Center of Excellence for Reproductive and Regenerative Medicine. At present, a significant number of doctoral dissertations are being conducted within the Laboratory, ensuring the ongoing education of the next generation of scientific leaders.

4. Organization of Internationaland National Scientific Confereneces

The Laboratory has made substantial contributions to the organization of both international and national scientific conferences, as well as to the activities of scientific societies, including the International BMP Society/Conference and the European Calcified Tissue Society (Figure 6).

The International BMP Conference is the foremost global congress dedicated to bone morphogenetic proteins, founded by A. Hari Reddi in 1994 in Baltimore. Since its inception, a total of 14 congresses have been held worldwide, including in the USA, Japan, Croatia, Belgium, and Germany. The Laboratory played a leading role as the main organizer of the 6th International BMP Conference in Cavtat in 2006 and the 13th International BMP Conference in Dubrovnik in 2022 (102). In addition, the Laboratory organized the 1st and 2nd European Conferences of Bone Morphogenetic Proteins in Zagreb in 1998 and 2002, respectively. These congresses brought together leading scientists from around the world and served as important platforms for the exchange of knowledge, the presentation of key discoveries, and the dissemination of innovations in the field.

The European Calcified Tissue Society (ECTS) is the umbrella organization for researchers in the musculoskeletal field in Europe. Scientists from the Laboratory have been actively involved in ECTS activities for many years and participate annually in the ECTS Congress. Furthermore, in 2002, the Laboratory organized the 29th ECTS Congress in Zagreb. Laboratory staff also played a foundational role in establishing the Croatian Calcified Tissue Society, which has remained highly active over the years in organizing professional events and educational activities. Specifically, the Laboratory and the Croatian Calcified Tissue Society jointly organized ten Croatian Congresses on Osteoporosis (2001, 2003, 2005, 2007, 2009, 2011, 2013, 2014, 2015, 2017). These congresses served as important forums for the exchange of the latest knowledge and advances in the treatment of osteoporosis, as well as other musculoskeletal diseases. In recent years, Laboratory staff have also been actively participating in congresses organized by the Tissue Engineering and Regenerative Medicine Society (TERMIS). At the most recent Congress of the European Section of TERMIS held in Palma de Mallorca (Spain) in 2026, they organized the symposium "Advanced Biomaterials for Bone Regeneration," while at the previous congress held in Freiburg (Germany) in 2025, they organized the symposium "Novel Strategies and Devices for Bone Regeneration: Preclinical and Clinical Trials", where the latest insights into therapeutic approaches for achieving bone regeneration were presented and discussed.



Figure 6. Major international scientific conferences organized by the Laboratory for Mineralized Tissues. (A–B) The First European BMP Conference, held in Zagreb in 1998. (A) Opening ceremony of the conference. (B) Academicians Slobodan Vukicevic and Marko Pecina with Professor A. H. Reddi. (C) Invited speakers at the 6th International BMP Conference, held in Cavtat in 2006.(D) Slobodan Vukicevic, Nikola Stokovic, Natalia Ivanjko, and Mihaela Peric organized a symposium at the TERMIS Congress in Palma de Mallorca, Spain. (E–G) The 13th International BMP Conference, held in Dubrovnik in 2022. (E) Official conference logo. (F) Slobodan Vukicevic with Professor A. H. Reddi. (G) Group photograph of conference participants.

5. Books And Special Issues On Bmp Biology

The Laboratory has played a significant role in publishing books that synthesized available knowledge and key insights into bone morphogenetic proteins. In particular, Slobodan Vukicevic, Head of the LMT, together with his long-term collaborator Kuber T. Sampath (Massachusetts, USA), co-edited four landmark volumes on BMPs: Bone Morphogenetic Proteins: From Laboratory to Clinical Practice (Birkhäuser Verlag and Springer Basel AG, 2002) (103), Bone Morphogenetic Proteins: Regeneration of Bone and Beyond (Birkhäuser Verlag and Springer Basel AG, 2004) (104), Bone Morphogenetic Proteins: From Local to Systemic Therapeutics (Birkhäuser Verlag, 2008) (105), and Bone Morphogenetic Proteins: Systems Biology Regulators (Springer International Publishing AG, 2017) (106) (Figure 2D-G). These volumes brought together leading international experts in the field, who provided comprehensive overviews of BMP biology, translational research, and clinical applications. The books cover a broad spectrum of topics—from the historical perspective of BMP discovery and their systems biology, to roles in embryonic skeletogenesis and craniofacial development, structural and functional aspects of BMP signaling, and preclinical studies on their role in osteogenesis and chondrogenesis. In addition, on the occasion of the 13th International BMP Conference held in Dubrovnik, a special issue of the distinguished journal Bone was published, entitled "The Role of Bone Morphogenetic Proteins in Musculoskeletal System Biology". This issue highlighted recent advances in BMP biology and provided an up-to-date synthesis of the field.

