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Editorial

A return to stem cells ?

In the last few weeks, stem cells and regenerative medicine appear to have made a public comeback. Since Barack Obama's arrival in the White House, there has been regular talk of a possible move by the US President to revoke the decision by his predecessor, George W. Bush, to block federal funding of embryonic stem cell research. Bush's initiative, however, did not put an end to this line of research, with funds being raised from private investors or individual States, like California, where another Republican, governor Arnold Schwarzenegger, has encouraged the creation of the *California Institute for Regenerative Medicines* in order to support and fund such activity in Californian universities and research establishments. At the end of January, the FDA gave its seal of approval to the first clinical trial ever to be performed in human beings using a therapy based on stem cells **(1)**.

In early February, the UK Bioindustry Association (BIA) reiterated its plans and its determination to ensure that the United Kingdom remains at the cutting edge of the field with the creation of a group dedicated to regenerative medicine, the RegenMed Industry Group (RIG). This week, two research centre networks, one in the United Kingdom, the UK *National Stem Cell Network*, and the other in Germany, the *Regenerative Medicine Initiative Germany*, organised a conference aimed at facilitating exchange between scientists and researchers from the two countries and identifying themes for collaboration. At the same time, StemCells, a US company specialising in stem cell research, purchased the stock of another specialist in the field, UK-based Stem Cell Sciences. Is this a signal of real reawakening and renewed interest in stem cells or does it simply mark the continuation of studies in these lines that have not yet proven their therapeutic potential? The results of the first clinical trial authorised by the FDA in January will no doubt provide us with a clearer picture. To be continued...

Anne-Lise Berthier

(1) A phase I clinical trial conducted by US firm Geron to establish the safety of its product GRNOPC1, based on oligodendrocyte precursors, in the treatment of patients with acute spinal cord injury.

Industry and partners

Exonhit Therapeutics: a successful mutation

Just over one year ago, Exonhit Therapeutics began its transition towards the market with the transformation from its R&D-oriented structure towards a specific commercial organisation built around two newly created departments, a genomic services and diagnostics department and a therapeutic department (see *BioPharmaceutiques* No 50). Today, company reorganisation is complete, with the creation of a marketing department and the incorporation of regulatory know-how based around a triple-pillar general strategy. "We have reviewed our positioning with regard to genomic services and the sale of chips for analysis of gene expression and detection of splice variants," explained Exonhit CEO Loïc Maurel. These activities, which have helped raise the French company's profile and enabled it to work hand-in-hand with major research bodies such as the NIH in the US and the Institut Gustave Roussy (IGR) in France, will now become increasingly integrated in partnerships in both the therapeutic and diagnostic fields. Regarding diagnostics, the studies conducted by IGR form the subject of an article in *The Lancet Oncology* clarifying the role of alternative splicing in breast cancer profiling **(1)**. "This study should produce a specific signature for the diagnosis of breast cancer in mammary tissue," added Loïc Maurel. Results are also anticipated in September 2009 from the partnership initiated with bioMérieux in 2005 concerning the development of diagnostic blood tests for breast cancer,

colorectal cancer and prostate cancer.

Two solid branches. In addition to repositioning its service activities, Exonhit Therapeutics has reiterated its desire to retain its diagnostics and therapeutics activities, which will allow the company to develop towards personalised medicine. In the diagnostics field, the company is aiming to strengthen its product portfolio and its development capacity, particular through the purchase of products and companies, and with EUR 21 m, the company had two years' of cash flow available at the end 2008. But above all, it must complete a major step in the final quarter of 2009, at which point it should be in a position to market its lead product, EHT Dx21, a blood diagnostic test for Alzheimer's disease. This test, currently undergoing clinical validation in a study in around 550 patients, which could become the first blood diagnostic test for Alzheimer's disease to reach the market, will initially be aimed at the clinical trials market. "This market is worth USD 30 to 40 m and we will be selling our test kit through our head office in Paris and our subsidiary in Gaithersburg in the United States. Transition to a broader marketing strategy oriented towards medical diagnostics will come later, with the support of a partner," stated the Exonhit CEO.

