Cell therapy : a strategic choice for BIOWIN

The competitiveness cluster BIOWIN, set up in July 2006 in the context of Plan Marshall 1.0, has almost 520 members from industry (including 70 innovative companies), laboratories and research centres.

Its 4 strategic choices are:

• To support innovation and excellence by facilitating collaboration between academia and industry, by ensuring that technologies and products developed meet the needs of the market and can be commercialised as quickly as possible;

• To optimise the structuring of skills to meet the needs of enterprises;

• To continue the internationalisation policy of BIOWIN, which is particularly to the advantage of SMEs;

• To facilitate the setting up of technology and infrastructure platforms encouraging the development of the biomedical sector in the Walloon Region.

The development of activities in cell therapy can be thought of in terms of these four key areas.

Cell therapy is based on in-depth knowledge of stem cells. These are undifferentiated cells taken from adult or embryonic tissues which, when grown in culture, have the capacity to reproduce almost indefinitely and/or to differentiate into specialised cells.

However, despite the scientific excellence and the large number of ongoing academic and industrial projects, access to the market can prove difficult.

There is not enough production capacity at the moment to let companies such as Cardio3 Biosciences, Bone Therapeutics and Promethera go on to Phase III clinical trials and subsequently launch their products on the market. They need clean rooms to ensure their economic expansion.

It’s to meet the needs of these industrial players that the Walloon Government has appointed BIOWIN for the implementation of an infrastructure platform aimed at clinical trials and the commercial production of cell therapy products. It will be able to accommodate start-ups, spin-offs and other emerging companies in the Walloon Region.

This project has already resulted in the creation of the company MaSTherCell which, as a CMO, provides manufacturing services to Walloon and European companies.

As the transfer of results from pure research to the industrial world is not easy, BIOWIN is working on a project for an inter-university research platform. By making available a variety of shared technological services such as optimisation of culture conditions, phenotyping and genetic stability testing or, for example, helping with regulatory affairs or the implementation of a quality system, this platform will at the same time create economies of scale and facilitate putting cell therapy products on the market.

The industrial dynamics project will create several hundred jobs in this area of cutting-edge technology.

In this context, the training project BioCel, coordinated by Biopark Formation/Training and recognised by BIOWIN within the scope of the 6th call for projects has found its ‘raison d’être’.

Finally, as a partner in the European project TERM (Tissue Engineering and Regenerative Medicine), a project which groups 8 European regions, BIOWIN has the assignment of drawing up a European research plan.

Among the actions which will be taken is the launch of a specific call for projects.

France Fannes
General Manager
BIOWIN
MaSTherCell, « Manufacturing Synergies for Therapeutic Cells »

Starting from an idea, which developed over many months, from the competitiveness centre, BioWin, and the three Walloon industrial players active in cell therapy (Bone Therapeutics, Promethera and Cardio 3-Biosciences), the aim of the MaSTherCell project is to strengthen the position of Wallonia in this high tech area. By creating a company capable of producing «cell medicines» for third parties, Wallonia aims to become a centre of attraction for foreign companies who will find in our region the skills and tools required for the production of their clinical materials and commercial batches.

On the strength of its convincing business model, MaSTherCell (Manufacturing Synergies for Therapeutic Cells) has today secured funding of over 5 million euros, part of which is capital provided by the management, the ULB Fond Théodorus, the Sofipôle (SRIW) and Sambrinvest, joined by the duo, Hugues Bultot / José Castillo, co-founders of Artelis.

MaSTherCell wants to provide quality production services to the cell therapy community. In order to be able to do this it will have high tech GMP (Good Manufacturing Practice) facilities, focused on the production of cells to be used for therapeutic purposes. The company could also produce cell lines for pre-clinical use (e.g. in drug discovery) or recombinant cell banks.

«We plan to set up a team which has both scientific expertise in cell therapy and knowledge of the industry and its requirements. We’re going to concentrate on the production of human cells with therapeutic effects and on developing our network of quality partners, preferably local, for any additional or more specialised services» says Patrick Stragier, COO of MaSTherCell. In the immediate environment we have, in particular, DNAVision, ImmuneHealth and the imaging centre, CMMI, and, within less than 50km, Quality Assistance, Aseptic Technologies, SGS, etc., who have the expertise necessary and are recognised internationally.