6. Future Directions and Perspectives

Regenerative medicine is today one of the most dynamic and transformative areas of biomedical research, with the potential to profoundly improve human health and quality of life. Over the past four decades, the LMT has significantly contributed to this field, from fundamental discoveries in BMP biology to the translation of these findings into novel therapeutic concepts.

A central focus of current translational activities is the completion of clinical trials of OSTEOGROW, a unique bone regeneration drug fully developed within the Laboratory. Building on this success, efforts are directed toward the next generation of OSTEOGROW formulations, such as OSTEOGROW-D, which combines rhBMP6 with the bisphosphonate zoledronate to further enhance therapeutic efficacy and durability of regenerated bone. At the same time, the Laboratory continues to pursue pioneering research on the fundamental mechanisms of skeletal biology and regenerative medicine. This includes elucidating the processes of ectopic osteogenesis induced by BMPs, optimizing calcium phosphate–based ceramics and other biomaterials for bone repair, and designing novel strategies that integrate biological and synthetic components for bone regeneration. Beyond skeletal regeneration, LMT actively contributes to the broader field of regenerative medicine through its research on fibrosis and the development of innovative antifibrotic therapies targeting BMP1.3. Equally important, LMT continues its long-standing research tradition on the systemic functions of BMPs, particularly BMP3 and BMP6, which play key roles not only in bone biology but also in the regulation of systemic physiology, tissue homeostasis, inflammation, and organ regeneration (107-111).

As it enters its fifth decade, the Laboratory for Mineralized Tissues remains firmly committed to integrating basic, translational, and clinical research with the goal of developing innovative, safe, and effective solutions for skeletal diseases. With its multidisciplinary expertise, strong international collaborations, and dedication to mentoring the next generation of scientists, LMT is well-positioned to continue innovative research in skeletal biology and regenerative medicine.

