OSTEOPROSPINE

Newsletter Issue 2 - December 2020

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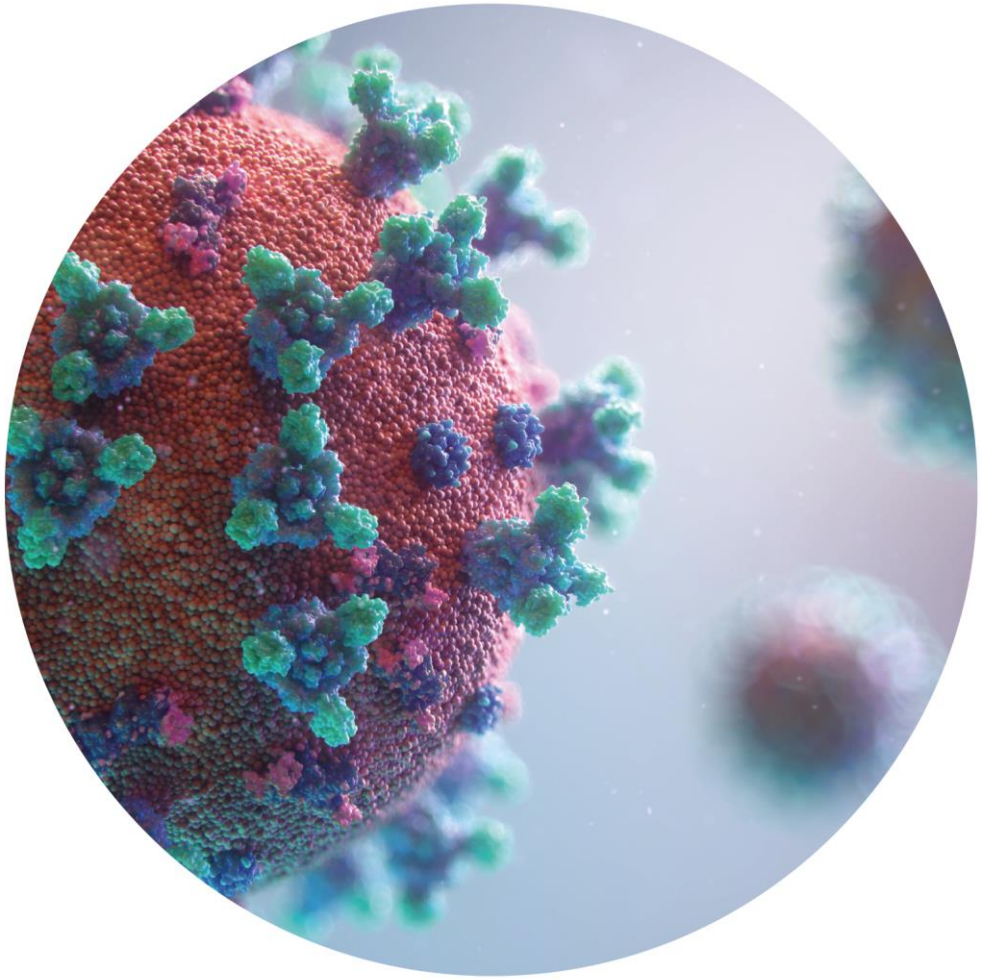


This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779340.

Introduction

Dear colleagues and followers of the OSTEOproSPINE Newsletters,

Prof. Slobodan Vukicevic,
OSTEOproSPINE Coordinator

allow me to introduce the second issue of the OSTEOproSPINE Newsletter! 2020 was full of unexpected situations, which were very challenging for the project implementation.

Due to the COVID-19 spread, the emergency rule and limited access to hospitals was introduced. In Austria, the medical activities were adjusted towards fighting COVID-19, so we temporarily postponed the clinical study patient recruitment. However, after few months the study was successfully continued although under complex conditions. In addition, the earthquake that hit Zagreb in March and damaged buildings of the University of Zagreb School of Medicine put another challenge in front of the project coordination team. Below you can read how we managed this situation.

