# Challenge based learning (CBL)

# Controlled release of bio-active molecules to tune the healing of large bone defects

**Note for teachers: A CBL user guide can be found at** www.jandeboerlab.com/TissueEngineering with instructions and tips to run an effective CBL teaching session.

**Background and vision**

Bone defects due to trauma, congenital defects, diseases, and aging are a serious threat to human health. A complex but well-orchestrated fracture healing cascade is triggered when bone fractures. This process includes an acute inflammatory response, the release of specific biomolecules at the injury site, and the recruitment of cells to generate bone callus. To facilitate the spontaneous biological healing cascade, both ends of the fracture need to be in close proximity. If the gap is too big, fractures do not heal adequately. Therefore, critical-sized bone defects (CSBD) are treated in the clinic with autologous bone. Autologous bone grafts are the current gold standard but are limited by the volume that can be harvested from the donor and involve an invasive harvesting procedure. Allografts have limited clinical application mainly due to donor shortage. Additionally, the extracellular matrix and growth factors can be degraded or leached out during processing and sterilization steps, making allografts less biologically active. The long-term goal of this research field is to generate materials with osteo-induction capacity similar to autologous bone grafts.

**Motivation and stakeholders**

Osteo-induction requires the recruitment of progenitor cells and the stimulation of these cells to differentiate into bone-forming cells. During bone healing after a fracture, most of the repair is dependent on osteo-induction. Thus, there is a clinical need to develop biomaterials that can trigger the regenerative machinery of bone and modulate the spontaneous healing cascade to fix CSBDs. Solutions to mitigate this problem should consider the needs, requirements and regulatory, financial and technical boundary conditions defined by stakeholders such as patients with CSBDs, orthopedic surgeons, bone biologist, and biomaterial engineers.

**Problem definition**

Currently, bone grafts do not actively respond to the local regenerating tissue nor sense the stage of the healing cascade. Therefore, there is a lack of dynamic crosstalk between the tissue and the graft. Smart bone grafting would require materials which can sense the stages of the healing cascade, and respond by down- or upregulating inflammation, recruitment of stem cells, inducing cartilaginous bony callus revascularization or deposition of mineral matrix.

**Challenge**

To design a biomaterial that responds to one or several stages of the bone healing cascade to release bioactive molecules in a triggered and controlled manner to effectively treat CSBDs.

**Learning scaffold**

Reading the Controlled Release and Bone Tissue Engineering chapters and related literature will help you to understand:

1. The different ways to release bioactive signals from biomaterials.
2. Bone structure (lamellar vs. cancellous) and bone metabolism.
3. The bone healing cascade and direct vs. indirect fracture healing.
4. The bioactive signals (molecules, growth factors, cytokines)that can accelerate bone deposition and healing.

For a more focused examination of the challenge, read scientific literature and create a mind map to include information about the following:

1. Clinical and bioengineered strategies to heal bone critical-sized defects.
2. Strategies to release bioactive signals in the fracture niche to promote bone formation and treatment of critical-sized defects.
3. Natural and synthetic biomaterials to accelerate fracture healing and the treatment of critical-sized defects.

**End product**

# A three-minute video explaining the solution of your challenge. Please include your motivation and the steps to execute your solution.

# © Jan de Boer. CBL available for classroom use and CBL videos and can be found at www.jandeboerlab.com/TissueEngineering.