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References

1. Vukicevic S, Oppermann H, Verbanac D, Jankolija M, Popek I, Curak J, et al. The clinical use of bone morphogenetic proteins revisited: a novel biocompatible carrier device OSTEOGROW for bone healing. International Orthopaedics. 2014;38:635-647.
2. Kim RY, Robertson EJ, Solloway MJ. Bmp6 and Bmp7 are required for cushion formation and septation in the developing mouse heart. Developmental Biology. 2001;235:449-466.
3. De Santa Barbara P, Williams J, Goldstein AM, Doyle AM, Nielsen C, Winfield S, et al. Bone morphogenetic protein signaling pathway plays multiple roles during gastrointestinal tract development. Developmental Dynamics. 2005;234:312-322.
4. Simic P, Vukicevic S. Bone morphogenetic proteins in development and homeostasis of kidney. Cytokine Growth Factor Rev. 2005;16:299-308.
5. Simic P, Vukicevic S. Bone morphogenetic proteins: from developmental signals to tissue regeneration. Conference on bone morphogenetic proteins. EMBO Rep. 2007;8:327-331.
6. Vukicevic S, Peric M, Oppermann H, Stokovic N, Ivanjko N, Erjavec I, et al. Bone morphogenetic proteins: From discovery to development of a novel autologous bone graft substitute consisting of recombinant human BMP6 delivered in autologous blood coagulum carrier. Rad CASA - Medical Sciences. 2020;544:26-41.
7. Vukicevic S, Stavljenic A, Pecina M. Discovery and clinical applications of bone morphogenetic proteins. European Journal of Clinical Chemistry and Clinical Biochemistry. 1995;33:661-671.
8. Dawson E, Bae HW, Burkus JK, Stambough JL, Glassman SD. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. Journal of Bone and Joint Surgery (American Volume). 2009;91:1604-1613.
9. Prodoehl JA, Bakaes Y, Tucker M, Voss F. Off-label: The results of adjunctive bone morphogenetic protein for challenging femur fractures; a review of two cases. Trauma Case Rep. 2024;50:100979.
10. Bilic R, Simic P, Jelic M, Stern-Padovan R, Dodig D, van Meerdervoort HP, et al. Osteogenic protein-1 (BMP-7) accelerates healing of scaphoid non-union with proximal pole sclerosis. International Orthopaedics. 2006;30:128-134.
11. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. Journal of Spinal Disorders & Techniques. 2002;15:337-349.
12. Dimar JR, 2nd, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. Journal of Bone and Joint Surgery (American Volume). 2009;91:1377-1386.
13. Kim HJ, Buchowski JM, Zebala LP, Dickson DD, Koester L, Bridwell KH. RhBMP-2 is superior to iliac crest bone graft for long fusions to the sacrum in adult spinal deformity: 4- to 14-year follow-up. Spine. 2013;38:1209-1215.
14. Jones AL, Bucholz RW, Bosse MJ, Mirza SK, Lyon TR, Webb LX, et al. Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. A randomized, controlled trial. Journal of Bone and Joint Surgery (American Volume). 2006;88:1431-1441.
15. Geesink RG, Hoefnagels NH, Bulstra SK. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. Journal of Bone and Joint Surgery (British Volume). 1999;81:710-718.
16. Magin MN, Delling G. Improved lumbar vertebral interbody fusion using rhOP-1: a comparison of autogenous bone graft, bovine hydroxylapatite (Bio-Oss), and BMP-7 (rhOP-1) in sheep. Spine. 2001;26:469-478.
17. Moghaddam-Alvandi A, Zimmermann G, Buchler A, Elleser C, Biglari B, Grutzner PA, et al. Results of nonunion treatment with bone morphogenetic protein 7 (BMP-7). Unfallchirurg. 2012;115:518-526.
18. Pecina M, Giltaij LR, Vukicevic S. Orthopaedic applications of osteogenic protein-1 (BMP-7). International Orthopaedics. 2001;25:203-208.
19. Pecina M, Haspl M, Jelic M, Vukicevic S. Repair of a resistant tibial non-union with a recombinant bone morphogenetic protein-7 (rh-BMP-7). International Orthopaedics. 2003;27:320-321.
20. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, et al. A pilot safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. European Spine Journal. 2003;12:495-500.
21. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, et al. A 2-year follow-up pilot study evaluating the safety and efficacy of op-1 putty (rhbmp-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. European Spine Journal. 2005;14:623-629.
22. White AP, Vaccaro AR, Hall JA, Whang PG, Friel BC, McKee MD. Clinical applications of BMP-7/OP-1 in fractures, nonunions and spinal fusion. International Orthopaedics. 2007;31:735-741.