In the last ten months project partners made an exceptional effort to implement the project continuation. We are all grateful primarily to our clinical sites for successful continuation of recruitment under these new and unexpected rules and regulations. I believe that our clinical study is among only few currently recruiting patients in EU except those related to COVID-19, regardless of the sponsor and medical condition tested.

Prof. Slobodan Vukicevic
Project coordinator

OSTEOproSPINE– Update

OSTEOproSPINE and Covid-19

On Wednesday 11 March, the World Health Organization (WHO) announced a pandemic in response to the SARS-CoV-2 virus spread and COVID-19 disease outbreak. Subsequently, numerous governments have presented comprehensive packages of measures to contain the rapid spread of COVID-19. Due to the fact that from March 16th, 2020 Austria entered the emergency rule there was a number associated restrictions at Austrian hospitals. At that moment, we were faced with medical system that was blocked and all medical activities were addressed towards fighting COVID-19. The resources for clinical studies and research activities were thus very limited, surgeries – if not highly urgent – were postponed.

With all study sites of OSTEOproSPINE being located in Austria this looked like it could lead to a notable delay in the clinical trial. Since the non-clinical consortium partners confirmed that they were still able to perform their tasks in OSTEOproSPINE as planned, the whole consortiumwas working closely together with clinical sites in Austria to keep the project progressing and mitigate the effects of COVID-19.

During the lockdown, the project team discussed and organized the implementation of emergency security measures during its regular teleconferences so that clinical studies could continue despite the situation. During this period, the project was primarily faced with problems related to the smooth performance of laboratory activities as well as those related to clinical monitoring of patients. Regular scheduled patient inspections took place by telephone, which enabled patients to communicate their condition and obtain sufficient feedback, but the inability to perform physical and specialist diagnostic examinations caused failures in data collection. In addition, the supervision of the study and clinical centers could not be done on site, but the clinical monitor checked the work and documentation remotely.

Following a positive opinion of the Independent Data and Safety Monitoring Board (IDSMB) on the safety of the first 60 patients who received OSTEOproSPINE therapy or placebo during spinal fusion surgery in three clinical centres in Austria, the clinical trial entered its third stage of phase II after a three-month delay. Thanks to dedicated staff and the efforts of investigators and clinical centers, 27 new patients have been included in the study so far, making up a total of 87 recruited patients. Despite the pandemic, patient recruitment at one of the clinical centers is very successful and will soon recruit all planned patients. The other two clinical centres following initial interruptions are also accelerating and they are including an increasing number of patients. This makes OSTEOproSPINE project one of the few clinical studies that were only shortly discontinued at the time of the COVID-19 pandemic and successfully resumed thereafter.

