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Book of Abstracts

BBCE Summer School 2020

23-27 November 2020 (online event)

Organized by Prof. Aldo R. Boccaccini and Dr. Liliana Liverani
(Institute of Biomaterials, FAU)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

Review of Commercially Available Injectable Synthetic Ceramic Bone Cement Products: Design Guidance

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Abstract

In the last few years, a large number of injectable ceramic bone fillers have been developed and commercialized. With its special advantages, the number of calcium phosphate (CP) and calcium sulphate (CS) bone cement products keeps growing. The review of detailed product information is still lacking. In this review, I collected and analyzed the information of ceramic products from both commercial brochures, patents and academic papers. All the products analyzed in this review have been certificated by CE and/or FDA. A table of product data (components, applications, working and setting time, pore size, porosity, biodegradability, and other properties) was organized. In addition, the necessity and rationality of each mentioned property were assessed, leading a list with standards for injectable bone cement design. As guidance, this review provides information about ceramic bone cement products for all professionals, including surgeons and engineers.

Keywords: bone substitute, calcium phosphate, calcium sulphate, injectable bone cement

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Injectable organic-inorganic biocomposites for bone tissue regeneration. A mini review.

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Bone regeneration and fracture healing is still a substantial medical challenge in today's clinical routine. Traditional clinical treatment with autografts is limited availability and donor-site morbidity, but metal implants are not bioactive. In recent years, fabrication of inorganic-organic composites mimicking the nanostructured composite nature of bone has attracted research interest in the field of bone regeneration. The review will summarize the main strategic tools for the development of injectable biocomposites: biopolymer-based hydrogels (chitosan, hyaluronic acid, alginate etc.), bioactive inorganic fillers (hydroxyapatite, bioactive glass etc.) and biologically active components (cells, growth factors, drugs etc.), as well as the fabrication techniques and synthesis methods.

The analysis of the literature reveals that biopolymer hydrogels and bioactive inorganic fillers demonstrate high functional and biological performance: mimicking the key features of natural hybrid structure of bone, including, the natural extracellular matrix of the bone, filling small and irregular defects in a minimally invasive way, delivering the incorporated biologically active therapeutic agents, providing a controlled degradation rate, flexibility, porosity, surface morphology, mechanical strength and structural support.

This review also covers issues such as limited mechanical stability, rapid degradation and post-injection phase separation, highlighting the necessary improvements in biomedicine for injectable biocomposites.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Sintering of amorphous calcium phosphate by uniaxial pressing at room temperature

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Despite considerable interest in amorphous calcium phosphate (ACP) bioceramics, it remains a challenge to sinter ACP to high relative density while maintaining its structural characteristics. The difficulty is mainly related to its unique hydrated structure that is heat sensitive and does not allow to use high sintering temperatures. Here, for sintering of ACP, we used simple uniaxial pressing. We investigated the effect of sintering temperature (room temperature, 100, 120, 150 °C) and the pressure applied (≥500 MPa), on densification and structure of ACP. Relative density of the samples that were produced at room temperature under 500 MPa pressure (the samples retained ACP structure) already exceeded 75%. Relative density of the samples that retained ACP structure was not significantly affected by sintering temperature, while increase in the applied pressure improved relative density of the samples. Our findings indicate that by applying moderate uniaxial pressure, ACP can be sintered to relatively high relative density already at room temperature.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Application of chemometrics in differentiation of synthesized and natural calcium phosphate

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These smart materials can be used to develop innovative third-generation biomaterials.

The stoichiometric calcium hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$ is considered as an idealized bone and dental inorganic composition model.

In this work, as an inorganic bone composition model, nanosized (particle size 1 nm – 70 nm) amorphous calcium phosphate and hydroxyapatite compounds containing carbonate ions are mainly considered.

Research is based on FTIR spectroscopy (DRIFT, PAS) investigation of bone like-apatites in conjunction with chemometrics.

All spectra were analysed in their full length and in functional group areas. Pearson Correlation Coefficients, Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) were used in the work. The standard substances of calcium phosphate with varying degrees of crystallinity and particle size were used: amorphous (~1 nm), microcrystalline (10 nm) and two crystalline samples (60, 70 nm).

Research prove possibility to predict the position of the sample in the cluster and crystallite parameters (size and degree of crystallinity), A/B type carbonate formation and high effectivity of FTIR methods for fast and accurate bone like apatite description and analyses. The PCA and HCA analysis helps to confirm or reject out assumptions and evaluate the effects of factors on cluster formation.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

Biomineralization of Calcium salts.