«A dozen European and American contacts have already shown great interest in the services of MaSTherCell, reinforcing our vision which is oriented towards «Client-Quality-Excellence in Operations», continues Didier Argentin, CBO.

MaSTherCell has an area of 640m² (200m² of which are GMP laboratories) in Biopark Incubator2 which it should move into in 2012, thus rivaling the European competition (at the moment Europe has just over 1000 m² of GMP rooms in CMOs dedicated to cell therapy). Its extension has already been planned. In 2016, it’s going to double the area of its GMP laboratories, allowing it to take over the position of leader, which it hopes to achieve in the next 36 months.

Concerning human resources, since its creation, MaSTherCell has had the advantage of having experienced management: Jean-Paul Prieels (ex-VP, R&D of GlaxoSmithKline Biologicals) as CEO, supported by Patrick Stragier (COO), Didier Argentin (CBO), François Lesage (CFO) and Alex Bollen, ex-CEO of Henogen (an advisor). Before the end of 2011, the team plans to take on 5 people – an industrial pharmacist, a project leader, a production operator/field manager, a Quality Control technician and a maintenance technician. By the end of 2012, MaSTherCell should have around fifteen employees and, by 2019, if the forecast is confirmed, around fifty people (technicians, pharmacists, biologists, biochemists…) should be working there.

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What is cell therapy?

Cell therapy concerns biological products with a therapeutic effect produced from preparations of living human or animal cells. It is used for three types of treatment: oncology (bone marrow transplantation), immunotherapy (in the treatment of cancer) and regenerative medicine (reconstitution of deficient cells or damaged organs). The cells used for cell therapy are selected, cultivated and treated or modified outside the body. Three types of cell are used: differentiated cells (the majority of those used today), stem cells (used, for example, for the reconstruction of bone or cardiac tissue) and induced pluripotent stem cells (which can give rise to any type of cell).
Bone Therapeutics: New developments

One of the world leaders in bone cell therapy, the spin-off Bone Therapeutics is soon to invest in bricks and mortar in the Biopark.

Bone Therapeutics is one of the spin-offs which have the wind in their sails. In scarcely 5 years, it’s gone from 4 to 42 employees and now has a capital of almost 15 million euros. It’s become the European leader and world co-leader (with an Anglo-Saxon competitor) in bone marrow cell therapy. It will soon be erecting its own building on the Aéropole of Charleroi.

Looking back… Bone Therapeutics originated from the expertise of Valérie Gangji, a researcher from the Erasme hospital, and her laboratory on the Erasme Campus. In the Cell Therapy Unit, the researcher and her colleagues were developing a new cell therapy product made of osteoblasts (cells responsible for bone formation) which seemed promising against osteonecrosis. Literally «bone death», osteonecrosis especially affects young patients (between 30 and 50 years old). There are between 50 and 100 000 new cases a year in Europe.

**Flagship product PREOB®**

That’s how the enterprise came about. The spin-off Bone Therapeutics was set up in 2006. In close collaboration with the Rheumatology Unit of the Erasme Hospital (Prof. V. Gangji) and the CHU Sart-Tilman (Prof. JP Hauzeur and M. Malaise), it carried out tests on the efficacy of the cell therapy product. In three years, the enterprise has applied for seven patents and obtained two Orphan Designations, (one in Europe and one in the US) giving it commercial exclusivity for its most advanced product, PREOB®. Specialised in the treatment of osteoarticular diseases by cell therapy, Bone Therapeutics develops cell products for the treatment of invalidating diseases which are most often incurable. The most important of these are pseudarthrosis (fractures which don’t consolidate naturally) and osteonecrosis (the bone dies and breaks).

In 2010, Bone Therapeutics came to a turning point. The company had to find funding for Phase III clinical studies... and the investors were up for it. Today the capital of Bone Therapeutics is around 15 million euros, coming principally from the Théodore fund (ULB), SRIW, Sambrinvest, BAF (Business Angel Fund) and private investors.

