The Biopark Charleroi Brussels South Newsletter

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A few days before hosting the “Cell Therapy” B4B-Connection, Dominique Demonté – Director of the Biopark – and Marie Bouillez – General Manager of the i-Tech Incubator – take stock of the current state of cell therapy on the Biopark.

A flourishing cell therapy sector

Bone Therapeutics was floated on the stock market in February. Is this also good news for the Biopark’s cell therapy cluster?

Marie Bouillez: It certainly is, because Bone Therapeutics, a ULB spin-off, has been the leading player in cell therapy on the Biopark, and indeed it was the initial spark that set things in motion. While still in the validation phase, Bone Therapeutics asked itself the following question: what do we need to produce large quantities of products? This question resonated with us and the i-Tech Incubator, in partnership with BioWin, carried out European market research that revealed an opening for a cell therapy company that could make products for third parties, in line with specific standards and in large quantities. That was how MaSTherCell was born, and three years later the Biopark is home to a real cell therapy ecosystem.

What exactly do you mean by an ecosystem?

Dominique Demonté: At the Biopark, we believe in the synergies and complementarity that exist between research, training, business, and services. Cell therapy is an example of this, given that we have research centres such as the CMMI or ImmuneHealth that have adapted their expertise to suit the particularities of cell therapy. Biopark Training has also set up programmes for jobseekers and people already working in the sector, so that cell therapy companies have access to a qualified workforce.

The European Social Fund (ESF) has also renewed its trust in the Biopark, and with European and local Walloon funding, Biopark Training will be able to continue training the sector’s staff and jobseekers for the next five years. Today, the Biopark is home to companies working to develop products (Bone Therapeutics, Promethera, Orgenesis, Pluriomics), companies providing services for the cell therapy sector (with Ovizio - another...
ULB spin-off - and Univercells accompanying MaSTherCell), and research centres. And all of this is underpinned by a human resources growth strategy. That is what I mean by an ecosystem.

Marie Bouillez: And that is all supported by our longstanding partners who have all played a role in creating a favourable ecosystem for cell therapy: Igretec, SAMBRINVEST, Sofipôle, Theodorus, Awex, BioWin, WBC, Biolog Europe, etc. For example, the project that led to MaSTherCell came about when Igretec was building the i-Tech 2. They halted the work in progress, redrew the plans to incorporate an additional floor with extremely stringent technical standards, submitted a new planning application, and recommenced construction. It’s extraordinary. Without this flexibility and openness to ideas, MaSTherCell could never - or at least not as quickly - have joined the Biopark, and it was through MaSTherCell that cell therapy took off on the campus.

WHAT MAKES CELL THERAPY SO PROMISING?

Dominique Demonté: Cell therapy is an emerging sector: 15 years ago there was no mention of it, and today it is recognised as one of the most promising areas of modern medicine. Wallonia sees this very clearly and plays a key role in the development of cell therapy, namely through the BioWin competition cluster but also through direct funding for businesses via DGO6. Cell therapy also creates jobs: in three years, around 120 jobs appeared on the Biopark and recruitment is set to continue, especially for production technicians. In Wallonia, we have now reached critical mass, enabling us to become a European player with a truly global appeal. The Cell Therapy B4B-Connection event organised for 1 and 2 April is just one example of this.

DOES THIS MEAN THAT AN INTERNATIONAL STRATEGY IS REQUIRED?

Marie Bouillez: Yes. All of our cell therapy companies already have an international outlook, whether in terms of their customers, shareholders, or partners, and we are already home to foreign companies like Israel’s Orgenesis. Wallonia is an attractive location for foreign companies seeking to open a subsidiary in Europe, and we are currently working to accentuate the Biopark’s appeal even further, in particular by working with Charleroi Airport: as neighbours, together we could provide bio-logistic solutions for business. By working with our partners we are able to provide comprehensive support, from identifying financial partners to moving into new premises.

ON THAT NOTE, IS THERE STILL ROOM FOR NEW COMPANIES?

