



Edition n°85 - 20 November 2008

## Editorial

---

### German Biotech companies show commitment

Between teetering stock markets and the prospects of recession and deflation, the current financial crisis seems set to become a redoubtable indicator of the commitment of governments towards their respective national industrial tissue and of the importance they attach to their most innovative sectors such as the pharma and biotechnology fields. At a time when the support of venture capital companies and state initiatives are proving decisive, Germany appears perfectly placed to contest the European leadership of the "other country" of biotech that is Switzerland. While European funding announced over the last few days has totalled almost EUR 100 million, German companies have without doubt fared best, alone accounting for over EUR 90 m. Furthermore, in a context in which convergence between the biotech and pharma sectors has become a matter of course, the recent decision by Roche, Merck Serono and Abbott to combine forces to promote the development of the Rhine-Neckar biotech cluster (BioRN) attests to the quality and attractiveness of the German biotech industry. This decision came the day after the allocation to BioRN of a EUR 40 m federal grant.

Anne-Lise Berthier

## The stock market, fundraising and milestones

---

### Good news from beyond the Rhine

Life seems sweet at the moment for biotechnology companies across the Rhine. Since the start of the month, three German biotech firms have managed to raise almost EUR 90 m, primarily through fellow German investors and venture capital companies (see [Summary Table of Fundraising](#)).

**EUR 65 m for Ganymed...** The most substantial funds were raised by Ganymed, a company specialising in monoclonal antibodies, which obtained EUR 65 m from three German venture capital companies and private investors. This new investment is particularly significant since the sum raised is practically twice the amount collected through the previous round table eighteen months ago and it also exceeds the total funding raised by Ganymed in the three rounds since its creation in 2001 (see *BioPharmaceutiques* No 20). These funds will be used to speed up the development of claudiximab, a candidate monoclonal antibody for the treatment of gastro-oesophageal carcinoma in which a phase Ib multicentre study is due to begin in Germany before the end of 2008. Ganymed, which has a further five projects currently in pre-clinical development for the treatment of breast, lung, pancreatic, prostate and colorectal cancer, is focusing on the development of monoclonal antibodies directed against two target proteins (differentiation protein GC182 and foetal-embryonic protein GT468) associated with different types of solid tumours.

**EUR 18.3 m for Sygnis...** Sygnis Pharma, another beneficiary of German funding, has just increased its capital by EUR 18.3 m thanks to the issue of around 12.7 million new shares. Following the announcement of the operation last month, the new shares were purchased essentially by existing investors, with the two main shareholders, dievini Hopp and BASF SE increasing their stake in Sygnis Pharma respectively from 20.22% to 36% and from 7.45% to 13%. These new funds are intended in particular to support the

development of AX200 (filgrastim, a G-CSF or *granulocyte colony stimulating factor*) for which Sygnis Pharma is currently preparing a second phase II trial in the treatment of acute ischaemic stroke. Since good news never comes alone, AX200, which is also being developed in amyotrophic lateral sclerosis and spinal lesions, has been granted orphan drug status for these two major CNS indications. The CHMP delivered a favourable opinion in September regarding the treatment of spinal lesions (see *BioPharmaceutiques* No 78).

**and EUR 3.9 m for JADO.** The third of these companies to have enjoyed the confidence of its countrymen, JADO Technologies, now has access to an additional EUR 3.9 m to continue its clinical trials of two formulations of its drug TF002, currently in phase II studies in the treatment of atopic dermatitis and urticaria (see [Summary Table of Clinical Studies](#)). This company, which is currently working on RAFT domains, i.e. membrane zones containing high concentrations of many molecules involved in cellular signalling processes, will use this funding to develop its portfolio of anti-allergy drugs. Its aim is to reach the stage of proof of concept in animal models of asthma. The objective is not simply to develop new compounds but also to create a data bank of existing molecules suitable for modification to allow their development in new indications. JADO Technologies is counting on the nature of its RAFT targets against which products active on lipid membranes should also prove effective.

### **Ares Life Sciences funding for Santhera**

Swiss group Santhera Pharmaceuticals has just found a new and powerful partner to fund its development programme. Its increased capital in the form of an issue of some 370 000 new shares was purchased outright by a single investor, Swiss venture capital company Ares Life Sciences. Although only created this year, Ares has already acquired a solid base following its creation by the Bertarelli family, which two years ago sold Serono to the German group Merck KGaA for the handsome sum of EUR 10 m (see [Summary Table of Purchases](#)).

Thanks to this injection of CHF 15.9 m (EUR 9.9 m) in the capital of Santhera, Ares Life Sciences, with its 10.6% stake, is now the second largest shareholder in the biotech company, which was floated on the stock market in November 2006 (see *BioPharmaceutiques* No 3). Although the venture capital company plans to invest across the entire health sector (pharma, biotech, diagnostic, medical technologies and health services), Santhera constitutes its first investment in the biotech domain. This investment could prove extremely interesting; following a launch price of CHF 90 in 2006, Santhera agreed to sell its shares at a price of CHF 43 in the fundraising operation. More importantly, however, the company, which specialises in neuromuscular diseases, has a promising future. Partnerships have already been created, first with Novartis in 2007 for omigapil in congenital muscular dystrophy (see [Summary Table of Agreements](#)) and second with Takeda Pharmaceutical for idebenone in Duchenne muscular dystrophy (see [Summary Table of Agreements](#)), and the latter drug is currently being launched in Canada under the trade name Catena® (see *BioPharmaceutiques* No 74).