**New building**

The pivotal Phase II/III clinical studies involving 100 to 150 patients will be started this year. If they are positive, they will lead to the registration and commercialisation of PREOB®, probably in 2014.

By that time Bone Therapeutics should be settled into its new building on the Aéropole - the company is about to buy a building plot opposite IMI and CMMI. «The construction of our new building should begin in 2012 and will meet our R&D and production needs (especially regarding GMP norms) and our perspectives for expansion. We’ll combine all our activities on the one site, with 45 people in 2013, and we hope in the long term to reach 100 to 150 employees», says Enrico Bastianelli, CEO of Bone Therapeutics. He continues, «The enterprise Promethera envisages setting up a production unit beside us. Even if we each develop our own activities in our own buildings, we could have a common platform and shared services».

www.bonetherapeutics.com
Cell therapy is growing rapidly but companies are running into a great difficulty, that of recruiting people with good knowledge of the cell, and cell culture and its norms, and who can therefore be operational immediately. With this demand for a qualified workforce in mind, Biopark Formation/Training has designed a training programme oriented towards cell culture, especially cell therapy», says Béatrice Goxe, education coordinator.

We set up BioCel, a project of around 2 million euros for the period 2011-2014, with financing from the Walloon Region and recognition by its competitiveness cluster BioWin. Customer-oriented, BioCel has several courses and training modules, each adapted to a certain profile or function, and evaluated and followed by an external industrial jury. «Our steering committee unites industrial partners (Novasep, Bone Therapeutics, Promethera, Cardio3 Biosciences, Lonza, Euroscren, MaSTherCell) and academic partners (universities and «Hautes Ecoles») who help us focus on the needs in the field and give us feedback on the training» explains Béatrice Goxe.

With Cefochim

Four training modules will be on offer every year for four years: two courses for job seekers, in collaboration with Cefochim and Forem, one for managers and another for teachers. «We’re starting mid-August with a course for laboratory biotechnologists while Cefochim is organising with us a course for production biotechnologists. The two courses are aimed at job seekers of level BAC+3 (3 years’ higher education) or people with an equivalent profile. The courses will last several months and will finish with work experience in a company. At the end, the trainees will have good knowledge of what cell culture is and how to become competent in it, the rigour necessary, how to work in compliance with Good Laboratory Practice...», explains Béatrice Goxe who continues «We’re also organising a five day course for technicians so that they can acquire expertise in cell culture and the quality constraints which are closely associated».

«Hautes Ecoles»

In 2012, Biopark Formation/Training is launching a course for managers, 20 days spread over several weeks. The objective? To acquire expertise in regulatory affairs, knowledge of European norms relating to biomedicines, notions of clean rooms and GMP laboratories, etc. A Summer School (planned for summer 2012) will be aimed at teachers in «Hautes Ecoles». «Cell culture requires equipment which is often too expensive for many schools to be able to purchase. As a consequence, students are rarely trained in this sector which is, however, looking to recruit personnel. During the Summer School teachers will acquire the knowledge and skills indispensable for cell therapy and they’ll then be able to pass them on to their students. In the end, when we have new laboratory premises, we’ll even be able to accommodate teachers and their students», concludes Béatrice Goxe.

The complete programme is on www.biopark.be/formations
ImmuneHealth, coordinator of the IMTOX project

ImmuneHealth, a recognised collective research centre, is the coordinator of project IMTOX supported by the Walloon Region. The ImmuneHealth team presented the project which aims to validate immunotoxicity biomarkers in cell therapy.

You’re participating in the IMTOX project. What is this?

ImmuneHealth: IMTOX is a collective research project subsidised by the Walloon Region. It’s being done in collaboration with the Paediatric Clinical Department and Professor Etienne Sokal’s Laboratory of Paediatric Hepatology and Cell Therapy in UCL. The overall objective of the IMTOX project is to provide companies in the cell therapy sector with tests to measure immunotoxicity biomarkers.