Marie Bouillez: We still have some space in i-Tech Incubator 2 but we are already planning a third building in partnership with Igretec, and i-Tech 3 should spring up within two years.

Cell Therapy B4B Connection

1-2 April on the Biopark Charleroi Brussels South.

A 1.5 day networking event for the European cell therapy sector, with conferences, company presentations, and business meetings.

Learn more and register: buzz4bio.com/u-4567
MaSTherCell quickly established itself as a key player in cell therapy in Belgium and abroad. Its recent financial transaction with the Israeli company Orgenesis – a share exchange agreement – demonstrates it.

“We are always furthering our understanding of the cell therapy sector, and its most interesting, valuable, market segments”, reports Hugues Bultot, CEO of the services company specialising in cell therapy. In existence for just over three years, MaSTherCell is already a leader in this booming sector. And it won’t be resting on its laurels.

“Being in Belgium, and Wallonia in particular, is a huge advantage for us. Our position has enabled us to introduce a number of foreign companies to this Walloon ecosystem, companies that could relocate their businesses to the region or found a subsidiary in Belgium”, Hugues Bultot continues, “This was the case with Orgenesis, from Israel, for example. They are developing a treatment for type 1 diabetes. We have just concluded a share exchange agreement with the company: this will allow us undoubtedly expand our global presence”.

USA, ASIA

The company’s ambition is now to use its firm local moorings as a base from which to expand its international business, mainly in the USA but also in Asia.

“We also use technology (some of which provided by highly innovative Belgian companies) to provide our customers with optimised production strategies”, the CEO explains, “This means that our clients can provide their treatments to as many patients as possible (large scale), all while guaranteeing consistently high quality. Furthermore, it should enable them to reduce production costs and move through clinical test phases more quickly”.

To do so, MaSTherCell can count on a team that has not stopped growing since it was first formed. Made up of 32 staff – biologists, chemists, technicians, GMP (Good Manufacturing Practices) or quality experts, and high-flying project managers – MaSTherCell is planning to create more jobs in the near future, reaching a staff of 50 within the next two or three years. “We proved our worth very quickly and gained recognition in Belgium, Europe, and around the world”, the CEO concludes.
Bone Therapeutics floats on the stock market

A leader in bone cell therapy, Bone Therapeutics has just announced its flotation on the Euronext Brussels and Euronext Paris stock exchanges. It is the first company from the Biopark, and the second Walloon cell therapy company, to float on the stock market. Its aim? To accelerate the company’s growth and innovation process, in particular with regard to repairing and preventing fractures.

Founded in 2006 and based on the Biopark, Bone Therapeutics has just announced its flotation on the Euronext Brussels and Euronext Paris stock exchanges. By doing so, the company can raise new funds that will be used to accelerate testing of its candidate drugs, PREOB and ALLOB, or to launch new clinical trials in the USA.

“We are delighted to join Euronext Brussels and Paris, where we were welcomed by over 50 new European corporate investors of the highest quality, as well as private investors”, beams Enrico Bastianelli, CEO of Bone Therapeutics. “The results obtained this far have been extremely positive, and address indications with very important unresolved medical needs and where there is limited competition. In order to continue the development of the clinical studies that are currently underway and plan ahead for our products going on sale, we thought it was the right time to launch our flotation on the stock market”.

In an effort to overcome the major constraints relating to the repair and prevention of fractures, Bone Therapeutics has developed a range of innovative regenerative products that includes ALLOB, an allogenic product (the cells for which are taken from a healthy donor) designed to treat bone disease. The initial results are quite promising: 3 of the 4 patients observed in phase I/IIA - in which the effectiveness and safety of the treatment is determined - displayed full consolidation of their fractures.

“Alongside the recent confirmation that the product is safe to use, these results are very promising”, Enrico Bastianelli continues. “The radiological improvement confirms, thus far, the treatment’s success and reaffirms our belief that ALLOB may provide major therapeutic advantages to patients.