23. El Bialy I, Jiskoot W, Reza Nejadnik M. Formulation, Delivery and Stability of Bone Morphogenetic Proteins for Effective Bone Regeneration. Pharm Res. 2017;34:1152-1170.
24. Paralkar VM, Grasser WA, Mansolf AL, Baumann AP, Owen TA, Smock SL, et al. Regulation of BMP-7 expression by retinoic acid and prostaglandin E(2). Journal of Cellular Physiology. 2002;190:207-217.
25. Chang SC, Hoang B, Thomas JT, Vukicevic S, Luyten FP, Ryba NJ, et al. Cartilage-derived morphogenetic proteins. New members of the transforming growth factor-beta superfamily predominantly expressed in long bones during human embryonic development. Journal of Biological Chemistry. 1994;269:28227-28234.
26. Paralkar VM, Vail AL, Grasser WA, Brown TA, Xu H, Vukicevic S, et al. Cloning and characterization of a novel member of the transforming growth factor-beta/bone morphogenetic protein family. Journal of Biological Chemistry. 1998;273:13760-13767.
27. Martinovic S, Borovecki F, Miljavac V, Kisic V, Maticic D, Francetic I, et al. Requirement of a bone morphogenetic protein for the maintenance and stimulation of osteoblast differentiation. Arch Histol Cytol. 2006;69:23-36.
28. Vukicevic S, Luyten FP, Reddi AH. Stimulation of the Expression of Osteogenic and Chondrogenic Phenotypes Invitro by Osteogenin. Proceedings of the National Academy of Sciences of the United States of America. 1989;86:8793-8797.
29. Vukicevic S, Latin V, Chen P, Batorsky R, Reddi AH, Sampath TK. Localization of osteogenic protein-1 (bone morphogenetic protein-7) during human embryonic development: high affinity binding to basement membranes. Biochem Biophys Res Commun. 1994;198:693-700.
30. Luyten FP, Yu YM, Yanagishita M, Vukicevic S, Hammonds RG, Reddi AH. Natural bovine osteogenin and recombinant human bone morphogenetic protein-2B are equipotent in the maintenance of proteoglycans in bovine articular cartilage explant cultures. Journal of Biological Chemistry. 1992;267:3691-3695.
31. Dieudonne SC, Semeins CM, Goei SW, Vukicevic S, Nulend JK, Sampath TK, et al. Opposite effects of osteogenic protein and transforming growth factor beta on chondrogenesis in cultured long bone rudiments. J Bone Miner Res. 1994;9:771-780.
32. Buijs JT, Henriquez NV, van Overveld PG, van der Horst G, Que I, Schwaninger R, et al. Bone morphogenetic protein 7 in the development and treatment of bone metastases from breast cancer. Cancer Research. 2007;67:8742-8751.
33. Buijs JT, Rentsch CA, van der Horst G, van Overveld PG, Wetterwald A, Schwaninger R, et al. BMP7, a putative regulator of epithelial homeostasis in the human prostate, is a potent inhibitor of prostate cancer bone metastasis in vivo. American Journal of Pathology. 2007;171:1047-1057.
34. Lyons KM, Pelton RW, Hogan BL. Organogenesis and pattern formation in the mouse: RNA distribution patterns suggest a role for bone morphogenetic protein-2A (BMP-2A). Development. 1990;109:833-844.
35. Helder MN, Ozkaynak E, Sampath KT, Luyten FP, Latin V, Oppermann H, et al. Expression Pattern of Osteogenic Protein-1 (Bone Morphogenetic Protein-7) in Human and Mouse Development. Journal of Histochemistry and Cytochemistry. 1995;43:1035-1044.
36. Vukicevic S, Kopp JB, Luyten FP, Sampath TK. Induction of nephrogenic mesenchyme by osteogenic protein 1 (bone morphogenetic protein 7). Proceedings of the National Academy of Sciences of the United States of America. 1996;93:9021-9026.
37. Vukicevic S, Basic V, Rogic D, Basic N, Shih MS, Shepard A, et al. Osteogenic protein-1 (bone morphogenetic protein-7) reduces severity of injury after ischemic acute renal failure in rat. Journal of Clinical Investigation. 1998;102:202-214.
38. Bosukonda D, Shih MS, Sampath KT, Vukicevic S. Characterization of receptors for osteogenic protein-1/bone morphogenetic protein-7 (OP-1/BMP-7) in rat kidneys. Kidney International. 2000;58:1902-1911.
39. Andriopoulos B, Jr., Corradini E, Xia Y, Faasse SA, Chen S, Grgurevic L, et al. BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. Nature Genetics. 2009;41:482-487.
40. Pauk M, Kufner V, Rumenovic V, Dumic-Cule I, Farkas V, Milosevic M, et al. Iron overload in aging Bmp6(-/-) mice induces exocrine pancreatic injury and fibrosis due to acinar cell loss. International Journal of Molecular Medicine. 2021;47.
41. Pauk M, Grgurevic L, Brkljacic J, Kufner V, Bordukalo-Niksic T, Grabusic K, et al. Exogenous BMP7 corrects plasma iron overload and bone loss in Bmp6-/- mice. Int Orthop. 2015;39:161-172.
42. Eddowes LA, Al-Hourani K, Ramamurthy N, Frankish J, Baddock HT, Sandor C, et al. Antiviral activity of bone morphogenetic proteins and activins. Nat Microbiol. 2019;4:339-351.
43. Djapic T, Kusec V, Jelic M, Vukicevic S, Pecina M. Compressed homologous cancellous bone and bone morphogenetic protein (BMP)-7 or bone marrow accelerate healing of long-bone critical defects. International Orthopaedics. 2003;27:326-330.