Are the objectives of IMTOX only scientific?

ImmuneHealth: The project has several objectives, scientific, clinical and regulatory. The principal scientific objective of the project is to validate biomarkers from the host immune system response to transplanted cells and to develop methods to measure them. The biomarkers are selected from recent data in the literature and the model studied here is liver transplantation in children. At the clinical level, biomarkers allow us to follow the evolution of the transplant from a blood sample, thus avoiding having to resort to more invasive procedures. As far as regulations are concerned, few tests are available to verify the absence of immunotoxicity in cell therapy. The validation of innovative tests is therefore necessary for the evaluation of new strategies developed by industry.

What is the role of ImmuneHealth in this project?

ImmuneHealth: We’re involved at different levels of the project. First of all, we participate in the selection of candidate biomarkers and we study the technical feasibility of measuring them, assessing in particular the reproducibility of the tests. At the same time, we treat the clinical samples in accordance with the principles imposed for the creation of biobanks. We then do tests on clinical samples and analyse the correlation between biomarker expression and clinical evolution of the graft. Finally, we validate the relevant tests in accordance with international criteria (ICH) so that the results from the clinical studies can be presented to the regulatory authorities.

Could the expertise developed in IMTOX be transposed to other projects?

ImmuneHealth: The project is centred on liver transplantation in children as a model for the study of the immune response to transplantation antigens. Tests validated in the context of this model will be analysed in cell therapy and also after transplantation of other solid organs. One of the technological challenges of the project is doing the tests on small volumes of blood. We miniaturise the techniques used, in particular the flow cytometry and multiplex assays, so as to be able to measure repeatedly a high number of biomarkers in small blood volumes.

The Biopark at Harvard

In the context of the trade mission organised in the US at the end of June and headed by Prince Philippe, Walloon players in the field of cell therapy are prominent: a special session is organised with Harvard Medical School. Presided by HRH Prince Philippe and closed by the Minister Jean-Claude Marcourt, the aim of this session is to showcase the strategy set up by Wallonia to strengthen its leadership in cell therapy. Biopark enterprises are represented by Bone Therapeutics and MaSTherCell.
Guillaume Oldenhove

«Artists are sometimes like researchers»

In IBMM, Guillaume Oldenhove is doing research on the intestinal immune system. This year he has been given a permanent appointment as «Premier Assistant» in ULB.

«Since I was very young, I’ve always loved animals, plants, nature in general. When I was ready for university, biology seemed to fit my needs» remembers Guillaume Oldenhove.

He therefore started studying biology at ULB and very quickly became interested in plant physiology. However, the first practical work made him change his mind and he opted for immunology. «My end of study project was on the capacity of dendritic cells to activate a protective immune response to a pathogen. My interest in immunology increased as I worked on my project and I was very enthusiastic when I started a doctorate, with the objective to understand the regulation mechanisms of the immune response», he says. «By the time I’d finished my thesis I was interested in the immunology of intestinal mucous membranes».

Washington

After he had finished his PhD, Guillaume Oldenhove wanted to increase his knowledge. «I worked for two years in a research laboratory specialised in this area at the National Institute of Health in Washington, DC.

I had acquired solid technical knowledge so my objective was to make the most of my ability in Belgium. It was almost natural for me to apply for a full time post as researcher in ULB».

He came back to Belgium in 2011 and got a permanent post as «Premier Assistant» at ULB.

Immune response

In the Institute of Molecular Biology and Medicine (IBMM), Guillaume Oldenhove is continuing his work on immunology. To be more precise, he explains, «My current research is related to the fact that the intestinal immune system faces a major challenge. It has to tolerate not only the bacterial flora present in the intestines, but also food antigens. It must also be capable of reacting to external attacks by bacteria, viruses and various parasites. This supposes a complex regulation system which is the subject of my research. I’m trying to understand the way our immune system in the intestines reacts when it’s faced with a pathogen. Understanding the immune response at this level could especially contribute to curing patients with degenerative diseases of the digestive system, such as Crohn’s disease».

