

Innovation Across Borders – Forum VBO-FEB

Innovation Case Preparation Form

WHO

- Welke onderneming(en) werd(en) hierbij betrokken? (grootte, bedrijfssector,...)?
- Met welke partner(s) (clusters, O&O-centrum, spin-offs, hubs,...)?

Three partners are involved in the CERACELL project: Bone Therapeutics, SIRRIS and Image Analysis.

Bone Therapeutics (the project coordinator) is a leading international biopharmaceutical SME located in Wallonia (Belgium) that specialises in innovative cell therapy products for the treatment of bone diseases. Bone Therapeutics has developed two top-class products: PREOB[®], an autologous bone cell therapy product, currently in Phase III clinical trials for the treatment of osteonecrosis and non-union fractures, and ALLOB[®], an allogeneic bone cell therapy product, now in Phase IIA clinical trials for the treatment of delayed union and spinal fusion. Bone Therapeutics also benefits from the support of university and academic hospitals.

SIRRIS is the Belgian research centre for the technological industry. It fosters innovation and supports the transfer of technology to 2,500 companies in the metalworking, plastics, medical, mechanical, electrical and electronic engineering, information and communication technology, and automotive sectors.

Image Analysis is a UK-based medical imaging company set up to bridge the gap between the best of academic research and routine clinical practice.

WHAT

- Wat was de doelstelling van de innovatie?
- Waarin bestaat precies de innovatie (toepassing, soort innovatie – product/procedé/businessmodel/support diensten/management,...)?

Porous bioceramic materials, cements and allografts are already used to treat bone defects, but these treatments are not fully satisfactory and reportedly have limited efficacy. CERACELL is a unique opportunity to **manufacture biocompatible 3D pieces tailored to a patient's defect, to be used in conjunction with differentiated bone-forming cells to treat large bone defects**. The use of stem cells for cellular therapy offers interesting and important prospects with regard to replacing damaged or lost tissue function. Through the use of mesenchymal stem cells (MSCs), an unlimited supply of fully differentiated cells is within reach, making cellular therapy a reality. In order to directly influence MSCs' behaviour, biomaterials are chemically or biologically modified and treated to ultimately manipulate the signal transduction pathways of MSCs towards osteoblasts.

Progress/innovation 1

Bone Therapeutics has developed a reproducible manufacturing process to obtain already differentiated bone-forming cells from MSCs. This innovation will allow better control over the cell fate resulting in enhanced efficacy and greater safety for the patient.

In the CERACELL project, Bone Therapeutics is in charge of the preclinical (*in vitro* and *in vivo*) studies: (i) the behaviour and biocompatibility studies of bone-forming cells with the 3D bioceramic pieces and (ii) the *in vivo* preliminary studies (biocompatibility and efficacy).

Progress/innovation 2

In the CERACELL project, Image Analysis will develop algorithms and software to provide the necessary input (i.e. printer instructions) to create personalised scaffolds via a 3D printer. This approach is innovative as Image Analysis will attempt to model what is 'no longer there' from the CT scan of bone defects.

Progress/innovation 3

The 3D printing of bioceramics is an innovative development as it combines (i) the conception and manufacturing of a tailored and personalised ceramic piece (for which the company already has background in the field), (ii) the integration of adequate microarchitecture (e.g. porosity) tailored to the inclusion of cells, and (iii) the internal design of the 3D pieces to promote the integration, survival and growth of bone-forming cells.

In the CERACELL project, SIRRIS uses the 3D modelling algorithms developed by Image Analysis to manufacture tailor-made 3D bioceramics.

IMPACT

- Voor de business/ de onderneming (verwerving van een nieuwe markt, groei, kostenvermindering,...)
- Op de markt (eindafnemers, tussenpersonen)
- Over het geheel genomen, ten aanzien van de maatschappelijke thematiek

The number of bone graft procedures performed in EU and the US is increasing year-on-year. Procedures involving bone grafts are predominantly used in the field of spinal surgery and, to a lesser degree, trauma. Fractures characterised by significant bone loss (large defects) and non-unions of long bones are the two main areas in this field.