In the first half of 2014, Bone Therapeutics’ clinical department and production facilities underwent expansion. Additional staff were recruited to support the development of its preclinical products, as well as the clinical programmes currently underway. In 2012, Bone Therapeutics employed 46 staff: this rose to 52 in 2013, and 72 the following year.

31% of staff have a PhD and are specialists in the following scientific fields: cellular and molecular biology, pharmaceutical sciences, veterinary medicine, and physiology. Among them, they represent 10 different nationalities.*

*The figures cited above refer to staff at Bone Therapeutics and its subsidiary Skeletal Cell Therapy Support (SCTS).
Pluriomics: the “new kid” at the Biopark

With the recent arrival of Pluriomics – a company that develops stem cells for use in the research and treatment of heart problems – the Biopark is consolidating its position as leader in the biotechnology sector and affirms its expansion into cell therapy.

Pluriomics, a Dutch company, has recently moved in to the Biopark, bringing with it an investment of €4.5m from SAMBRINVEST, the Société régionale d’investissement de Wallonie (SRIW), and the Vesalius Biocapital Fund.

“Wallonia was our first choice”, specifies Herman Spolders, CEO of Pluriomics. “The environment is perfectly suited to our plans for development, as the Biopark is home to numerous big names in cell therapy. This will mean that in the future, we will have rapid access to the particular services and resources we need”.

Founded in 2010, the Leiden-based company (the research centre and sales department are located in the Netherlands) decided to set up its new stem cell production facility here in Gosselies. “Pluriomics manufactures stem cells derived from heart cells, destined for the pharmaceutical industry. These cells can be used to carry out cardiac testing without the need for animal models. The reliability of our research is beyond reproach and our service for businesses is very promising in terms of production”, highlights Herman Spolders.

Pluriomics’ precise role involves creating cardiomyocytes, or cardiac muscle cells (the muscular cells that make up the human heart), for use in various stages of the search for new drugs. “We are ready to launch our Pluricyte cardiomyocytes”, Herman Spolders confirms, “In addition to improving decision-making in industry, these cells will be used to detect any potentially toxic side effects of new drugs under development”.

This represents a new area of expertise that may be useful to the Biopark and its cell therapy cluster, “We have not yet launched any definite partnerships with other members of the campus, but it is only a matter of time as our new technology could play an important role in manufacturing and supplying certain cells”.

Damiano Di Stazio
For several years now, the various stakeholders on the Biopark have been attentive to sector-specific needs, resulting in a true ecosystem developed around *biotherapy*. Biopark Training, the CMMI, and ImmuneHealth stand testament to this.

**BIOCEL: A FINE EXAMPLE OF EDUCATIONAL/INDUSTRIAL INTEGRATION**

BIOCEL is an innovative cell culture training programme. Coordinated and delivered jointly by Biopark Training and Cefochim since 2011, it is certified by the BioWin competition cluster. Feedback has been positive over the four years that have seen 3 BioCel R&D courses, 6 Biocel Production courses, and a plethora of short courses delivered.

“Since it was launched, the programme has provided training for people of all backgrounds: staff working for multinationals or SME, teaching staff at high schools, PhD students, and even jobseekers”, explains Béatrice Goxe, scientific coordinator and trainer at Biopark Training.

“BIOCEL has met and exceeded its objectives”, continues Arnaud Termonia, the training centre’s director. “Its long courses for jobseekers have provided companies with a pool of qualified candidates from which to recruit, its short courses have topped up the knowledge and skills of industry staff, and it is working to bring initial qualifications into line with the sector’s needs through a short programme designed for teaching staff at high schools”.

In total, more than 310 people have completed cell therapy and culture courses, a cohort made up of 25 teaching staff, 35 students, 70 members of staff in major companies or SME, and 180 jobseekers, 80% of whom found work after completing their course. The programme has even led to the acquisition of highly effective cutting edge facilities (cell counters, microscope cameras, hoods, etc.), inspired by the equipment used by major players in industry.