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Biomineralization is observed in organisms since the Cambrian radiation event occurred approximately 520 million years ago. Most of the animals use calcium salts for skeletal reinforcement. According to biomineral distribution vertebrates utilize calcium phosphate (CaP) for their endoskeleton while invertebrates employ calcium carbonate ($CaCO_3$) for their exoskeleton. Both of these calcium salts exist in the polycrystalline phase which means the physicochemical properties depend on the shape, size, and orientation of the crystal. Every organism has a specific physiochemical requirement, this can be attained by having optimum mixture of crystalline and amorphous material. Both CaP and $CaCO_3$ in the crystalline state offer rigidity while the amorphous state offers flexibility. This property of material gives an advantage to both vertebrates and invertebrates to synthesize skeleton with specific physicochemical requirements. In Invertebrates synthesis of CaP is complex because of different types of tissues such as bone, dentin, cementum, enamel, calcifying cartilage, and tendon. Every tissue requires a specific mineral-protein composite, within which the development of crystals takes place. Further, specific tissue required CaP with predetermine Ca:P ratio as crystal orientation of CaP in vertebrate is essential to attain biocompatibility. Moreover, colloidal CaP is used to form micelles, which is a vital component of milk.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Ag- and/or Ti-doped calcium phosphates as antibacterial agents: influence of thermal treatment on antibacterial activity

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Regeneration of bone defects caused by injuries, infections or tumours is a significant challenge in modern medicine. Repairing bone defects often requires surgery where implants are used. About 10% of these procedures are at risk of bacterial infections. Methods are being sought to ensure local delivery of antibiotics at the site of implantation. However, an increasing rate of bacteria becoming resistant to the existing antibiotics has led to the resurgence in the use of alternative antimicrobials, such as bacteriophages, bacteriophins and inorganic agents (Ag, Cu, Zn, Ti compounds, *etc*.). Thus, the aim of this study was to impart antibacterial properties to calcium phosphate (CaP) bioceramics, which are widely used in orthopaedic and dental surgery, by doping them with Ag(I) and Ti(IV) ions, and to evaluate the synergy and cumulative effects of dopants.

The influence of high temperature treatment on the physicochemical, namely, phase and chemical composition, thermal stability, and antibacterial properties of the Ag- and/or Ti-doped CaP was evaluated. Minimum inhibitory concentration of the Ag- and/or Ti-doped CaP powders calcined at 900, 1100 or 1300 °C against gram-positive *S. aureus* was determined.

Acknowledgement: This work has been supported by the European Regional Development Fund within the Activity 1.1.1.2 “Post-doctoral Research Aid” of the Specific Aid Objective 1.1.1 “To increase the research and innovative capacity of scientific institutions of Latvia and the ability to attract external financing, investing in human resources and infrastructure” of the Operational Programme “Growth and Employment” (No. 1.1.1.2/VIAA/2/18/339).

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 857287

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In situ synthesis of calcium phosphate in silk solution

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Silk fibroin composite materials are used for bone regeneration for their elasticity, biocompality and biodegrability. Hydroxyapatite is widely used ceramic, due to its similarity to human bone minerals. Hydroxyapatite ceramics are fragile; thus, creation of silk fibroin and hydroxyapatite composite material would combine the valuable properties of both materials in one [1]. The aim of this study is to produce silk fibroin and hydroxyapatite composite materials and evaluate their physicochemical characteristics and bone regeneration potential. A methodology for the synthesis of calcium phosphates in silk solution was developed. By adding more orthophosphoric acid, the pH of the environment reduces, and thus result in different calcium phosphates. It was studied that pure hydroxyapatite in silk solution was formed when the environment pH is 10, but only 95.33% hydroxyapatite is formed in water at the same pH value.

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

Precision of the fully digital 3D treatment plan

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Introduction. Virtual 3D planning of orthognathic surgery has become a leading trend in modern orthognathic surgery, but questions about precision remain crucial.

The objective of the study was to evaluate precision of the digital 3D orthognathic surgery plan for bimaxillary surgery compared to the actual surgical outcome in all three dimensions.

Methods. 30 patients were involved in the present study (11 male; 19 females; average age 23.7 years). 24 patients were Class III and 6 were Class II.

