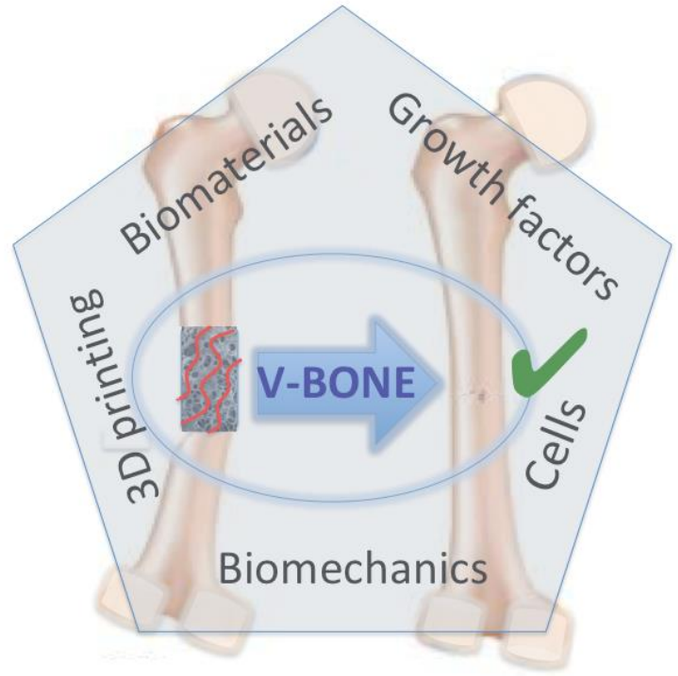
H.F.R.I.
Hellenic Foundation for Research & Innovation

Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment



Title of the research project: Development of tissue-engineered vascularized bone grafts

Principal Investigator: Prof. Maria Chatzinikolaidou

Reader-friendly title: V-BONE

Scientific Area: Sciences of Engineering and Technology

Institution and Country:

Host Institution: Foundation for Research and Technology Hellas (FORTH)

Collaborating Institution(s): -

Project webpage (if applicable): -

PI	Research Team	
Maria Chatzinikolaidou	**Konstantinos Loukelis**	**Varvara Platania**

Budget: 189,981.00 €

Duration: 36 months

H.F.R.I. Hellenic Foundation for Research & Innovation

Research Project Synopsis

Large bone defects are a major clinical and socioeconomic problem, as they negatively impact patients' quality of life. Osteogenesis and vascularization are coupled during bone development and growth. In the bone marrow, endothelial progenitor cells form an osteoblast-vascular niche by close proximity to osteoprogenitor cells. Several studies have investigated the combined effect of osteogenic and angiogenic growth factors on differentiation of mesenchymal stem cells. However, the integration of a fully functional vascular network inside bone grafts remains a biological and engineering challenge. The general objective of V-BONE is to develop a multifunctional platform including (1) a porous scaffold frame, (2) angiogenic and osteogenic growth factors incorporated in hydrogel microspheres, and (3) mesenchymal stem cells from the bone marrow and Wharton's jelly, to crosstalk in co-culture and promote the reconstruction of vascularized bone, which is crucial to treat large bone defects. To achieve this breakthrough in the field of tissue-engineered vascularized bone, in V-BONE we propose (i) to design, manufacture and characterize channeled porous scaffold frames based on chitosan and other natural biomaterials, with tunable chemical, mechanical and architectural properties, and hydrogel microspheres from gelatin and PEG for the encapsulation of angiogenic and osteogenic growth factors, inserted into the porous scaffold frame; (ii) to evaluate the angiogenic and osteogenic effectiveness in vitro in relevant cell cultures, and in vivo in mice. The multifunctional scaffold platform is expected to control the spatiotemporal release of growth factors and paracrine signaling factors that stimulate specific mesenchymal stem cell populations infiltrated inside the pores of the scaffold in co-culture, under dynamic conditions. Thus, the proposed platform will maintain cell survival and control tissue growth leading to effective reconstruction of vascularized bone grafts. The cell-scaffold constructs will be translated to a GMP, low cost, high-scale production level.