Targeting α -secretase. Regarding the therapeutics domain, although the selected strategic option is standard, with the conclusion of partnerships and the creation of licensing agreements, once the candidate drugs have been developed to phase IIa, or in some cases earlier phases, the French company has a major advantage with its candidate for the treatment of Alzheimer's disease, EHT 0202. This drug, which acts both as a GABA_A modulator and an inhibitor of phosphodiesterase 4, acts on α -secretase, an enzyme able to cleave beta-site amyloid precursor protein, resulting in the production of a soluble fragment (sAPP α) with pro-cognitive and neuroprotectant properties. Since its neuroprotectant qualities have been demonstrated in animal model, EHT 0202 is potentially able to act both on the disease symptoms and its outcome. A phase IIa study is currently ongoing under the direction of Prof. Bruno Vellas of Toulouse University Hospital, with the primary aim of examining the safety in use and good tolerability of the drug. This three-month trial is being conducted in 158 patients, all of whom have now been included, and is being performed against placebo + Exelon® or placebo + Aricept®. The results are scheduled for the final quarter of 2009. "We have already had meetings with some twenty pharmaceutical companies and we are providing them with regular status reports on our studies of EHT 0202", noted Loïc Maurel. "We are confident an agreement will be signed in 2010."

Epitopes with Allergan. Exonhit Therapeutics can also reckon on its ability to manage partnerships and deliver results, as attested by the renewal until December 2011 of its partnership with US company Allergan and the extension of its agreement. EHT/AGN0001, an initial lead compound synthesised by Exonhit Therapeutics is currently completing phase I studies in the treatment of neuropathic pain, while EHT/AGN0002 and other drugs are undergoing preclinical development. The agreement extension concerns the discovery of epitopes in ophthalmology.

(1) Exonic expression profiling of breast cancer and benign lesions: a retrospective analysis. Fabrice André and al. *The Lancet Oncology*. Early Online Publication, 26 February 2009.

A new company for a new anticancer drug

A newly created German company has just joined the ranks of the half-dozen European SMEs to have a candidate drug in clinical development in pancreatic cancer. MBiotec was set up in November 2008 to develop and market a new anticancer compound discovered by the research team under Prof. Peter Mühlradt at the Helmholtz Centre for Infection Research (HZI). This compound, MALP-2S (macrophage-activating lipopeptide-2 synthetic), is a macrophage-activating synthetic lipopeptide and is an analogue of a lipopeptide derived from the bacterium *Mycoplasma fermentans*. It has already undergone a phase I/II study in the treatment of pancreatic carcinoma in which its safety and antitumoral efficacy were demonstrated (see *BioPharmaceutiques* No 48).

HZI's partner in intellectual property management, German consultancy firm Ascenion has negotiated a licensing agreement with the Institute and the new company co-founded by Prof. Mühlradt. True to form (it already holds stock in some 15 companies), Ascenion has acquired a 10% stake in this new company (see *BioPharmaceutiques* No 85). The agreement between HZI and MBiotec provides the latter with exclusive development and marketing rights for MALP-2S and its derivatives in oncological applications. In 2007, HZI

already granted a licence to the Swiss firm AmVac for applications involving use of this product as a vaccinal adjuvant (see *BioPharmaceutiques* No 48). Other licences may be accorded by HZI for other applications of MALP-2S in infectious diseases, wound healing and autoimmune diseases.

MBiotec has already submitted an application for orphan drug status in Europe and the United States for MALP-2S in the treatment of pancreatic carcinoma. An initial round of fundraising is currently underway and should be completed by mid-2009. Subject to FDA and EMEA approval of the drug, the resulting funds will be used to finance a randomised, double-blind, placebo-controlled phase II/III pivotal study conducted in some ten centres throughout Europe and the United States. The results of this study will complete the MA dossier for this drug. There are already plans to develop the product in other indications with solid tumours such as hepatic carcinoma and gastrointestinal cancers.

Genfit to enter theranostics market

Genfit has added a further string to its bow with the theranostics field. The French company is now working on three biomarker programmes in atherosclerosis, diabetes and Alzheimer's disease. "Our decision to enter the theranostics market with the use of early biomarkers in disease was prompted by two observations," proffered Genfit CEO Jean-François Mouney. "The first general observation in the field of cardiometabolic disease, and in particular in the field of atherosclerosis, is that current imaging methods for the detection and follow-up of atheromatous plaque are complex and invasive. Consequently, they are unsuitable for monitoring large cohorts of patients in pivotal clinical trials required for new drug registration. There is thus a need for simple markers previously validated in animal models in order to allow us to select and develop the most promising anti-atherosclerosis drug. This need for new markers is even more pronounced in our field of predilection, namely diabetes prevention. There are in fact no methods or specific biomarkers for detection of the initial signs of pancreatic involvement heralding disease onset."

