**Personalised bioactive scaffolds for maxillofacial bone regeneration**

This project will develop 3D printed personalized bioactive scaffolds for maxillofacial bone regeneration. Using a melt syringe extruder direct printing method we will create poly-(caprolactone) (PCL), bioactive glasses and octacalcium phosphate (OCP) hybrids (from micro-nano sized particles) that can be printed for specific sized defects and promote bone formation through the release of bioactive ions. This printing approach allows the rapid formulation of different inorganic polymer hybrids and the production of patient specific scaffolds with digitally controlled pore structures, whilst maintaining appropriate mechanical and bioactive properties.

Using equipment and expertise in 3D polymer printing (Wenhui Song), material characterisation, cell-material interaction and bone tissue engineering (Gavin Jell), in addition to a surgical lead (Kaveh Shakib) this project will enable the design-led creation of a novel but translation approach to maxillofacial bone reconstruction.

**Work Plan**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Work Packages | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **27** | **30** | **33** | **36** |
| **W1. Scaffold development**1.1 Development of the 3D printed scaffolds1.2 Personalised 3D image defect reconstruction – printing conversion |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 1.3 Scaffold internal interconnective pore structure design |  |  |  |  |  |  |  |  |  |  |  |  |
| **W2. Physicochemical characterisation**2.1 Mechanical (bulk & micro- mechanical)2.2 Chemical (batch & surface variability)2.3 Ion release (ICP) and degradation studies |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **W3. Biological characterisation**3.1 Protein interactions and bioactivity 3.2 Cell interactions (mesenchymal stem cell & osteoblast proliferation) |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 3.3 Bone nodule formation |  |  |  |  |  |  |  |  |  |  |  |  |
| **W4. Optimized Implant development**  |  |  |  |  |  |  |  |  |  |  |  |  |
| **W5. Project management & Dissemination**  |  | M1 |  | M2 |  | M3 |  | M4 |  | M5 |  | M6 |

M1 Development of printable hybrid, M2 optimised scaffold structure, M3 physicochemical characterisation, M4 initial cell studies, M5 bone nodule studies, M6 in vivo studies &/or re-optimisation of scaffold

**Work packages**

**Work Package 1. Scaffold creation**

**1.1** Development of the 3D printed scaffolds. Optimisation of the composition of the hybrid (% of bioactive glasses and OCT) and processing conditions of the scaffold (including rheology, printing temperature and printing speed).

**1.2** The reconstruction and design of “real” maxillofacial patient defects (CT scans/ MRI) using Mimics Software™ (Materialise, Belgium).

**1.3** Design and optimisation of scaffold structure. Printing pattern, pore size and porosity will be optimized using CAD design and printed structure characterisation.

**Work Package 2. Physicochemical characterisation**

**2.1** The bulk mechanical properties (including elasticity) as well as the substrate stiffness (AFM) will be determined and optimised. The scaffold should have the mechanical properties to support bone formation, maintain porosity and have a desired degradation profile.

**2.2.** The chemical properties will be characterised and optimised. The surface chemistry (ATR-FTIR, XRD, water contact angle, SEM, µCT) is important in determining protein adhesion, confirmation and subsequent cell interactions. The physicochemical characterisation will also allow an assessment of batch-to-batch variability.

**2.3.** To promote bone regeneration the scaffold will release “bioactive” ions (silicate, calcium and phosphate) to promote bone remodelling, The release of the ions needs to be controlled for desired cellular interactions and will be measured using ICP. The scaffold degradation rate is also an important consideration for total regeneration, whilst maintaining mechanical support.

**Work Package 3. Biological characterisation**

**3.1** Protein interaction and bioactivity. The protein interactions are an important component of host response and determine cellular interactions, they can also effect spontaneous apatite formation. Both protein adsorption and will be studied using total protein assays and characterisation of apatite formation following immersion in simulated body fluid (SBF). The apatite formed will be characterised using FTIR and Raman spectroscopy.

**3.2.** Cell interactions with the scaffold are a vital component of desirable output. Osteoblast-like proliferation (total DNA), metabolic activity (Alamar Blue), toxicity (membrane permeability assays), inflammatory response (IL-1, TNFα ELISA) and angiogenic response (VEGF ELISA) will be studied.

Furthermore the recruitment (Stro-1 ELISA) and human mesenchymal stem cell differentiation into bone cells will be studied (with ALP activity, RUNX+ and SOX9- gene expression, Collagen type I & II, protein and BMP expression).

**3.3.** To determine optimum parameters for bone regeneration, in vitro assays for bone nodule formation will also be performed and characterised with Raman spectroscopy (mineral to protein ratio), TEM (mineralisation of collagen fibres) and Alizarin Red staining.

**Work Package 4. Optimized Implant development**

Optimisation of an implantable patient specific construct. Based on the WP1-3, a final construct will be developed with optimised function and structure based on a patient case study. This will lead to future pre-clinical in vivo studies.

**Work Pack 5. Management and delivery.**

The project surgical lead will be Mr. Kaveh Shakib, who will responsible for finance management and overall direction. Gavin Jell is responsible for project management, deliverables and characterisation of material and biological interactions (WP2 & 3). It in anticipated that the 1st publication would be achieved at M3. Dr. W. Song will lead the scaffold development (WP1). The work package leaders will meet at least once every month to discuss progress.

**Funding**

Additional funding will be provided by the Royal Free Charity Maxillofacial research fund, to enable a PhD student to undertake this project (fees and remaining non-consumable/bench fee costs). BAOMS will support all bench fees and consumables. A meeting with BAOMS to report progress will be arranged every 6 months, together with a 500 word summary of progress.