Project originality

The originality of the V-BONE project is the combination of cutting-edge technologies to create a multifunctional platform including a porous scaffold, angiogenic and osteogenic growth factors incorporated in hydrogel microspheres, and mesenchymal stem cells from the bone marrow and Wharton's jelly, to crosstalk in co-culture and promote the regeneration of vascularized bone, which is crucial to treat large bone defects. To achieve this breakthrough in the field of tissue engineered vascularized bone, in V-BONE we propose to design and manufacture (i) channeled porous scaffold frames based on chitosan and other natural biomaterials, with tunable chemical, mechanical and architectural properties, and (ii) hydrogel microspheres from gelatin and PEG to be used for the encapsulation of angiogenic and osteogenic growth factors, inserted into the porous scaffold frame. The multifunctional scaffold platform will be able to control the spatiotemporal release of growth factors and paracrine signaling factors that stimulate the mesenchymal stem cells populations infiltrated inside the pores of the scaffold in co-culture, under dynamic conditions. A key novel aspect proposed in V-BONE is mimicking the 'osteoblast-vascular niche' during bone development by gaining fundamental understanding of the effect of spatiotemporal release of BMP-2, VEGF and FGF on localized secretion of paracrine signaling factors by differentiating BM-MSCs in co-culture with Wharton's jelly (WJ)-MSCs inside the channels of the porous scaffold frame. V-BONE represents an approach beyond the state of the art in the field of multifunctional tissue-engineered scaffolds, to address challenges on vascularization in new bone formation in a scalable GMP manner close to a lab-to-market product.

Expected results & Research Project Impact

Large bone defects present a major clinical and socioeconomic problem, as repeated operations and long hospitalization periods impair patients' quality of life and have a high healthcare cost. Poor vascularization in large bone and critical size defects is a challenge in orthopedics and craniomaxillofacial surgery. Three types of bone grafts are used in the clinical practice to repair defects in long bones: synthetic bone void fillers, autografts and allografts. These methods have shown the ability to treat bone with a certain degree of success. The future of clinical treatments depends on decreasing surgical complexity, accelerating the regeneration time, and reducing the potential for treatment failure. To face these challenges, bone tissue engineering (BTE) constructs have been the focus of recent research. The general strategy has been described in the 'diamond concept', in which the final outcome in a fracture healing is determined by the combination of osteogenic cells, osteoconductive scaffolds, growth factors and the mechanical environment. Developing bone grafts that can concurrently restore vascular function to the regenerating bone tissue remains the most difficult aspect to address. The main cause of large graft failure is related to inner graft necrosis and lack of integration with the host tissue. Host tissue remodeling capabilities for severely damaged vascular beds are limited, while integrating a functional vascular network inside bone grafts is technically and biologically challenging. Incomplete graft viability is therefore a problem, and results in failure of the implanted constructs. The objectives proposed in V-BONE for the development of advanced tissue-engineered vascularized bone grafts are expected to address the limitations of current strategies to treat large bone and critical size defects.

The importance of this funding

The funding of the research project through programs by H.F.R.I for Faculty Members and Researchers is particularly useful and extremely important, as it gives them the freedom to develop ambitious research programs with high goals in cutting-edge science and technology fields over a three-year period. Within the frame of such a program, one has the opportunity to train young researchers, PhD candidates and postgraduate students, giving them the opportunity to be introduced to the field of cutting-edge scientific excellence, to be inspired by it, and to contribute to its continuation and expansion. In addition, through the continuous dissemination of the research project results in form of publications in international peer-review, high-impact scientific journals, as well as presentations at international conferences in the field, the university, the research center, and the country with its remarkable scientists are distinguished for their long-term vision and creativity.

H.F.R.I.
Hellenic Foundation for Research & Innovation

COMMUNICATION

185 Syggrou Ave. & 2 Sardeon St. 2
171 21, N. Smyrni, Greece
+30 210 64 12 410, 420
communication@elidek.gr
www.elidek.gr