Initiatives in the cell culture field are set to continue. “In addition to launching our MasterClass (*featured in Biopark News* 24) in late March, we are also planning to update our long training programme for jobseekers”, Béatrice Goxe reports. “Biopark Training, Cefochim, In vivo culture, and the GIGA are currently working on a joint cell therapy course that will be the only one of its kind in Wallonia”.  

**THE CMMI AND IN VIVO RESEARCH**

“For the CMMI, partnerships with various players on the Biopark are essential as the campus is home to some powerful scientific resources that make rapid growth possible”, explains Serge Goldman, Head of Nuclear Medicine at Erasme Hospital and manager of imaging at the CMMI. “The Biopark’s laboratories boast extremely advanced expertise, in particular with regard to fundamental biological processes, that we do not necessarily have ourselves, and for the Biopark’s scientific community, having access to a preclinical biomedical imaging facility is a huge asset. To give a very specific example, we have recently been working with an academic on the campus, Denis Lafontaine, who is interested in how cancer cells proliferate. Our preclinical tests provided a speedy answer to his hypothesis. *In vivo* imaging in animals offers the best way to study and understand organisms as a whole (when several different tissues or organs are involved)”.

This may also be very appealing for businesses and the development of innovative treatments. Through a partnership between the CMMI and Bone Therapeutics, – that has currently been extended as part of the Osteomod project – the CMMI is looking into cells that may regenerate bones. Its
aim? To study the circulation of these special therapeutic agents, as well as their ability to produce the expected effects: once injected, do the cells travel to the intended area? Do they remain there or do they leave to reside elsewhere in the organism? Is the ability of the tissue that hosts them to repair and regenerate improved?

“The process can be shown visually: that’s the advantage of imaging”, adds Serge Goldman. “It is extremely persuasive as it’s a very strong argument, especially when companies or laboratories want to apply for European funding”.

IMMUNEHEALTH: AT THE HEART OF THE CELL THERAPY SECTOR

“Our structure that combines an immunomonitoring laboratory and a clinical unit is able not only to support and approve the design of innovative treatments, but also to discover new biomarkers”, confirms Brigitte Genard, CEO of ImmuneHealth.

For several years now, the ImmuneHealth joint research centre has built a wide network both within the Biopark and across Europe, accompanied by a solid reputation, especially within the cell therapy sector. “ImmuneHealth is one of the most sophisticated technical facilities in Europe”, reports Julien Isoard, Business and Marketing Manager. “We have cytometers that can measure the expression of 10 markers simultaneously, meaning that we can provide an extremely powerful characterisation of a sample in a single analysis”.

Through its immunomonitoring platform, ImmuneHealth offers businesses – such as Promethera, in particular – its expertise in the development, validation, and transfer of analytic methods to characterise cells produced for cell therapy, as well as evaluating the immune response of patients receiving the treatment.

In 2013, ImmuneHealth secured Good Manufacturing Processes (GMP) certification for its quality control of clinical batches using flow cytometry. “This certification is compulsory for producing and testing clinical products that will be injected into humans”, specifies Julien Isoard. “Armed with this certification, we have supported Cardio3 Biosciences in their product development. This enabled us to fully live up to our role as a joint research centre by contributing to the development of a regionally flourishing sector of industry”, adds Brigitte Genard.

Partnerships between ImmuneHealth and the cell therapy sector have intensified, in particular over the past two years: two contracts have been signed with MaSTherCell, Cardio3 Biosciences, ImCyse, and Promethera Biosciences. Further partnership opportunities are currently being discussed with specialist players in cell therapy.

Damiano Di Stazio
Biopark Training: going further, faster, thanks to the ESF

The European Social Fund has reaffirmed its trust in Biopark Training by awarding it a budget of €2.5m for 2014-2020. Today we hear from Arnaud Termonia, Director of Biopark Training and Lifelong Learning at the ULB.