44. Mihelic R, Pecina M, Jelic M, Zoricic S, Kusec V, Simic P, et al. Bone morphogenetic protein-7 (osteogenic protein-1) promotes tendon graft integration in anterior cruciate ligament reconstruction in sheep. American Journal of Sports Medicine. 2004;32:1619-1625.
45. Pecina M, Jelic M, Martinovic S, Haspl M, Vukicevic S. Articular cartilage repair: the role of bone morphogenetic proteins. Int Orthop. 2002;26:131-136.
46. Smoljanovic T, Grgurevic L, Jelic M, Kreszinger M, Haspl M, Maticic D, et al. Regeneration of the skeleton by recombinant human bone morphogenetic proteins. Collegium Antropologicum. 2007;31:923-932.
47. Katic V, Majstorovic L, Maticic D, Pirkic B, Yin S, Kos J, et al. Biological repair of thyroid cartilage defects by osteogenic protein-1 (bone morphogenetic protein-7) in dog. Growth Factors. 2000;17:221-232.
48. Jelic M, Pecina M, Haspl M, Kos J, Taylor K, Maticic D, et al. Regeneration of articular cartilage chondral defects by osteogenic protein-1 (bone morphogenetic protein-7) in sheep. Growth Factors. 2001;19:101-113.
49. Haspl M, Pecina M, Orlic D, Cicak N. Arthroplasty after war injuries to major joints. Military Medicine. 1999;164:353-357.
50. Grgic M, Jelic M, Basic V, Basic N, Pecina M, Vukicevic S. Regeneration of articular cartilage defects in rabbits by osteogenic protein-1 (bone morphogenetic protein-7). Acta Medica Croatica. 1997;51:23-27.
51. Bordukalo-Niksic T, Kufner V, Vukicevic S. The Role Of BMPs in the Regulation of Osteoclasts Resorption and Bone Remodeling: From Experimental Models to Clinical Applications. Frontiers in Immunology. 2022;13:869422.
52. Grasser WA, Orlic I, Borovecki F, Riccardi KA, Simic P, Vukicevic S, et al. BMP-6 exerts its osteoinductive effect through activation of IGF-I and EGF pathways. Int Orthop. 2007;31:759-765.
53. Fan Q, Ma Q, Bai J, Xu J, Fei Z, Dong Z, et al. An implantable blood clot-based immune niche for enhanced cancer vaccination. Sci Adv. 2020;6.
54. Fan Q, Bai J, Shan H, Fei Z, Chen H, Xu J, et al. Implantable blood clot loaded with BMP-2 for regulation of osteoimmunology and enhancement of bone repair. Bioact Mater. 2021;6:4014-4026.
55. Shiu HT, Goss B, Lutton C, Crawford R, Xiao Y. Formation of blood clot on biomaterial implants influences bone healing. Tissue Eng Part B Rev. 2014;20:697-712.
56. Ivanjko N, Stokovic N, Milesevic M, Rumenovic V, Windhager R, Sampath KT, et al. rhBMP6 in autologous blood coagulum is a preferred osteoinductive device to rhBMP2 on bovine collagen sponge in the rat ectopic bone formation assay. Biomedicine and Pharmacotherapy. 2023;169:115844.