The preoperative and postoperative CBCT after bimaxilary surgery of each patient was superimposed. Eleven dental and skeletal points were used for comparison between the real and digital outcome in all three planes.

Results. The measurements did not exceed 2 mm in most cases, so deviations could be deemed clinically insignificant

Conclusion. Method of surgical outcome precision analysis presented in this article provides better insight about discrepancies that may arise from virtual plan to surgical outcome. Surgical outcomes can be considered precise when compared to 3D virtual plan.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Platelet-rich Fibrin as Carrier System

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Platelet-rich fibrin (PRF) is a second-generation platelet concentrate derived from centrifuged blood (1) that combines properties such as biocompatibility, biodegradability, and contains growth factors and peptides that provide tissue regeneration (2). These properties make it possible to obtain a new biomaterial that will be applicable not only in maxillofacial surgery, but also in other areas of biomedicine. This opens up new horizons for the use of all beneficial ingredients in a blood sample for biomedical purposes. By itself, PRF has an unstable effect on osteogenesis, therefore, advanced approaches, including the combination of PRF with materials or drugs, are of great interest in clinics. The ability of PRFs to degrade naturally is considered an advantage for their use as a “warehouse” of controlled drugs. However, there is now a need to further explore the ability of this biomaterial to be a drug delivery system, combining the ability of PRFs to retain growth factors and incorporate drugs without interacting and hindering drug release. Only a perfect understanding of the ability of these materials to combine with other biomaterials and drugs will allow us to obtain new biomaterials with the necessary properties for use not only in maxillofacial surgery, but also in healing burns, neurosurgery, cartilage and tendon repair and other fields.

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This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 857287

Towards Tumour-selective Nanomedicines Using Monodisperse Stealth Particles

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Nanomedicine is an emerging field that applies concepts in nanotechnology to develop novel diagnostics and therapies. Despite intensive study of nanoparticles (NPs) for drug delivery in cancers, the median reported efficiency of NP delivery to tumour sites is less than 1%.(1) We will solve this problem using previously developed polymeric NPs with unique stealth-like properties. The central hypothesis is that by avoiding biofouling these NPs can circulate sufficiently long to reach and accumulate in tumour mass. Our preliminary studies using monodisperse stealth NPs with DH=30 nm indicate that upon both i.v. and i.p. injections, NPs avoid rapid clearance and distribute across all major organs in healthy mice. In contrast, in triple-negative breast cancer (TNBC)-bearing mice, after the initial uniform distribution we observed gradual NP accumulation in tumour, with post mortem analysis revealing tumour to be the principal accumulation site. We will prepare a library of NPs, develop a novel method for simultaneous pharmacokinetic and biodistribution analysis of multiple NPs in a single animal, and identify the optimal stealth NP to maximize accumulation in TNBC tumours in mice. For the first time, we will answer longstanding questions of nanomedicine and create an NP platform for cancer therapy.

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Improved Administration of Cannabidiol using Liposomes as a Drug Delivery System Carrier - Mini review

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Cannabidiol (CBD) is a main non-psychoactive cannabis (*Cannabis sativa*) compound that has (but is not limited to) pain-relief, anticonvulsive, antianxiety, antinausea, antipsychotic, sleep improvement, anti-inflammatory and cancer cell antiproliferative effects (1,2). Since CBD is highly lipophilic, it has low solubility and absorption into body fluids when administered to the body by classical methods: orally or by smoking. CBD has low stability in presence of oxygen and light. To improve CBD bioavailability and stability under environmental conditions, drug delivery systems such as transdermal (for example, patches, gels, oils, sprays and creams), polymer-based and lipid-based have been studied in the scientific literature (3). Liposomes are spherical form drug carriers that can encapsulate both hydrophilic and hydrophobic drugs and improve drug absorption and bioavailability. Among other delivery systems, liposomes are distinguished by the fact that they can be made of lipids whose structure and properties correspond to the cell membrane lipids present in the body, which makes liposomes highly biocompatible. Liposomes are non-toxic, biodegradable and they provide sustained and controlled drug release as well as improve drug stability (4,5). Therefore, liposomes are promising drug carriers to be used to improve the administration of CBD.

