**ABSTRACT – Ph.D. Thesis Contest**

# Physico-chemical cues to guide bone regeneration in calcium phosphate-based biomaterials

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Bone has a natural ability to self-repair, but severe damage, such as critical size defects or infections, exceeds its healing capacity, requiring alternative treatments. Classical bone tissue engineering (BTE) combines biomaterials, cells, and growth factors to create implants. The demand for improved biomaterials has driven advances in scaffold design, enhancing geometric, mechanical, and biological properties. Calcium phosphates (CaP) are ideal for bone regeneration due to their similarity to natural bone and ability to promote osteogenesis. However, optimizing CaP-based scaffolds for maximum bone healing remains a challenge.

In this thesis, we aimed to develop a combined experimental-computational framework to explore the key morphological drivers of bone regeneration in CaP-based scaffolds and to utilize these insights to design, manufacture and test optimized scaffolds under static and dynamic conditions *in vitro*.

Initially, we built a theoretical foundation through a systematic literature review and meta-analysis of CaP-based biomaterials in craniomaxillofacial (CMF) animal models. The study highlighted the impact of structural properties like composition, particle size, and pore size, along with experimental factors such as implantation time and animal species. This analysis quantitatively emphasized the key structural parameters influencing bone regeneration in CaP biomaterials.

Then, a data-driven model was developed to optimize CaP bone biomaterials. It combined histomorphometrical data from seven commercial bone grafts with their physico-chemical properties. Partial least square regression (PLSR) showed that chemical composition and macroporosity significantly impact bone regeneration. This study improved understanding of biomaterial properties in healing and provided a tool for designing more controlled bone biomaterials.

Next, we conducted experimental trials using key physico-chemical drivers from previous studies. Disk-shaped scaffolds of hydroxyapatite (HAp), tricalcium phosphate (TCP), and biphasic calcium phosphate (BCP) with varied channel geometries were created and seeded with bone marrow derived immortalized mesenchymal stem cells (hTERT-BMMSCs). Cell growth under static conditions showed curvature-based neotissue formation across all pore geometries, confirming prior mechanistic models. An optimized 3D scaffold was predicted, produced, and validated *in vitro*, showing strong agreement between predicted and observed neotissue growth.

Subsequently, the study advanced scaffold design by developing 3D-printed TPMS scaffolds with and without microstructural gradients, manufactured in HAp. Seeded with hTERT-BMMSCs, they were cultured under static and dynamic conditions, the latter using a modified bioreactor. All scaffolds showed excellent cell viability, gene expression, and bone formation, with dynamic conditions performing best. This work highlighted the impact of spatial pore architecture and structural gradients on 3D CaP scaffold functionality.

In conclusion, this PhD thesis provides valuable insights into the role of CaPs in bone tissue regeneration, highlighting how their physico-chemical properties and internal design influence biological functionality. This newfound knowledge directly contributes to designing and additively manufacturing optimized CaP-based scaffolds for BTE applications.