Three biomarker programmes. To this end, the company has developed and patented a technology of early markers able to predict the potential efficacy of candidate drugs for the treatment of certain metabolic and neurodegenerative diseases. Although this technique may be used with plasma and other physiological fluids such as cerebrospinal fluid, proof of concept was acquired in animal models. "Using the identity card created with these biomarkers, we were able to detect the beginning of plaque formation in animals before vascular impairment became microscopically discernible," added Jean-François Mouney. While these identification tests for plasma biomarkers may be used to determine whether or not the development programme for a given candidate drug should be continued, Genfit has opened channels for funding of these three programmes (BMGFT01 in atherosclerosis, BMGFT02 in diabetes and BMGFT03 in Alzheimer's disease). In addition to developing its own preclinical and clinical programmes, the Lille-based firm intends to apply its technology to the development of companion tests that would allow the pharmaceutical industry to rapidly evaluate their drugs during the various clinical development phases. Discussions are already underway with potential partners, particularly two new drug companies who have not previously worked in partnership with Genfit.

Clavis Pharma enters critical phase

What is the best way to finance several concomitant phase II development programmes with limited financial resources? Such is the dilemma facing Norwegian firm Clavis Pharma. With available cash flow on 31 December 2008 of 85 million Norwegian kroner (9.5 million euros), the company is hoping to continue unaided until the end of 2009. However it is already investigating ways of financing its activities at this point, and its plans could include a share issue or a partnership.

Multiple indications for Elacyt®. A partnership may soon be created to continue the development of its lead product, Elacyt®, which is now in phase II in several indications. Clavis' products use lipid vector technology (LVT) to bind a specific fatty acid to a given pharmaceutical agent. Elacyt® is the outcome of application of this LVT to a cytotoxic agent, cytarabin. This product holds orphan drug status in the treatment of acute myeloid leukaemia (AML) in Europe and the United States (see *BioPharmaceutiques* No 34 and 71). In this disease, Elacyt® is currently undergoing phase II investigation as monotherapy as a second salvage treatment and the study is due to finish during the second quarter of 2009. At the same time, another phase II study is due to start in order to evaluate the drug in combination with idarubicin after failure of initial therapy. The company has not yet decided for which of these two approaches it will submit the first MA application in Europe

and the United States. Elacyt® has also reached phase II in the treatment of ovarian cancer and malignant melanoma (see [Summary Table of Clinical Trials](#)). Although Clavis does not intend to market the drug without the support of a partner, it may retain the rights for certain geographical zones. Discussions are currently underway with potential partners. The drug could soon have a change of name, with Clavis proposing "elacytarabine" as the international non-proprietary name for its product. If this term is approved, the company will also create another trade name.

Gemcitabine improved. Elacyt® will soon be joined by another compound in phase II. CP-4126, which unites the company's LVT technology with a gemcitabine analogue, is being developed in two forms for the treatment of solid tumours. In its intravenous form, it will begin a multicentre European study for first-line treatment of pancreatic cancer in the second quarter of 2009, and meanwhile, an oral form of the drug is currently undergoing phase I investigation in the same indication (see [Summary Table of Clinical Trials](#)). Marketed by Eli Lilly under the trade name Gemzar®, gemcitabine is currently the principal treatment for pancreatic cancer. According to Clavis, CP-4126 may be beneficial to patients resistant or refractory to gemcitabine.

NeuroSearch seeks funding through partnerships

Partnership as by means of combating the crisis is proving a successful strategy for NeuroSearch. As part of its recent partnership with Eli Lilly, the Danish company last week issued new shares that were entirely taken up by the US pharmaceutical company (see [Summary Table of Agreements](#)). This operation brought NeuroSearch 99.2 m Danish kroner (EUR 13.3 m). Another agreement signed a short time earlier with GSK gives the biotech company the option of selling up to 20 m shares to its UK partner until November 2010 (see *BioPharmaceutiques* No 94). Independently of this option, NeuroSearch, with available cash flow of DKK 481 m (EUR 65 m) as of 31 December 2008, is confident of being able to fund its R&D activities until the second half of 2010. Securing continued cash flow thereafter remains one of the company's priorities until it is able to fund itself. Its lead product, ACR16, could reach the market in 2011 in the treatment of Huntington disease. The company has just recovered full rights for this dopaminergic stabiliser, recently returned by Japanese company Astellas which purchased them in 2005 before ACR16 fell to the Danish company through the purchase of Swedish firm Carlsson in August 2006. Under the terms of the agreement concluded with Carlsson, Astellas held worldwide rights for the development and marketing of ACR16 in schizophrenia and other CNS diseases, with the exception of Huntington disease, for which the Swedish firm kept the rights for North America and Europe, before handing them over to NeuroSearch. The phase III study conducted by NeuroSearch is due to be completed during the course of the year (see [Summary Table of Clinical Studies](#)).

