The angiogenesis plays an essential role in effective treatment of bone defects. However, poor vascularization within tissue-engineered grafts has been identified as one of the greatest limitations of the use of bone tissue engineering (BTE) approaches in repair of large bone defects. Consequently, developing multifunctional biomaterials that can simultaneously promote bone formation (osteogenesis) and stimulate the formation of new blood vessels (angiogenesis) is one of the priority challenges of modern regenerative medicine and bone tissue engineering.

One of the most effective strategies for inducing angiogenesis at bone defect site is to target the cellular hypoxia inducible factor 1α (HIF-1α) pathway, which responds to low oxygen concentration (hypoxia) and results in the activation of a cascade of a number of genes and secretion of a cocktail of growth factors associated with angiogenesis and tissue regeneration. Hypoxia can be artificially mimicked in normoxic conditions (normal oxygen concentration) by stabilizing HIF-1α expression by using inorganic ions, such as transition metal (TM) ions like Cu^{2+} and Co^{2+}. Such biologically active ions can be delivered at the site of bone defect by their controlled dissolution from the biomaterial structure.

Silicate bioactive glasses (BGs) are one of the most attractive biomaterials for BTE that can be used as effective carriers for therapeutic ions because of their ability to incorporate a large variety of elements and their controllable dissolution properties in physiological fluids. BGs are widely studied for bone regeneration primarily because of their ability to bond to living bone, which is attributed to the formation of a hydroxyapatite layer on the glass surface in contact with the body fluids. Ionic dissolution products (i.a. Ca, Si, P) of bioactive glasses in appropriate concentration have been shown to stimulate bone formation via activating osteogenic genes. Therefore, the incorporation of hypoxia-mimicking TM ions into bioactive glass structure is expected to give multifunctional, gene-activating biomaterial with high osteogenic and angiogenic activity. However, exposure to high concentrations of Cu^{2+} and Co^{2+} ions has been shown to cause toxicity *in vitro* and *in vivo*. Hence, understanding the dissolution behavior of biologically active ions (Si, Ca, P, Cu, Co) form BGs structure is the key to control their biological properties. In order to be able to design and develop highly biocompatible, multifunctional bioactive materials it is important to identify their structural and textural properties and factors affecting them.

In the proposed project, biomaterials with high osteogenic potential, namely bioactive glasses from the basic SiO_2–CaO–P_2O_5 system, will be used as carriers for hypoxia-mimicking transition metals – inorganic proangiogenic agents. BGs will be doped with Cu and Co, at different concentrations. The primary goal of this project is to investigate the effect of concentration of TMs, CaO/SiO_2 molar ratio and glass preparation method (melt-quenching, sol-gel, sol-gel-EISA) on glass structure (including glass network connectivity), transition metal valance state and oxygen coordination number, as well as textural properties of obtained glasses. Additionally, the aim will be to explain the structural consequences of incorporating TMs into bioactive glasses, and to explore how glass structure (and chemical composition) affects the role of TMs in glass matrix (network modifier/network former). This will allow us to answer the important question how these glass characteristics affect the profiles of therapeutic element dissolution (especially Ca, Si, Cu, Co) and glass surface reactivity, and thus the *in vitro* calcium-phosphate layer-forming ability, as well as angiogenic and osteogenic activity. The second equally important goal of the proposed project is to fabricate biodegradable, bioactive, hypoxia- and extracellular matrix-mimicking fibrous composite scaffolds with high angiogenic and osteogenic potential for BTE. Scaffolds, containing TM-doped bioactive glass particles with the most promising biological properties, will be produced using electrospinning method. We believe that controlled dissolution of biologically active elements from composite structure and fibrous 3D form of scaffold will give synergistic effect of chemical and morphological stimulation of the cells towards osteogenesis and angiogenesis.

The proposed project assumes to establish and systematize factors affecting the kinetics of therapeutic element dissolution from TM-doped bioactive glasses and their surface reactivity, and thus the *in vitro* bioactivity, as well as biological performance. Furthermore, completely new type of multifunctional composite biomaterials with high angiogenic and osteogenic potential, comprehensively supporting bone regeneration, is expected to be obtained. Thus, successive completion of the project objectives by the use of advanced methods for structural and biological analysis may channel and dictate further progress in the field of bone tissue engineering by providing basic knowledge for optimizing the design of TM-doped bioactive glasses and composites produced with their contribution. Consequently, this may lead to the development of modern therapies, and thus raise a quality of life of patients suffering from difficult to treat large bone defects. What is more, improved understanding of the angiogenic effect of bioactive glasses, used as carriers of angiogenic ions, will increase the attractiveness of this materials and extend the range of their application outside of the skeletal system, e.g. in soft tissue engineering, where angiogenesis play a crucial role (i.a. wound healing).