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Design, analysis and optimization of drug delivery systems based on biomaterials

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The current phD thesis work involves sinthesys of optimized, multisubstituated, amorphous, drug loaded hydroxyapatite (HAP) nanoparticles. The goal is to obtain HAP particles with enhanced antimicrobial properties. To do so, the calcium in HAP is planned to be substituated with up to three different meatl ions. The literature on sysnthesis methods will be gathered, the sysnthesis process will be optimized to obtain HAP particles with predetermined properties and different levels of multiple ion substitution. The test methods for these particles will be devised which will involve element analysis to determine element ratios, crystal structure analysis to confirm HAP, HPLC method to monitor drug release and anti microbial properties will be tested *in vitro*. Further plans for optimization involves design of experiment (DOE) approach which, judging from literature, hasn't been used in this type of work. To build an appropriate statistical model in DOE, the different synthesis conditions will chosen as an input, like reagent ratios, temperature etc. It is important to choose the necessary inputs which have the most impact on desired HAP properties, this is why DOE approach is so usefull since statistically insignificant conditions will be excluded.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

Synthesis of amorphous Calcium Phosphate with controllable synthesis parameters

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Amorphous calcium phosphate (ACP) play important role in biological process, such as bone formation. It serves as precursor phase for hydroxyapatite formation in living body. ACP is highly soluble and has good remineralization ability. In this work ACP was synthesised via wet precipitation method from calcium oxide and orthophosphoric acid with different initial Ca/P molar ratio and synthesis end pH. The influence of synthesis parameters on ACP properties were studied. Obtained ACP was characterized with different analytical methods and to determine Ca/P molar ratio of the product, ACP was calcinated at 1100 ° C.

For synthesized ACP powder, characteristic amorphous structure was observed in XRD pattern and FT-IR spectrum. Calcinated ACP reveal β-tricalcium phosphate (β-TCP) or biphasic CaP with composition of β-TCP/Hydroxyapatite. Ca/P molar ratio was obtained in range from 1.50 to 1.55. Synthesis parameters did not affect ACP properties, such as specific surface area, particle size and long-term stability.

Acknowledgements: This research is funded by the Latvian Council of Science, project Future of synthetic bone graft materials - in vivo guided biosynthesis of biomimetic hydroxyapatite, project No. lzp-2018/1-0238.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Octacalcium phosphates: promising instruments for local drug delivery in bone regeneration

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Disadvantages of conventional drug delivery systems (DDS), such as systemic circulation, interaction with physiochemical factors, reduced bioavailability, and insufficient drug concentration at bone defect site, have underlined the importance of developing efficacious local drug delivery systems. Site specific delivery of the active substance allows the controlled release of drugs which remain locally at bone defect site, thus ensuring proper concentrations, while limiting undesirable effects. Drugs delivered in this manner have to retain biodegradability and non-toxicity when interspersed on the site. An appropriate choice among different calcium phosphates is crucial for later modification and exploitation in this field. Octacalcium phosphate (OCP) is presumed to be the precursor of biologically formed apatite owing to its similarity to hydroxyapatite (HAp) and readiness to convert to it. Tailoring drug-loading sites of OCP, as a carrier material, is mostly done through chemisorption from solution and coprecipitation. Functionalization of OCP can propagate the current state of CaP as DDS by enabling large specific surface area together with higher loading capacity and prolonged drug release. In addition, the osteoconductive performance and biological activity of OCP is proving to be of pivotal value for bone formation and regeneration.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Platelet rich fibrin perspectives in orthognatic surgery

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Keywords: Platelet rich fibrin (PRF), biomaterials, orthognatic surgery.

Introduction: Orthognatic surgery is a common treatment approach for severe dentofacial deformities. Despite favorable result and development of 3D planning to get predictable outcomes, still remains adverse results after jaw repositioning. **Materials and methods:** Literature review was done using articles searched in PubMed (National Library of Medicine) using key words. Articles were screened by title and abstract, including publishing years from 2009. 16 full text articles were analyzed. Articles were cited using PubMed citation in AMA format.

Results: Skeletal stability of the osteotomy sites is dependent on the quality of bone union. After large mandibular movement, insufficient bone contact may result in bony defect in mandible and can create unpleasant mandibular notching or lower border irregularities. To improve bone healing variable biomaterials are used. Further careful research is needed to find best suitable biomaterial. There is a lack of evidence in literature regarding PRF application for the osteotomy sites in orthognatic surgery.