The application under development here primarily targets long bone defects and those involving the spine. Without taking into account the patient population suffering bone loss following a disease, we are looking at an overall population of 160,000 to 240,000 patients per annum in the EU and US.

Bone autograft is considered the gold standard for repairing bone defects. However, its usage is limited by donor-site morbidity and supply. Limitations of **bone allografts** include the host's immunogenic response to the foreign tissue of the graft and the potential for disease transmission. Because of these limitations, the development – as well as the availability – of new orthobiologic materials to aid the management of bone defects is increasing.

CERACELL's bone tissue engineering products are expected to **equal the performance of autografts without affecting the patient** of the bone graft harvesting and without having to deal with limited supply issues. The developed products should be able to gain a market share in the current allograft sector of the market as well as provide better solutions for patients currently treated with autografts.

KATALYSATOREN & OBSTAKELS

- Hoe verloopt / verliep de ontwikkeling van het project (duur, algemene indruk)?
- Wat vergemakkelijkt / vergemakkelijkte het verloop van het project (katalysatoren)?
- Wat zijn / waren de moeilijkheden en uitdagingen waaraan het hoofd moet /moest worden geboden (hinderpalen)?

- CERACELL is progressing as planned, having reached the mid-term project period.
- One obstacle is the **high level of innovation** required to offer an effective and patient-tailored cell therapy treatment for repairing large bone defects. Indeed, according to the Target Product Profile, the product must (i) mimic the natural bone in terms of shape, structure and biomechanical properties and (ii) promote bone formation, remodelling and angiogenesis, (iii) while the scaffold must be progressively bio-resorbed and replaced by natural bone tissue.
- Another identified obstacle is that the **current regulatory framework** is not suitable for the next generation of 'combined advanced-therapy medicinal products (ATMP)' like Ceracell's. Indeed, in a Reflection paper dated June 2014, the EMA acknowledged that the requirements for the non-clinical and clinical development of ATMPs depended on the specific nature of each product and need to be designed and validated on a flexible case-by-case basis. For cell/scaffold products in particular, the difficulty lies in clarifying whether the scaffold is considered a medical device, an excipient or an active substance.
- In parallel with the approval granted by the competent authorities based on the product's benefit/risk profile, a solid Health Technology Assessment (HTA) will have to be prepared and thorough discussion will have to be held with the INAMI in order to determine the price, availability, and level of adequate reimbursement by third parties, such as insurance companies, government bodies and other healthcare organisations. These steps may pose an obstacle to commercialisation and the company's financial profit if the maximum price set by ministerial decision is too low to reconcile the company's economic needs. In contrast, the INAMI may decide not to reimburse a pharmaceutical product if its price is considered too high.
- As a 'catalyst', the project benefits from the top expertise and complementarity supplied by all three parties, including the highly valuable expertise of Bone Therapeutics in ATMP development from preclinical up to the advanced Phase III clinical stage.

LESSONS LEARNT

Wat kon er / had er kunnen verbeterd worden om deze innovatie te vergemakkelijken? (enkel invullen indien van toepassing)

- Organisatie/management van het project
- Samenwerking/partnerschap
- Beheer van de intellectuele eigendom
- Lancering van de innovatie op de markt
- Financiering van het innovatieproject (fiscaal beleid, beschikbaarheid van kapitaal, investeringsubsidies, enz.)
- Andere beleidsaspecten /regelgevingsaspecten

Market Launch

One of the major challenges will be to **timely and effectively introduce into medical practice** the cell therapy approach as a convincing alternative to standard orthopaedic interventions. To facilitate this process, it will be important to raise physicians' awareness of the superior beneficial effects of cell-based products for the treatment and/or prevention of bone diseases and orthopaedic conditions. Bone Therapeutics has already introduced this for its ongoing clinical programmes (e.g. fractures with impaired healing or spinal fusion).

Regulatory Pathway

To validate the product development and secure future approval from regulatory authorities, it will be necessary to have **thorough discussions with the EMA** (e.g. through a request for ATMP classification and scientific advice). This dialogue could be initiated during the preparatory phase of the pilot study.