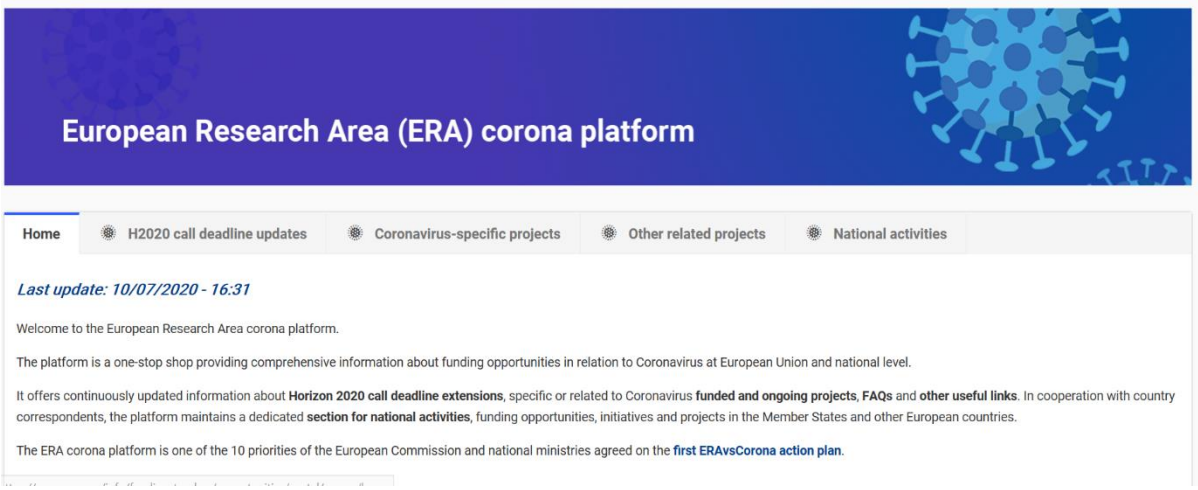
The European Commission and Covid-19

With the start of the COVID-19 pandemic the European citizens and governments faced challenging times. Those also affected projects and consortia within the Horizon 2020 program. As a reaction to the pandemic, the European Commission took various measures to face the difficulties the virus caused.

From the funding perspective, the EC unlocked new grant funds and released COVID-19 specific tenders to advance knowledge for the clinical and public health response to the 2019-nCoV epidemic. All information on actions against COVID-19 and tenders can be found on the newly implemented **"European Research Area (ERA) corona platform"** on the funding & tenders portal (https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/covid-19).

Current projects receiving funding within the Horizon 2020 program are confronted with various challenges caused by the virus. Consortia are unable to continue their work on the projects as planned due to closed institutions and laboratories, contact restrictions, increased workload in the health care sector and travel restrictions all over the globe. The EC is eager to provide the most possible flexibility within the rules and guidelines of the Horizon 2020 program to solve the issues that consortia are confronted with.

The EC regularly publishes and updates **Frequently Asked Questions (FAQs)** on the funding & tenders portal. The latest FAQs can be accessed over the **"European Research Area (ERA) corona platform"**. Beneficiaries can quickly find answers to common questions e.g. on delays in project implementation, reports and deliverables, travel costs, the clause on "force majeure" in relation to COVID-19, extension of project duration, postponement of the project starting date and many more. In every case and for more specific project relevant matters regarding COVID-19 the Project Officers are the first contact point for beneficiaries and will help to find the best possible solution that benefits the success of the project.



OSTEOproSPINE Consortium meetings – collaboration on a European level

OSTEOproSPINE annual meeting in Zagreb – an efficient start into project year 3

On January 30-31, the OSTEOproSPINE consortium followed the kind invitation of their coordinator, University of Zagreb School of Medicine, and came together in Zagreb for the 2nd progress meeting. The partners met in the historical building of Andrija Stampar School of Public Health in the heart of the city, where they found perfect conditions to discuss the latest developments in the project and prepare upcoming tasks. The School was named after dr. Andrija Stampar who was one of the founders of the World Health Organization. The building was built on the initiative of a group of public health workers led by Dr Andrija Štampar and the financial support of the Rockefeller Foundation.

After a warm welcome by coordinator Slobodan Vukicevic, the partners dived into work right away. In a very efficient atmosphere, the consortium members discussed the presented status updates and current challenges in clinical trial management, regulatory support, the GMP production and BMP stability as well as the preclinical work conducted in OSTEOproSPINE.

elaborate on communication, dissemination and exploitation measures as well as ethics requirements.

As the work package-based discussions finished ahead of schedule, there was still time to form working groups to discuss future challenges, before the partners headed for the joint dinner.

The second meeting day focused on the clinical trial itself, as well as data and general project management. Again, the partners were efficient in their discussions and took important decisions to make sure that the OSTEOproSPINE study will be concluded successfully. In the management part, upcoming tasks, such as the second internal progress report, were planned and a short overview on the financial status of the project was presented after the 1st Periodic Report had been accepted by the European Commission. All in all, the coordinator and the project partners are pleased with the progress and achievements the project made since the last meetings.

OSTEOproSPINE news

University of Zagreb School of Medicine hit by the earthquake

On 22 March 2020, on top of pandemic, the coordinators of the OSTEOproSPINE project were faced with another unexpected and serious situation. A series of devastating earthquakes that hit Zagreb badly damaged the facilities of the University of Zagreb School of Medicine. Fortunately, Laboratory for Mineralized Tissues were OSTEOproSPINE preclinical studies are performed, was relatively quickly adapted for further work. With walls still cracked, team members successfully conduct experiments. Most of the other facilities were closed until the reconstruction is completed.