Clinical progression. The other major clinical step that remains to be completed by NeuroSearch this year is the start of phase III studies of a second substance, tesofensine, a neurotransmission stimulator developed for the treatment of type 2 diabetes and obesity (see *BioPharmaceutiques* No 83). NeuroSearch is in fact actively seeking an industrial partner for this product, the clinical data for which is soon to be examined by the European and US regulatory agencies. Two other drugs, both dopaminergic stabilisers from the Carlsson portfolio, should begin phase II studies this year. ACR325 will be evaluated in Parkinson's disease patients presenting L-dopa-induced dyskinesia. The phase IIa study to be initiated in the first half of 2009 will investigate the safety and pharmacokinetic profile of the drug in these patients. ACR343 will be developed in the treatment of schizophrenia and is set to begin phase II trials within the year.

The stock market, fundraising and milestones

New funds for Index Ventures

Anglo-Swiss venture capital company Index Ventures has just completed its fifth investment fund totalling EUR 350 m. Index Ventures V will concern itself exclusively with start-up funding and early investment in keeping with its initial vocation. At the start of 2008, the company brought together funds of EUR 400 m specifically for more mature companies seeking to attain a further development stage in order to press home their competitive edge in their chosen market (see *BioPharmaceutiques* No 50).

Index Ventures V concerns the biotechnology, general technology and clean technology sectors in particular for companies with projects located in Europe, United States and Israel. As regards biotechnologies, the priorities of Index Ventures continue to be focused on oncology, immunology, the central nervous system. Typical investments will be between €5-

15M, typically in tranches. Only one of the venture capital company's nine investments in the last few months has concerned the health and life sciences, with USD 8 m being raised in a series A funding round by Franco-American company NormOxys. This firm, created in 2004 between pharmaceutical companies in Boston and Strasbourg, is developing a new drug class known as oxyrens. Its products aim to increase the ability of red blood cells to release oxygen by modifying the affinity of haemoglobin for oxygen, and an initial application for clinical trial authorisation may be made for its lead drug this year. The target indications concern diseases settings in which increased and regulated oxygen supply to tissues can provide therapeutic benefits (e.g. cancers, cardiovascular disease, anaemia, diabetic retinopathy, etc).

Financial results

Ablynx quietly confident about its product portfolio and purse strings

Belgian firm Ablynx begins 2009 with a comfortable financial position and a strengthened product portfolio, which should include a third compound in clinical trials before the end of the year. In contrast with many of its European counterparts, whose financial visibility is currently reduced, this company is confident of its ability to fund its activities for at least three years, with EUR 113.6 million cash and assets available as of 31 December 2008. In 2008, the company's sales jumped 69% to EUR 16.8 m thanks to income from its R&D partnerships with Novartis, Wyeth, Boehringer Ingelheim and Merck Serono. Since the start of the year, it has already received a further staggered payment - of an undisclosed sum - from Novartis, as well as payment of EUR 3 m as part of its collaboration with Boehringer Ingelheim. Further payments are due throughout this year (see *BioPharmaceutiques* No 96).

Three products in clinical trials in 2009. 2008 saw the first administration of a Nanobody® to a human patient (see *BioPharmaceutiques* No 68). ALX-0081, the first member of this new class of therapeutic proteins derived from lama and camel antibodies directed against von Willebrand factor, was given intravenously in combination with a standard antithrombotic drug to patients with stable angina scheduled to undergo percutaneous coronary intervention. On the basis of the positive results of this phase Ib study unveiled last December, Ablynx plans to initiate a phase II study during the third quarter of 2009, the protocol of which is still under discussion. Another antithrombotic Nanobody®, ALX-0681 (a subcutaneous version of ALX-0081), began clinical trials in late 2008 (see *BioPharmaceutiques* No 89). This drug is designed for the treatment of thrombotic thrombocytopenic purpura, an indication in which the company intends to apply for orphan drugs status. A third product, ALX-0140, is due to reach the clinical phase in late 2009 in the extremely different therapeutic area of bone disease. This Nanobody® is directed against the cytokine RANKL (*Receptor Activator for Nuclear Factor Kappa-B Ligand*), which plays a role in the regulation of osteoclasts involved in bone destruction. It may enter phase I during the fourth quarter and has potential in a number of indications (post-menopausal osteoporosis, rheumatoid arthritis and bone cancer). Ablynx has recently reacquired the rights for a second programme in bone disease, which was started during its partnership with Procter & Gamble (see *BioPharmaceutiques* No 93). The company's growing activities will be supported as of summer 2010 by new laboratories to be built on the Ghent technology park site near its existing premises.