**HOW ARE YOU FEELING A FEW DAYS AFTER THE ANNOUNCEMENT OF THE WALLOON PROJECTS RECEIVING ESF SUPPORT?**

*Arnaud Termonia:* I’m happy, of course, because the European Social Fund has reaffirmed its trust in us; I’m thinking of the team at Biopark Training and its many partners who have made this success possible, not to mention the hundreds of people who have sat our courses. Receiving European support after being pre-selected by a panel of independent experts is extremely rewarding.

**HOW WILL YOU USE THE ESF SUPPORT?**

*Arnaud Termonia:* We will consolidate our integrated strategy: the Biopark is home to certain specialisms — expertise and facilities in imaging, cell therapy, and immunology, in particular — that we must be able to both accommodate and draw upon. Biopark Training must also be on the lookout for new scientific and technical profiles, as well as the managerial acumen that will be needed in coming years, thereby developing a course prospectus that produces appropriately qualified candidates and contributes to Wallonia’s economic revival. We firmly believe that lifelong learning is made possible through the research carried out by the University and businesses in the sector, and interaction with valuable partners like BioWin, skill clusters, and Forem.

**WHO IS BIOPARK TRAINING’S TARGET AUDIENCE?**

*Arnaud Termonia:* Our audience is varied: company employees, PhD students and researchers, teaching staff at high schools, and jobseekers. Our aim is to boost the skills of those with existing qualifications, as well as to create a pool of qualified candidates to meet recruitment needs.

**IS THERE ANYTHING NEW ON THE HORIZON?**

*Arnaud Termonia:* There is always something new on the way as the campus is always evolving, as are industry needs and teaching methods. We are also open to suggestions, and we have created a space on our website where people are free to submit ideas for courses. In 2015, we can boast a full prospectus, solid partnerships, and a set-up that has been in place for 7 years, etc. We plan to be going even further, even faster by 2020.

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**MIRVAL +**

The ESF is also supporting the MIRVAL+ project seeking to amplify the impact that applied research in universities and university colleges in the Fédération Wallonie-Bruxelles has on innovation in business. This will be the subject of an article in a future issue of Biopark News.
RIBOSOME BIOGENESIS: A COMPLEX ASSEMBLY LINE

Ribosomes convert genetic information into operational proteins. The components of this cellular nano-machine are known, as are most of the workers involved in manufacturing them. Among the various stages of ribosome biogenesis, the RNA Metabolism Laboratory (IBMM), headed by Denis Lafontaine, is paying particular attention to the addition of chemical groups to ribosomal RNA (rRNA), and trying to identify the order in which these changes are made, as well as the few remaining unknown workers involved in the process.

In two recent articles, published in PNAS and Nucleic Acids Research, the team describes the discovery of two of these workers: the Bud23-Trm112 complex, responsible for rRNA methylation, and the Kre33/NAT10 acetyltransferase, which carries out two modifications to the rRNA and one on the transfer RNA.

The study of ribosome biogenesis is essential to further our understanding of ribosomopathies, diseases resulting from incorrectly assembled ribosomes and that predispose sufferers to cancer. But much remains to be discovered: in a special edition of Nature Structural & Molecular Biology on non-coding RNA, published in January, Denis Lafontaine explains that contrary to all expectations, not all of a cell’s ribosomes are the same. Indeed, the differences lie in the modifications to the rRNA that may affect the ribosome’s ability to translate certain mRNA. The researcher suspects that this mechanism is involved in the development of cancer, following the differential translation of messenger RNA-encoding proto-oncogenes and tumour suppressors like p53. The researcher and his team will endeavour to follow this line of enquiry over the next few years.

N.J.

CANCER IMMUNOTHERAPY: AN INTERNATIONAL SYMPOSIUM

On 2 April, Biopark Training will hold an international symposium on cancer immunotherapy. The fruit of a partnership with the ULB’s Health Cluster, the event will take place on the Erasme campus. A number of European experts will discuss the most promising immunotherapy strategies and present their clinical results. Foundation level immunology courses will also be delivered at the Biopark in the run-up to the symposium.

