ABSTRACT FOR THE GENERAL PUBLIC

Bioabsorbable hydroxyapatite/polymer nanocomposite granules with enhanced osteoconductivity and anti-inflammatory properties for bone defect treatment

In the developing European population, there are still thousands of cases of severe fractures and defects in bone tissue requiring surgical intervention. Because of low risk of immune rejection, autografts are used most often in the case of small bone defects. However, in some cases – such as extensive bone defects, osteoporotic fractures or bone defects/fractures in oncological patients who underwent radiotherapy – regeneration of bone tissue is hindered and requires application of synthetic calcium phosphate (CaP) bioceramics. Although there is a large variety of CaP-based materials for bone regeneration on the market, CaP granules are still most frequently used in orthopedics and maxillofacial surgeries to fill bone defects and stimulate regeneration process.

Optimal CaP granules should have high biocompatibility and osteoconductivity (ability to promote cell adhesion, proliferation, and new bone formation), good mechanical parameters close to the human bone, high microporosity (pore diameter < 2 µm) and high specific surface area (SSA), which are essential for their bioabsorbability, high bioactivity (ability to form apatite layer on their surfaces) and good osseointegration with the host tissue. Most of the commercially available hydroxyapatite (HA) granules are sintered at high temperatures (≥ 900 °C). Although this type of ceramics is highly biocompatible and shows compositional and structural similarities with natural bone mineral, it reveals low SSA (5-10 m^2/g), reduced bioactivity and poor solubility thereby bioabsorbability. HA granules of high microporosity and SSA can be produced by application of low sintering temperatures (below 900 °C). Nevertheless, although HA sintered at low temperatures shows higher SSA (20-60 m^2/g) and improved bioabsorbability, it also exhibits high ion reactivity and cytotoxic effect under *in vitro* conditions. <u>Thus, there is huge need to develop a fabrication method, allowing to obtain bioabsorbable HA granules of high SSA without side effect in the form of cytotoxicity against bone cells.</u>

Successful bone regeneration upon CaP biceramics implantation is also increasingly challenged by post-surgery infections, prolonged inflammation, and impaired healing process. Importantly, chronic inflammation at the implantation site results in excessive reactive oxygen species formation and oxidative damage of the biomaterial and surrounding bone tissues, leading to the regeneration failure. Therefore, local delivery of antibacterial, anti-inflammatory, and osteopromotive agents that are released from bioceramics has been suggested as the promising approach to improve success in preventing such infections and prolonged inflammation.

Within this project we aim to produce highly microporous HA/polymer nanocomposite granules revealing high SSA, good bioabsorbability, improved osteoconductivity, antioxidant, anti-inflammatory, and antibacterial properties. Desired biological properties of the granules will be achieved by incorporation of vitamin C (strong antioxidant and stimulator of the synthesis of bone extracellular matrix) and essential oil-derived bioactive agent – R-(+)-limonene, which was demonstrated to have anti-inflammatory, antioxidant, antibacterial, and osteopromotive activity, whereas optimal microstructural properties will be obtained by application of novel production method combining freeze-drying with gas-foaming agent. Nanocomposite granules will be produced using nanohydroxyapatite (nanoHA) sintered at high temperature (1100 °C) to avoid cytotoxicity due to high ion reactivity and chitosan-based (agarose/chitosan or curdlan/chitosan) matrix that will serve as a binder for nanoHA. The project plan is also to comprehensively characterize mechanical, microstructural, physicochemical, and biological properties of the produced granules.