57. Mizrahi O, Sheyn D, Tawackoli W, Kallai I, Oh A, Su S, et al. BMP-6 is more efficient in bone formation than BMP-2 when overexpressed in mesenchymal stem cells. Gene Therapy. 2013;20:370-377.
58. Song K, Krause C, Shi S, Patterson M, Suto R, Grgurevic L, et al. Identification of a key residue mediating bone morphogenetic protein (BMP)-6 resistance to noggin inhibition allows for engineered BMPs with superior agonist activity. Journal of Biological Chemistry. 2010;285:12169-12180.
59. Grgurevic L, Oppermann H, Pecin M, Erjavec I, Capak H, Pauk M, et al. Recombinant Human Bone Morphogenetic Protein 6 Delivered Within Autologous Blood Coagulum Restores Critical Size Segmental Defects of Ulna in Rabbits. JBMR Plus. 2019;3:e10085.
60. Chiari C, Grgurevic L, Bordukalo-Niksic T, Oppermann H, Valentinitsch A, Nemecek E, et al. Recombinant Human BMP6 Applied Within Autologous Blood Coagulum Accelerates Bone Healing: Randomized Controlled Trial in High Tibial Osteotomy Patients. J Bone Miner Res. 2020;35:1893-1903.
61. Durdevic D, Vlahovic T, Pehar S, Miklic D, Oppermann H, Bordukalo-Niksic T, et al. A novel autologous bone graft substitute comprised of rhBMP6 blood coagulum as carrier tested in a randomized and controlled Phase I trial in patients with distal radial fractures. Bone. 2020;140:115551.
62. Grgurevic L, Erjavec I, Gupta M, Pecin M, Bordukalo-Niksic T, Stokovic N, et al. Autologous blood coagulum containing rhBMP6 induces new bone formation to promote anterior lumbar interbody fusion (ALIF) and posterolateral lumbar fusion (PLF) of spine in sheep. Bone. 2020;138:115448.
63. Vukicevic S, Grgurevic L, Erjavec I, Pecin M, Bordukalo-Niksic T, Stokovic N, et al. Autologous blood coagulum is a physiological carrier for BMP6 to induce new bone formation and promote posterolateral lumbar spine fusion in rabbits. Journal of Tissue Engineering and Regenerative Medicine. 2020;14:147-159.
64. Li W, Luo X, Zhou X, Liu B, Yang H, Gao L, et al. Bezeotermin Alfa (rhBMP-6) Administration in Lumbar Interbody Fusion Surgery Using a Posterior Approach: A Randomized, Double-Blinded, Placebo-Controlled Phase-2 Study. Journal of Bone and Joint Surgery (American Volume). 2025;107:2735-2743.
65. Baldwin P, Li DJ, Auston DA, Mir HS, Yoon RS, Koval KJ. Autograft, Allograft, and Bone Graft Substitutes: Clinical Evidence and Indications for Use in the Setting of Orthopaedic Trauma Surgery. Journal of Orthopaedic Trauma. 2019;33:203-213.
66. Mroz TE, Joyce MJ, Lieberman IH, Steinmetz MP, Benzel EC, Wang JC. The use of allograft bone in spine surgery: is it safe? Spine J. 2009;9:303-308.