Since the extent of the damage by far exceeds the internal capacity of UZSM we are calling upon all those who are willing to help rebuilding UZSM by their donations.

Donations ZAJEDNO ZA MEF (TOGETHER FOR MEF) can be made in kuna and foreign currency as follows:

IBAN: HR8423400091110024619
Sveučilište u Zagrebu Medicinski fakultet,
Šalata 3, 10000 Zagreb
Model of payment: HR00
Reference: 1950
Description: ZAJEDNO ZA MEF
BANK SWIFT/BIC: PBZGHR2X
Privredna banka Zagreb d.d., Radnička cesta 50, 10000 Zagreb

OSTEOproSPINE news

"That's Osteoporosis": October 20 Marks World Osteoporosis Day

OSTEOproSPINE is raising awareness for better bone health.

World Osteoporosis Day (WOD), marked on October 20, is an annually recurring campaign aiming to raise global awareness for preventing, diagnosing and treating osteoporosis and related degenerative bone diseases. Osteoporosis is on the rise worldwide. Due to demographic change, bone degenerating diseases have a growing societal and financial impact on industrialised nations. In 2020, fractures related to this silent disease are already affecting one in three women and one in five men over the age of 50. This equals one osteoporotic fracture every three seconds. The WOD strives to make healthy bones and fracture prevention a global health priority.

The most common osteoporotic fracture sites are the wrist, shoulder and hip. Many osteoporosis patients are also at risk for spinal compression fractures that can deform the vertebral body. A loss of body height often is the first symptom. In later stages, osteoporotic spine fractures cause low back pain at various levels, which frequently results in adverse lifestyle changes for patients.

A long-term treatment solution for degenerative spine disorders through a personalised bone implant – the ultimate goal of the OSTEOproSPINE project – is therefore also a chance for osteoporosis patients to be able to return to a better live.

This year's campaign slogan "That's osteoporosis" puts a spotlight on the emotional impact of osteoporosis and wants to highlight stories of people living with fragility fractures all over the world. The campaign

emphasizes the life-changing, debilitating impact of fractured bones for patients in terms of pain and lost independence, while also focusing on the burden of osteoporosis for family caregivers.

We are proud to be ambassadors for change on World Osteoporosis Day for patients affected by degenerative bone diseases.

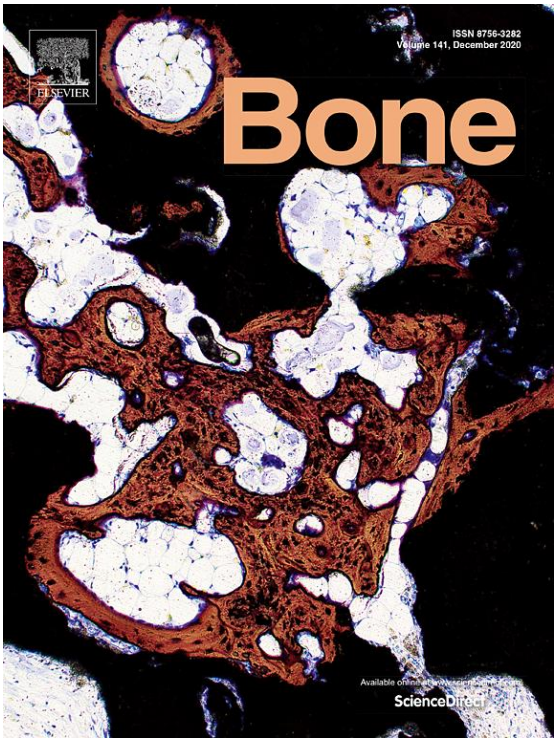
Learn more about the World Osteoporosis Day on Twitter under the hashtag #WorldOsteoporosisDay.

WorldOsteoporosisDay
October20

Special issue of the BONE

The scientific journal BONE, founded in 1978, is one of the most prestigious journals in the field of bone biology. On the occasion of the 13th International Bone Morphogenetic Protein Conference to be held in October 2021 in Dubrovnik, the editorial board of BONE decided to prepare a special issue dedicated to the role of bone morphogenetic proteins in bone biology. Editors of this special edition were Professor Slobodan Vukicevic (University of Zagreb School of Medicine, Croatia), Dr. Kuber T. Sampath (perForm Biologics, Holliston, USA) and Professor Frank Luyten (Faculty of Medicine, Catholic University of Leuven, Belgium).

