Development of novel bifunctional ceramic coatings with osteoinductive and anti-oncogenic properties on metallic implants dedicated to the bone reconstruction after tumor resection obtained via the dual-step ultrasonic micro-arc oxidation

The project aims to design, generate and characterize a novel osteoinductive and anti-oncogenic bifunctional ceramics coatings on metallic implants (Ti13Zr13Nb alloy and magnesium) via the dual-step ultrasonic micro-arc oxidation (UMAO), devoted to bone tissue engineering, especially for bone reconstruction after tumor resection. The proposed ceramics coatings will be based on (i) calcium acetate hydrate as a source of calcium that exhibits osteogenic properties, (ii) β-glycerophosphate disodium salt pentahydrate as a source of phosphorus that exhibits osteogenic properties as well as (iii) sodium selenite or selenium dioxide (inner layer) and cisplatin or methotrexate (outer layer) as a chemical compounds with anti-oncogenic and anticancer activities, respectively. The main issues to overcome are (i) the appropriate selection of the chemical composition of the solution and (ii) the adjustment of the oxidation process parameters in order to obtain coatings with the desired properties.

Bone, as a rigid organ of the skeletal system, has the ability to dynamic biological remodeling involving osteoclasts and osteoblasts. As a result, bone self-regeneration is possible, but if the damage is too large (> 2 cm) or there are other conditions (as cancer) in the bone, surgical intervention is required. Bone cancer is a term that describes several different cancers that develop in the bones, such as multiple myeloma, osteosarcoma and chondrosarcoma. Due to the development of chemotherapeutic drugs and prosthetic biomaterials, surgery to remove the affected bone is often accompanied with another treatment (e.g. chemotherapy or radiotherapy). Rescue of diseased parts of the limb, skull, spine or ribs usually involves resecting the tumor and then implanting a metallic implant to restore the bone function. Operations with inadequate surgical margins and indecorously applied chemotherapy have a negative impact on patient survival and local recurrence rate. It is stated that local recurrence of the malignancy occurs in as many as 20% of transplant patients, which is a serious complication and causes high mortality among such patients.

At present used metallic implants are predominantly made of stainless steel (316L), titanium and alloys (Cp-Ti, Ti6Al4V), cobalt–chromium alloys (Co–Cr) and aluminum alloys. These materials do not exhibit adequate mechanical properties (what may lead to stress shielding for load-bearing implants), show poor corrosion resistance in body fluids and some of their components are toxic to the human body (e.g. V and Al are toxic and can cause Alzheimer disease, osteomalacia or neuropathy). Therefore, different surface treatments of these metallic materials have been used to modify their properties. One of the newer ones is the ultrasound micro-arc oxidation process, which allows the generation of a porous coating that mimics the bone structure and accelerates the osseointegration process. It is an electrochemical method that enables the deposition of coatings with different microstructures and chemical compositions on metallic implants, and does not require specialized and expensive equipment.

The surface modification proposed in the project aims to change the properties of the implants in a way that prevents the recurrence of cancer after the implantation of metallic grafts. Novel bifunctional ceramic coatings on metallic implants dedicated to the bone reconstruction after tumor resection obtained via the dual-step ultrasonic micro-arc oxidation will consist of two layers:

- external (after II-step UMAO), containing chemotherapeutic compounds (cisplatin or methotrexate), the purpose of which will be to kill remaining cancer cells in the first post-implantation phase;
- inner (after I-step UMAO), which will be activated in the later phase, aimed at maintaining the inhibitory effect on cancer (due to the presence of selenium) and simulating cell proliferation (due to the presence of calcium and phosphorus), which will lead to osteosynthesis.

The following assays are planned, thanks to which it will be possible to characterize the coatings on both materials: (1) surface morphology and pore size; (2) surface roughness; (3) coating thickness; (4) chemical composition of the coating; (5) crystal structure; (6) wettability of coating; (7) evaluation of the cytocompatibility of the coatings and their impact on osteoblastic cells; (8) mechanical properties of coatings: hardness, Young's modulus; (9) adhesion of coatings; (10) anti-oncogenic properties on the human osteoblastic cell line - hFOB 1.19 and the human osteosarcoma cell line (SAOS-2); both will be used as individual cultures and/or as co-cultures; (11) degradation of coatings and evaluation of hydroxyapatite creation (bioactivity) at 0, 3, 7, and 21 days after immersion in simulated body fluid (Hank's solution) and assessment of the release of ions and/or bioactive agents.