VTT and art

And when we asked him what «being a researcher» meant for him, Guillaume Oldenhove replied without hesitating, «Being a researcher is observing, experimenting, learning, cross-checking, taking risks, understanding the unknown, developing strategies». His free time is for his family and friends. He also goes mountain biking and likes to browse in modern art exhibitions because «for me visual artists are sometimes very similar to researchers» he observes.
Building works on the Aéropole

When the building trade thrives, everything thrives... If the adage is true, the Aéropole of Charleroi is doing very well.
An update on the works which continue... with Pierre Rombaux, Director of Economic and Building Development in Igretec.

> Igretec manages the Aéropole where the Biopark Charleroi Brussels South is located. Is there anything special about the Aéropole?

Pierre Rombaux: The Aéropole is a park with economic and technological activities, it’s not an industrial site. There are, of course, production companies but there are also research institutes, training centres, etc. The activities are grouped and developed by sector: life sciences in the Biopark, TICs, aeronautics, printing/graphic art, metal fabrication, service activities. Our wager is that by bringing together different players active in the same sector of activity, exchanges and collaborations will start to be created and, finally, there will be a greater expansion of activities. The Biopark Charleroi Brussels South is the best example of this.

> The Biopark continues to grow...

Pierre Rombaux: The CMMI (an extension of the IMI-ImmuneHealth building) is being completed and beside it the Biopark Incubator II is being built. It should be finished in the first quarter of 2012 and will accommodate the Biopark Incubator team, MaSTherCell and also modules for rent. We already have a building for young biotechnology enterprises, Wallonia Biotech, where Delphi Genetics and Henogen are at the moment. It’s going to be rebaptised Biopark Incubator I (BI I) and will be managed by the Biopark Incubator team, just like BI II, and entirely given over to biotechnology enterprises. We’ve reserved the adjacent plots so we can, if necessary, build Biopark Incubators III and IV.

> Several Biopark enterprises are investing in bricks and mortar

Pierre Rombaux: Indeed, opposite IBMM, Delphi Genetics is constructing a building of 1500m² which will accommodate its activities in 2012. Opposite IMI, on the other side of the roundabout, Bone Therapeutics is going to start its building next year. It might be joined by two other cell therapy enterprises, Promethera and Cardio3.

> The Aéropole is also going to house the technology campus.

Pierre Rombaux: Yes, it’s an ambitious project which brings together many players at different levels of education and training, around certain themes. The technology campus will cover 21 000 m², behind Delphi Genetics. Two buildings are already occupied. First, the Home of Industry (a three-storey building, entirely in glass) where enterprise associations (Agoria…), training companies (CIFOP, Technofutur Industrie…), innovation (Sirris…) and the exportation agency (AWEX) are located and, second, the composite plastics engineering building (with black and white weatherboarding). The next buildings will be those of FOREM (on the road leading to the water tower) and the «Espace du Savoir», in the centre, where there will be a cafeteria, an exhibition area, shared rooms… The first ground should be broken in 2012.

> The arrival of AGC has also been announced.

Pierre Rombaux: That’s right. In 2015, AGC is going to set up its research centre which will employ around 200 people on a huge site between the water tower and the Aéro 44 Hotel-Restaurant. AGC will then have two research centres in the world, one in Japan and the other on the Aéropole of Charleroi. This is very appropriate given the Charleroi tradition of industrial glassware. Other businesses are also going to move in soon (Viridaxis, ORES, etc), meaning that today the Aéropole is virtually 99% occupied.

> Do you see the possibility of an extension?

Pierre Rombaux: For several months we’ve been submerged with requests from all over Belgium and also from abroad. The buildings we rent out have an occupancy rate of 98% minimum. The reputation and dynamism of the players already present on the Aéropole, the technology campus, the airport, an immediate neighbour of the Aéropole, and its 6 million passengers make it very attractive. If we want to meet demands, we have to make the Aéropole bigger. The only possibility, in our opinion, is to extend on the other side of the motorway but this zone is at present agricultural or rural. The Walloon Region has ordered a study on the possibility of developing to the north of the Aéropole and the results should be known in one year.