Some of the OSTEOproSPINE partners, scientists from the Laboratory for Mineralized Tissues, University of Zagreb School of Medicine together with colleagues from University of Zagreb Faculty of Veterinary Medicine, Genera Research Ltd. and Smart-Medico Ltd.contributed with 6 scientific articles in total for this special issue of Bone journal.



"*A novel autologous bone graft substitute comprised of rhBMP6 in blood coagulum as carrier tested in a randomized and controlled Phase I trial in patients with distal radial fractures*" presents the results of clinical trials (phase 1) of a new drug for bone regeneration, Osteogrow, in the indication of distal radius fracture that were conducted in the Clinical Hospital Sisters of Mercy, Traumatology Hospital Zagreb (Zagreb, Croatia) and the University of Sarajevo Clinical Center, Orthopedic and Traumatology Clinic (Sarajevo, Bosnia and Herzegovina).

In order to expand the range of clinical indications in which Osteogrow can be used, preclinical studies have been performed in models of Posterolateral Lumbar Fusion (PLF) and Anterior Lumbar Interbody Fusion (ALIF) in sheep. In this study, Osteogrow was used alone or with the addition of bone allograft as biomechanical material. Results of this study are presented in the paper "*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*". The success of the preclinical studies described in previously mentioned paper led to the OSTEOproSPINE project where clinical trials are carried out in Austrian hospitals (Vienna, Graz and Linz). Clinical trials are conducted in patients with degenerative disc disease, where anterior and posterior spinal fusion is performed with the Osteoprospine formulation containing bone allograft as biomechanical material.

In the continuation of preclinical research, synthetic, biocompatible ceramics based on calcium phosphate are examined, in order to replace the allograft as a biomechanical material in the final formulation. Synthetic ceramics of different particle sizes and different chemical composition (tricalcium phosphate, hydroxyapatite and their combination) were tested as part of an

osteoinductive implant in a subcutaneous assay in rats, and based on these experiments, formulations of osteoinductive implants were selected and successfully tested in the PLF rabbit model. The results of the subcutaneous assay model in rats are presented in the article "*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*", while the results of the PLF rabbit model are shown in the article "*Evaluation of synthetic ceramics as a compression resistant matrix to promote osteogenesis of autologous blood coagulum containing recombinant human bone morphogenetic protein 6 in rabbit posterolateral lumbar fusion model*".

Current findings in bone biology of bone morphogenetic proteins and challenges in their clinical application are described in the review article "*Biology of bone morphogenetic protein in bone repair and regeneration: A role for autologous blood coagulum as a carrier*".

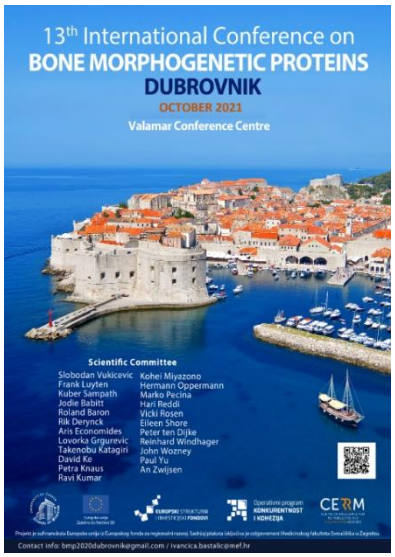
In the same edition, a review article "*What do we know about bone morphogenetic proteins and osteochondroprogenitors in inflammatory conditions*" by the Laboratory for Molecular Immunology, University of Zagreb School of Medicine was published.

It should be noted that the most of this articles published in the special edition of Bone journal were written and / or completed during the period when earthquake hit Zagreb in March 2020 and COVID-19 pandemic, hence the editors of the special edition thank all authors for their efforts to contribute, despite the difficult conditions, to the exceptional quality of the works and the presented results.