67. Tomford WW. Bone allografts: past, present and future. Cell Tissue Bank. 2000;1:105-109.
68. Stokovic N, Ivanjko N, Erjavec I, Milosevic M, Oppermann H, Shimp L, et al. Autologous bone graft substitute containing rhBMP6 within autologous blood coagulum and synthetic ceramics of different particle size determines the quantity and structural pattern of bone formed in a rat subcutaneous assay. Bone. 2020;141:115654.
69. Vukicevic S, Stokovic N, Pecina M. Is ceramics an appropriate bone morphogenetic protein delivery system for clinical use? International Orthopaedics. 2019;43:1275-1276.
70. Stokovic N, Ivanjko N, Rumenovic V, Breski A, Sampath KT, Peric M, et al. Comparison of synthetic ceramic products formulated with autologous blood coagulum containing rhBMP6 for induction of bone formation. International Orthopaedics. 2022;46:2693-2704.
71. Stokovic N, Ivanjko N, Milesevic M, Sampath K, Vukicevic S. A simple rodent subcutaneous assay for identification of new osteoinductive molecules: The key method for screening of novel bone regeneration implants. Rad CASA - Medical Sciences. 2022;553 40-53.
72. Stokovic N, Ivanjko N, Pecin M, Erjavec I, Karlovic S, Smajlovic A, et al. Evaluation of synthetic ceramics as compression resistant matrix to promote osteogenesis of autologous blood coagulum containing recombinant human bone morphogenetic protein 6 in rabbit posterolateral lumbar fusion model. Bone. 2020;140:115544.
73. Stokovic N, Ivanjko N, Milesevic M, Muzina K, Pecin M, Maticic D, et al. Bone Induction as a Function of Size and Chemical Composition of Calcium Phosphate Granules in Osteogrow-C Evaluated in Animal Models: A 1-Year Follow-Up. Biomater Res. 2026;30:0337.
74. Stokovic N, Ivanjko N, Milesevic M, Matic Jelic I, Bakic K, Rumenovic V, et al. Synthetic ceramic macroporous blocks as a scaffold in ectopic bone formation induced by recombinant human bone morphogenetic protein 6 within autologous blood coagulum in rats. International Orthopaedics. 2020;45:1097-1107.
75. Stokovic N, Ivanjko N, Javor A, Pecin M, Muzina K, Stepanic ZM, et al. Regeneration of a Rabbit Segmental Defect with a New Bone Therapy: Autologous Blood Coagulum with Bone Morphogenetic Protein 6 and Synthetic Ceramics. Biomater Res. 2025;29:0140.
76. Stokovic N, Ivanjko N, Maticic D, Luyten FP, Vukicevic S. Bone Morphogenetic Proteins, Carriers, and Animal Models in the Development of Novel Bone Regenerative Therapies. Materials. 2021;14:3513.
77. Stokovic N, Ivanjko N, Pecin M, Erjavec I, Smajlovic A, Milesevic M, et al. Long-term posterolateral spinal fusion in rabbits induced by rhBMP6 applied in autologous blood coagulum with synthetic ceramics. Scientific Reports. 2022;12:11649.
78. Ivanjko N, Stokovic N, Pecin M, Vnuk D, Smajlovic A, Ivkic N, et al. Calcium phosphate ceramics combined with rhBMP6 within autologous blood coagulum promote posterolateral lumbar fusion in sheep. Scientific Reports. 2023;13:22079.
79. Javor A, Stokovic N, Ivanjko N, Luksa I, Capak H, Vrbanac Z. Diagnostic Imaging of the Skeletal System: Overview of Applications in Human and Veterinary Medicine. Bioengineering-Basel. 2025;12.
80. Pecin M, Stokovic N, Ivanjko N, Smajlovic A, Kreszinger M, Capak H, et al. A novel autologous bone graft substitute containing rhBMP6 in autologous blood coagulum with synthetic ceramics for reconstruction of a large humerus segmental gunshot defect in a dog: The first veterinary patient to receive a novel osteoinductive therapy. Bone Rep. 2021;14:100759.
81. Vukicevic S, Peric M, Bordukalo-Niksic T, Blazevic V, Durdevic D, Ivanjko N, et al. Time to consider fracture nonunion an orphan disease? An update into pathophysiology, epidemiology and therapeutic solutions. European Journal of Trauma and Emergency Surgery. 2025;51:255.
82. Stokovic N, Ivanjko N, Erjavec I, Breski A, Peric M, Vukicevic S. Zoledronate Bound to Ceramics Increases Ectopic Bone Volume Induced by rhBMP6 Delivered in Autologous Blood Coagulum in Rats. Biomedicines. 2021;9.
83. Delimar D, Klobucar H, Jelic M, Cicak N, Korzinek K. Treatment of defect pseudoarthroses with bone segment transport. Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca. 2001;68:109-111.
84. Grgurevic L, Macek B, Healy DR, Brault AL, Erjavec I, Cipcic A, et al. Circulating bone morphogenetic protein 1-3 isoform increases renal fibrosis. Journal of the American Society of Nephrology. 2011;22:681-692.
85. Grgurevic L, Erjavec I, Grgurevic I, Dumic-Cule I, Brkljacic J, Verbanac D, et al. Systemic inhibition of BMP1-3 decreases progression of CCl(4)-induced liver fibrosis in rats. Growth Factors. 2017;35:201-215.
86. Vukicevic S, Colliva A, Kufner V, Martinelli V, Moimas S, Vodret S, et al. Bone morphogenetic protein 1.3 inhibition decreases scar formation and supports cardiomyocyte survival after myocardial infarction. Nat Commun. 2022;13:81.
87. Matic Jelic I, Stokovic N, Ivanjko N, Pecina M, Kufner V, Bordukalo Niksic T, et al. Systemic inhibition of bone morphogenetic protein 1.3 as a possible treatment for laminin-related congenital muscular dystrophy. Int Orthop. 2025;49:45-52.
88. Cvjeticanin B, Prutki M, Dumic-Cule I, Veir Z, Grgurevic L, Vukicevic S. Possible target for preventing fibrotic scar formation following acute myocardial infarction. Medical Hypotheses. 2014;83:656-658.