Conclusion: PRF may be useful in solving insufficient bone formation problem, to avoid mandibular contour defect. Besides it is necessary to evaluate PRF antibacterial and antifungal effect which can influence compromised bone healing and may lead to bone formation improvement.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Amorphous calcium phosphate with high specific surface area: synthesis and properties

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Amorphous calcium phosphate (ACP) is known as first phase in bone mineralization, thus making it an attractive material for bone regeneration and repair. ACP is chemically similar to the bone mineral. However, in order for ACP to mimic physical structure of the bone mineral higher specific surface area (smaller particle sizes) are needed. To fulfil that, new synthesis method of ACP was developed.

ACP was synthesized at room temperature by rapidly adding NaOH to solution containing both calcium and phosphate ions [1]. This solution was prepared by dissolving hydroxyapatite in HCl. Synthesis was stirred intensely, and pH was set to 8, 9, 10 or 11. Precipitated ACP was separated from mother solution, washed and dried at 80 °C. Obtained samples were studied using XRD, FT-IR and BET.

The developed synthesis method enabled obtaining of ACP with high SSA (see below) by drying at 80 °C, when synthesis pH was 10 or 11. At pH 8 and 9 low crystalline calcium phosphates were obtained, that was proved by XRD. The obtained ACP was carbonated as seen from FT-IR spectra. Further, the SSA and d_{BET} of prepared samples was 133-154 m^2/g and 14-16 nm, that was independent of pH.

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287

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Synthesis of Amorphous Calcium Phosphate with Fluoride

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Amorphous calcium phosphate (ACP) have been proposed for dental hard tissue remineralization. Current research is focused on ACP synthesis with fluoride (ACPF) to obtain material with remineralizing and anti-cariogenic properties. Further synthesized material will be applied in cold sintering to obtain bioactive bioceramic for dental restoratives.

CaO, 2M H_3PO_4 and NaF was used for ACP synthesis with fluoride. Obtained CaP precipitates were dissolved with 3M HCl, then solution was stirred for 30 min. Later NaOH was added for re-precipitation of ACPF. The product was washed with deionized H_2O, filtered and frozen in liquid N_2 right after the washing. Material was dried by lyophilization. XRD, FTIR, BET, pycnometry, EDS were used for characterization of material.

SSA of ACPF was 174.3±2.4 m^2/g and the density of the powder – 2.50 g/cm^3. Observed bands in FTIR analysis evidenced amorphous ACPF phase, although XRD pattern showed CaP phase with very low crystallinity. EDS confirmed presence of fluoride in the ACPF samples, additionally peaks in the XRD pattern after thermal treatment at 1100 ^oC indicate formation of crystalline fluorapatite and β-TCP.

Obtained results are promising for further investigations, because the obtained ACPF has a large surface area, it is amorphous and contains fluoride in the structure.

Acknowledgements

This work has been supported by the European Regional Development Fund within the Activity 1.1.1.2 “Post-doctoral Research Aid” of the Specific Aid Objective 1.1.1 “To increase the research and innovative capacity of scientific institutions of Latvia and the ability to attract external financing, investing in human resources and infrastructure” of the Operational Programme “Growth and Employment” (No.1.1.1.2/VIAA/3/19/459)

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 857287

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Isolation of Gingival mesenchymal stem cells (GMSCs) for soft tissue regeneration studies

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Oncological surgeries become more frequent due to the rising numbers of oral cancer patients, therefore research in soft tissue restoration is gaining importance. Development of mesenchymal stem cell-based therapies is a promising solution to enhance post-surgical healing in cancer patients.

GMSCs are adult stem cells derived from gingiva, capable of proliferation and multipotent differentiation. GMSCs are easily accessible and obtainable with minimal invasion, exhibiting great wound healing properties and characteristics of immunomodulation and thus are used in research on soft tissue regeneration.

Investigation methods: Cells will be isolated from gingival tissue of 15 healthy patients (approved by Research Ethics Committee of RTU) and digested with collagenase, then seeded in culture dishes for colony formation. MSCs population will be put in culture with Dulbecco's modified Eagle's medium (DMEM) for propagation. When primary cells passage reaches ~3million, cells will be frozen (-80°C).

To confirm, that isolated cells are MSCs, they have to show: plastic-adherence; self-renewal capabilities - ability to form colonies; ability to differentiate into osteoblasts, adipocytes and chondroblasts; and expression of CD73, CD90, CD44, CD166, CD105 surface markers, as well as lack of hematopoietic markers.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857287