Products

French portfolio: progress and problems

The number of French biotech SMEs developing between 5 and 10 drugs rose 5-fold between 2006 and 2008, according to the results of the third edition of the France Biotech survey of products (drugs, *in vitro* diagnostic kits, medical devices) developed in 2008 (**1**). With products included in the study required to be at least in the regulatory preclinical phase, 158 drugs were being developed by 51 companies, with each company having a mean 3 drugs in its portfolio. Marked progression was seen regarding candidates in the preclinical phase (57 products in 2006 compared with 85 in 2008) and in phase III, where their number more than doubled from 7 in 2006 to 16 in 2008. Regarding phase II products, the number remained unchanged (60 products in 2006, 61 in 2007 and 57 in 2008).

Innovative and orphan drugs. The study reveals an interesting characteristic highlighted by France Biotech: "Although this survey concerned SMEs in the biotechnology sector, 47% of the drugs in development are chemical products," noted the Association. Of the 56 biotech drugs listed, half (29 of 56) are recombinant proteins and 20% (12 of 56)

are vaccines. Further, two product categories, drugs coming under the most recent European regulation concerning innovative therapies (gene therapy, cell therapy, tissue engineering products) and orphan drugs, seem well represented in the French portfolio. There were a total of 11 products (8%) in the innovative therapies category with 13% of drugs in this sample under development enjoying orphan drugs status (either already obtained or planned). The most common therapeutic domains were oncology and infectious diseases, respectively with 20% and 19% of products, followed by immunology (12%) and neurology (9%). France Biotech states that "32 of the drugs included in the study are targeted at an indication for viral diseases, 11 for HIV, 15 for autoimmune diseases, 9 for neurodegenerative diseases and 11 for diabetes."

66% of drugs "available". While the provisional timetable suggests that around a dozen of the drugs in this study are aiming to reach the market by 2012-2013, the survey also highlights the persistent problems that continue to hinder the development of these products. These difficulties are primarily financial (49%), being seen most frequently in the preclinical phase or in phase II, but also technical (28%), supposedly due to a lack of suitable partners (external expertise, provision of services) and to difficulties in patient recruitment, for example, to which must be added regulatory complexities (17%). This latter problem primarily concerns innovative therapies, for which a number of procedures and guidelines remain to be defined and fine-tuned, with European regulatory requirements not yet complete. Finally, two figures merit attention: of the 158 drugs included in the survey, only 28% form the subject of at least one partnership while 66% are available for licensing, which according to France Biotech shows that "the French biotechnology industries constitute a reservoir for the product pipeline of pharmaceutical firms". The message is clear, particularly since the association decries the 79% drop in investment in 2008, which could hamper the possibilities for funding of all products currently under development.

(1) In conclusion, the "*Products Pipeline Review 2008*" published by France Biotech concerned 227 healthcare products being developed by 85 companies. It lists 158 drugs being developed by 51 companies, 41 in vitro diagnostics kits being developed by 22 firms and 28 medical devices being developed by 17 firms.

Retacrit® arrives in France

Hospira, a US group specialising in the distribution of drugs to hospitals, has just launched its first biosimilar medicine in France, Retacrit® (epoetin zeta). As with the four other biosimilar erythropoietins already validated by the EMEA's Committee for Medical Products for Human Use (CHMP), the reference product is Eprex®/Erypo® and the indications concern the treatment of anaemia associated with anti-cancer chemotherapy and with chronic renal failure. Since the drug's approval in Europe in late 2007, Retacrit® has been launched in Germany, the United Kingdom, Spain and ten other European member states (see *BioPharmaceutiques* No 47). This biosimilar drug, which is manufactured and packaged in Germany, is available in France in two types of packaging. For nephrology, pre-filled syringes are packaged in boxes of 6 syringes containing 1000, 2000, 3000, 4000, 5000, 6000, 8000 and 10 000 IU, while for oncology-haematology uses, it is supplied in unit boxes containing 20 000, 30 000 and 40 000 IU.

Fifth indication for Mabthera®

Mabthera® (rituximab) has just being crowded European authorisation in a fifth oncological indication. The monoclonal anti-CD20 antibody from Roche is now indicated in combination with standard chemotherapy (fludarabine and cyclophosphamide) in chronic lymphocytic leukaemia in hitherto untreated patients