89. Bordukalo Niksic T, Kufner V. BMP1.3 protein as potential target in treatment of fibrosis. Rad CASA - Medical Sciences. 2021;548:56-69.
90. Paralkar VM, Borovecki F, Ke HZ, Cameron KO, Lefker B, Grasser WA, et al. An EP2 receptor-selective prostaglandin E2 agonist induces bone healing. Proc Natl Acad Sci U S A. 2003;100:6736-6740.
91. Li M, Ke HZ, Qi H, Healy DR, Li Y, Crawford DT, et al. A novel, non-prostanoid EP2 receptor-selective prostaglandin E2 agonist stimulates local bone formation and enhances fracture healing. J Bone Miner Res. 2003;18:2033-2042.
92. Hoang B, Moos M, Jr., Vukicevic S, Luyten FP. Primary structure and tissue distribution of FRZB, a novel protein related to Drosophila frizzled, suggest a role in skeletal morphogenesis. J Biol Chem. 1996;271:26131-26137.
93. Vukicevic S, Luyten FP, Kleinman HK, Reddi AH. Differentiation of Canalicular Cell Processes in Bone-Cells by Basement-Membrane Matrix Components - Regulation by Discrete Domains of Laminin. Cell. 1990;63:437-445.
94. Sampath TK, Simic P, Sendak R, Draca N, Bowe AE, O'Brien S, et al. Thyroid-stimulating hormone restores bone volume, microarchitecture, and strength in aged ovariectomized rats. J Bone Miner Res. 2007;22:849-859.
95. Sun L, Vukicevic S, Baliram R, Yang G, Sendak R, McPherson J, et al. Intermittent recombinant TSH injections prevent ovariectomy-induced bone loss. Proceedings of the National Academy of Sciences of the United States of America. 2008;105:4289-4294.
96. Vukicevic S, Krempien B, Stavljenic A. Effects of 1 alpha,25- and 24R,25-dihydroxyvitamin D3 on aluminum-induced rickets in growing uremic rats. J Bone Miner Res. 1987;2:533-545.
97. Vukicevic S, Kracun I, Stavljenic A, Kelovic Z, Krempien B, Rosner H. The effects of aluminium on brain gangliosides in uraemic rats treated with 24R,25-dihydroxyvitamin D3. Neuropathol Appl Neurobiol. 1989;15:55-62.
98. Stokovic N, Trkulja V, Cukovic-Bagic I, Lauc T, Grgurevic L. Anatomical variations of the frontal sinus and its relationship with the orbital cavity. Clinical Anatomy. 2018;31:576-582.
99. Stokovic N, Trkulja V, Dumic-Cule I, Cukovic-Bagic I, Lauc T, Vukicevic S, et al. Sphenoid sinus types, dimensions and relationship with surrounding structures. Ann Anat. 2016;203:69-76.
100. Stokovic N, Ivanjko N, Bicanic I, Jalsovec D, Katavic V, Petanjek Z. The Zagreb Skull Collection-The unique identified collection of human skulls from fetuses to centenarians. Am J Biol Anthropol. 2023;182:476-486.
101. Štoković N, Ivanjko N, Pećin M, Bordukalo Nikšić T, Kufner V, Erjavec I, et al. Exploration of new platforms and potentials in regenerative medicine. Rad CASA - Medical Sciences. 2024;66-67:38-47.
102. Stokovic N, Ivanjko N, Matic Jelic I, Milesevic M, Rumenovic V, Blazevic V, et al. State-of-the-art of the Bone Morphogenetic Protein research field: 13th International BMP Conference, Dubrovnik 2022. Rad CASA. 2022;553 84-99.
103. Vukicevic S, Sampath KT. Bone morphogenetic proteins. From laboratory to clinical practice. Basel ; Boston: Birkhäuser Verlag; 2002. xii, 326 p. p.
104. Vukicevic S, Sampath KT. Bone morphogenetic proteins. Regeneration of bone and beyond. Basel ; Boston: Birkhäuser; 2004. xi, 310 p. p.
105. Vukicevic S, Sampath KT. Bone morphogenetic proteins. From local to systemic therapeutics. Basel ; Boston: Birkhäuser; 2008. xi, 343 p. p.
106. Vukicevic S, Sampath KT. Bone morphogenetic proteins. Systems biology regulators. Cham, Switzerland: Springer; 2017. xii, 445 pages p.
107. Rumenovic V, Ivanjko N, Kovacic N, Vukicevic S, Erjavec I. BMP3 Deficiency Accelerates Cartilage-to-Bone Transition in Ectopic Bone. Biomedicines. 2025;13.
108. Banovac I, Grgurevic L, Rumenovic V, Vukicevic S, Erjavec I. BMP3 Affects Cortical and Trabecular Long Bone Development in Mice. International Journal of Molecular Sciences. 2022;23.
109. Milesevic M, Matic Jelic I, Rumenovic V, Ivanjko N, Vukicevic S, Bordukalo-Niksic T. The Influence of BMP6 on Serotonin and Glucose Metabolism. International Journal of Molecular Sciences. 2024;25.
110. Erjavec I, Bordukalo-Niksic T, Brkljacic J, Grcevic D, Mokrovic G, Kesic M, et al. Constitutively Elevated Blood Serotonin Is Associated with Bone Loss and Type 2 Diabetes in Rats. PloS One. 2016;11:e0150102.
111. Aspenberg P, Basic N, Tägil M, Vukicevic S. Reduced expression of BMP-3 due to mechanical loading -: A link between mechanical stimuli and tissue differentiation. Acta Orthopaedica Scandinavica. 2000;71:558-562.