Find out more at www.biopark.be/bioparkformation/symposium.html

There is also a brand new way to interact with Biopark Training through its website: the team is eager to hear your suggestions so that it can deliver courses that meet your needs.


N.J.
FUNCTIONAL REGULATION OF T-LYMPHOCYTES IN FOETUSES

Cytomegalovirus (CMV) is the most frequent cause of foetal infections. Generally benign in adults, the virus can cause sometimes severe symptoms in 10-20% of children infected in utero. Various studies have previously shown that the foetus develops an immune response to CMV, but that the virus is present in larger quantities within adults, suggesting a weaker immune response.

In a recent publication in the Journal of Infectious Diseases, Ariane Huygens, Arnaud Marchant, et al (IMI) set out to understand the causes of this less effective immune response. In partnership with the Erasme and Saint-Pierre Hospitals, researchers analysed the presence and role of T-lymphocytes in foetuses infected with CMV. They revealed a reduction in the production of antiviral cytokines, with a concomitant increased expression of an inhibitor receptor by T-lymphocytes in infected new-borns.

This functional regulation may limit control of CMV replication in the foetus, but could also prevent an excessive inflammatory response that may endanger the foetus’s ability to remain within the uterus. This phenomenon may also limit the control of other pathogens that infect the foetus and young children, such as HIV, tuberculosis, and malaria.

N.J.

NEVERFLASH:

A large number of young researchers have just joined the campus! The reason? More excellent results in FRIA and FNRS grant applications. Welcome to the Biopark!

REACTIVE T LYMPHOCYTES IN THE FOETUS

Playing a key role in the immune response, T lymphocytes come in a wide range of varieties. The predominant variety in adults, Vγ9Vδ2 T lymphocytes, can detect the small molecules derived from pathogens, known as phospho-antigens. It is thought that the abundance of this kind of lymphocyte is the result of exposure to pathogens following birth.

But researchers led by David Vermijlen, recent winner of the Illier Award, working closely with the Institute for Medical Immunology at the Erasme Hospital, have recently shown that Vγ9Vδ2 T lymphocytes are also the main sub-variety of lymphocytes in foetal blood in humans.

Despite the sterile environment in which it grows, it would seem that the foetus develops a sub-group of T lymphocytes that react to pathogens before they are even exposed to them. Published in the PNAS journal in January, this discovery may lead to new vaccination strategies for foetuses and new-borns.
HIV: TWO VIRAL PROTEINS CONTROL THE NF-κB PATHWAY

Type 1 human immunodeficiency virus (HIV-1) and simian immunodeficiency viruses (SIV) have developed a very precise control of the NF-kappaB cellular activation pathway. This pathway promotes the antiviral immune response in the host, but is also involved in the expression of viral proteins.

Research carried out by members of the Molecular Virology Department (IBMM) under Carine Van Lint, and their German counterparts at the Institute of Molecular Virology at Ulm University Hospital, have shed light on the role played by the viral proteins NEF and VPU in controlling NF-kB, both in HIV-1 and most primate lentiviruses. Expressed early in the viral replication cycle, NEF increases activation of the NF-kB signalling pathway to effectively launch viral transcription. Then, VPU plays the opposite role by repressing the expression of antiviral genes in order to prevent too great an immune response.

These results, published in Cell Reports on 3 February 2015, would suggest that very specific regulation of NF-kB through the opposite effects of viral proteins NEF and VPU plays a key role in HIV-1 replication, immune evasion, and AIDS pathogenesis.

Furthermore, latent reservoirs of HIV, another component of AIDS pathogenesis, are a major obstacle to wiping out the disease and one of the main areas of research for Carine Van Lint’s team. The laboratory recently obtained the backing of the Maturation Fund for the study of various molecules that may reactivate these reservoirs in vivo, making it easier for them to be eliminated. This clinical trial, run in partnership with Saint-Pierre Hospital, has also received the support of the Fondation Roi Baudouin.

N.J.