Table 1 *List of scientific papers from the OSTEOproSPINE consortium in a special issue of the journal BONE dedicated to the biology of bone morphogenetic proteins. All manuscripts were published in an open access form and are available free of charge to all interested readers*

Article name	Authors
A novel autologous bone graft substitute comprised of rhBMP6 in blood coagulum as carrier tested in a randomized and controlled Phase I trial in patients with distal radial fractures	Durdevic D, Vlahovic T, Pehar S, Miklic D, Oppermann H, Bordukalo-Niksic T, Gavrankapetanovic I, Jamakosmanovic M, Milosevic M, Martinovic S, Sampath TK, Peric M, Grgurevic L, Vukicevic S
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	Grgurevic L, Erjavec I, Gupta M, Pecin M, Bordukalo-Niksic T, Stokovic N, Vnuk D, Farkas V, Capak H, Milosevic M, Bubic Spoljar J, Peric M, Vuckovic M, Maticic D, Windhager R, Oppermann H, Sampath
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	Stokovic N, Ivanjko N, Erjavec I, Milosevic M, Oppermann H, Shimp L, Sampath KT, Vukicevic S
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	Stokovic N, Ivanjko N, Pecin M, Erjavec I, Karlovic S, Smajlovic A, Capak H, Milosevic M, Bubic Spoljar J, Vnuk D, Maticic D, Oppermann H, Sampath TK, Vukicevic S
Biology of bone morphogenetic protein in bone repair and regeneration: A role for autologous blood coagulum as carrier	Sampath TK, Vukicevic S
What do we know about bone morphogenetic proteins and osteochondroprogenitors in inflammatory conditions	Lukac N, Katavic V, Novak S, Sucur A, Filipovic M, Kalajzic I, Grcevic D, Kovacic N
A cell-based combination product for the repair of large bone defects	Lammens J, Maréchal M, Delport H, Geris L, Oppermann H, Vukicevic S, Luyten FP

OSTEOproSPINE – Events



13th International Bone Morphogenetic Protein Conference in Dubrovnik

Due to the COVID-19 pandemia, the Organizing Committee has decided to postpone the 13th BMP International Conference until October 2021. The new information will be available on the web page http://cerrm.hr/bmp-conference-dubrovnik-2020 as soon as new arrangements will be done.

We hope you are staying healthy and safe and look forward very much to meet with you in Dubrovnik in 2021. Hopefully all participants will be vaccinated and protected against potential COVID infection.

1st virtual BMP forum

Appetizer for the 13th International BMP conference 2021 in Dubrovnik
15:00-16:30 European Summer Time (GMT + 02:00)

As the International BMP conference in Dubrovnik had to be postponed due to the COVID-19 restrictions, the time from September 2020 to summer 2021 will be covered with the 1st Virtual BMP Forum, as an Appetizer for the Dubrovnik Meeting October 2021. Forums are organized every 3 weeks for 2 talks (each 35 min plus 10 min QA) on a related topic, by 2 speakers from different institutions. This meeting series aim to complement rather than duplicate the Dubrovnik speakers list.

Registration form is available on the following link: https://fu-berlin.webex.com/fu-berlin-en/onstage/g.php?PRID=4d4752186a3687d15ea8df72fd932a22
All information will be available on the International BMP conference homepage: http://cerrm.hr/bmp-conference-dubrovnik-2020

Please save the following dates already:

Jan 13th 2021: BMP Signalling in Bone and Cartilage Biology
Feb 3rd 2021: BMP Signalling in Muscle Biology
Feb 24th 2021: Structure of BMP Signalling Components
Mar 17th 2021: BMP Co-receptors and Pro-domains
Apr 7th 2021: BMP Receptors
Apr 28th 2021: BMPs and Stem Cells
May 19th 2021: BMP antagonists
Jun 9th 2021: Unexpected Roles of BMPs
Jun 30th 2021: Modelling the Pathway
Jul 21st 2021: BMP-pathway in clinical settings

Partners and experts in OSTEOproSPINE

The OSTEOproSPINE consortium brings together internationally renowned scientists with many years of experience in orthopedics, orthopedic surgeries, BMP6 research, and clinical trial management.