> A growth in activity means an increase in traffic. What are the mobility projects on the Aéropole?

Pierre Rombaux: There should be a train station in 2019. It will be 20 metres underground and its platforms will extend from the Airport to the roundabout where Point Centre and IPG are. There should be six trains an hour, connecting Charleroi and Brussels. A Park & Ride scheme opposite N’Allo (near the creche) will also be set up, with 1500 SNCB parking places directly accessible from the motorway E42. The budget for these dossiers should be voted in 2012.
WelBio at IBMM

WelBio (a virtual Walloon research institute of excellence in life science) is supporting a research project in IBMM. Carried out in the Laboratory of Molecular Parasitology, headed by Prof. Etienne Pays, the research is on apoL1. The IBMM laboratory discovered that certain mutants of the protein apolipoprotein L1 (apoL1) are involved in the development of terminal renal insufficiency. Thanks to the support of WelBio, the researchers are going to study the role of apoL1 and its mutants in renal physiology, in order to understand the process of renal failure better and hence design appropriate treatments. Professor Pays’ team also discovered a protein which enables the African parasite Trypanosoma brucei gambiense to grow in human blood, causing the development of sleeping sickness. It’s therefore going to study the mechanism which makes this protein resistant to apoL1, the innate immune factor in human serum which normally eliminates the trypanosome. In addition, the laboratory has constructed a particular version of apoL which kills all the African trypanosome pathogens in cattle and man. They hope to develop a strategy using this protein to make local cattle easily resistant to all these parasites.

IBMM: Translational research

The IBMM Laboratory of Bacterial Genetics and Physiology has obtained research grants from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Society of Paediatric Infectious Diseases (ESPID) in order to pursue the characterisation of a case of nosocomial transmission of necrotising fasciitis. In March 2010, Pierre Smeesters, a research fellow in the laboratory, described clinically and microbiologically a case of nosocomial transmission of necrotising fasciitis, an infection which can be fatal. After sequencing the complete genome of the bacterium responsible (sometimes nicknamed “flesh-eating bacteria”), the researchers of the laboratory headed by Laurence Van Melderen are now creating knockout mutants lacking different virulence factors carried by this strain. The immune response generated by the wild strain and by the mutants will then be tested in vitro and in vivo. This research illustrates well the translational approach in microbiology adopted by the IBMM laboratory.

IBMM: Ubiquitin the activator

Ubiquitin is a small omnipresent protein which attaches to other proteins, causing them to degrade. This is a very common process in the cells, neutralising the function of a protein, as discovered by three Israeli and American scientists who won the Nobel Prize in Chemistry in 2004. Since then, researchers have known that ubiquitin sometimes bonds with a protein without, however, triggering its degradation. In this case, the ubiquitin simply regulates the activity of the protein. The malfunctioning of cell mechanisms controlled by ubiquitin is the cause of numerous pathologies including some cancers.

Researchers at IBMM, in Prof. Bruno André’s team at the Laboratory of Molecular and Cellular Physiology, have discovered a new example of non-proteolytic regulation by ubiquitin. The target of this regulation is an enzyme (a protease) present in yeast which is activated when cells detect the presence of amino acids in the external environment. Ten years ago, Professor André’s team showed that ubiquitin intervenes in this cell response. The researchers have now elucidated its precise role; ubiquitin binds with the inhibitor region of the enzyme, thus activating it. It’s therefore an original case of enzymatic activation by ubiquitin. This research was published in the The Journal of Biological Chemistry of 8 April.

Biopark Formation/Training

Find details of training
- Flow cytometry (June + September / October)
- Biocel (from 16 August)
- Biopoly - 2nd edition (May to September)
on www.biopark.be/formations

Change of direction within ImmuneHealth

Mr Marc Vander Kelen, who the Board of directors wishes to thank for the work done within the association, is no longer director of ImmuneHealth since June 9, 2011.

The new management team appointed by the Board of Directors consists of:
- General Management : Dominique Demonté
- Scientific Management : Arnaud Marchant
- Clinical Management : Jack Levy