### **SEK 8 million for Pharmalink**

Shareholders of Swedish company Pharmalink have provided the company with further evidence of their confidence through their participation in the latest round of fundraising via a new share issue. The funds collected, SEK 8 m (€ 0.78 million), have been earmarked to fast-track development of the company's three priority projects. Although the firm specialises in the repositioning of drugs already marketed by developing them in new indications, the products in question generally target orphan indications. The main products are Xepol®, an injectable biological drug to treat the neurological and the neuromuscular complications associated with poliomyelitis, and Nefecon® for the treatment of IgA-related nephropathy and for which phase II results are due this year. The third product, Busulipo® (a liposome-encapsulated formulation of the anti-cancer drug busulfan) is intended for preparatory treatment of patients prior to bone marrow grafting. For the latter two products, Xepol® and Busulipo®, Pharmalink is seeking partners to continue its phase III development programme.

## Bioproduction

---

### Merck Serono boosts its bioproduction

Merck Serono continues to strengthen its position in the biotechnology field. Since its takeover of Swiss company Serono a little over two years ago, the group, which proudly proclaims its biopharmaceutical vocation, has today made the largest investment in its long history to extend the former Serono production facilities in Corsier-sur-Vevey on the shore of Lake Lemman (Switzerland) (see [Summary Table of Acquisitions](#)).

**A six-fold increase in capacity.** EUR 300 m will be devoted to increasing production capacity at the site, which will be responsible for commercial-scale production of the monoclonal antibody Erbitux® (cetuximab) beginning in 2012. The installations set up in 1999 to produce Rebif® (interferon beta-1a) will thus undergo a major change in scale, with production capacity now six times higher. In addition to its present two production lines, one for Rebif® and the other for production of clinical trial batches, the site will house a further two lines, taking its capacity from 22 000 to 140 000 litres. One of the new lines will be used solely for the production of Erbitux® in order to meet demand for this monoclonal antibody, which, since the signature of the licensing agreement in 1998 with US firm Imclone for its development and marketing outside the US and Canada, has been granted a number of indication extensions **(1)**. The monoclonal antibody is currently produced under contract by German company Boehringer Ingelheim. "Boehringer Ingelheim will continue to be responsible for part of the production, both because of manufacturing quality and in order to guarantee supply," explained Hans-Eberhard Erle, vice-president in charge of operations with Merck Serono. However, while one of the main reasons for extending the Swiss site is to house production of Erbitux®, this development will also allow Merck Serono to prepare and gear up for internal production of future molecules in its portfolio, 61% of which now comprises biopharmaceutical products according to Managing Director Elmar Schnee. In addition, the group recently purchased the rights to atacicept with US firm Zymogenetics as well as acquiring new monoclonal antibodies from Lpath (see *BioPharmaceutiques* No 75 and 84). Work on the Corsier site is expected to be terminated by the end of 2010, with 90% of the buildings scheduled for completion by the end of 2009. Finally, the site extension will see staff size double, with today's figure of 250 employees rising to 450.

**(1)**. Initially used in combination with irinotecan chemotherapy as second-line treatment in metastatic colorectal cancer, Erbitux® was subsequently authorised for use as monotherapy. This monoclonal antibody has also been approved in locally advanced head-and-neck cancers in combination with radiotherapy. New extensions are pending for relapsing and/or metastatic head-and-neck cancers in combination with chemotherapy and others are expected. Erbitux® is currently in phase III studies for the treatment of non-small cell bronchial carcinoma and advanced and/or metastatic stomach cancer in combination with chemotherapy.

## Industry and partners

---

### Licensing agreements to follow BTG acquisitions

In its bid to secure growth, UK company BTG has opted to build a portfolio of drugs either in the final phase of development or close to reaching the market. Two months ago, this strategy led to the announcement of its takeover of fellow UK company Protherics, providing BTG with access to products already marketed or at an advanced stage of development (see *BioPharmaceutiques* No 78). During this month, the operation was approved by shareholders of both companies and the takeover should be finalised by 4 December. BTG has already identified opportunities for cost reduction and plans to assess the Protherics portfolio in order to decide which products to keep and which to licence.

**Thinning the oncology portfolio.** At the same time, the company is regularly reviewing its own portfolio in order to identify and select projects to be suspended and/or licensed out. BTG has just abandoned the development of its second most advanced candidate drug, plevitrexed, a thymidylate synthase inhibitor designed to treat stomach and ovarian

cancer, on account of the product's limited commercial potential (see *BioPharmaceutiques* No 8). Discussions with manufacturers have so far failed to entice a buyer, in contrast with another inhibitor of this key enzyme for DNA production, BGC945. While plevitrexed penetrates cells thanks to the physiological transport systems of reduced folate carrier, BGC945 relies on a targeted pathway, effectively entering cancer cells via a receptor overexpressed in certain types of tumour, but expressed to a far lesser extent by healthy tissue. Henceforth, US firm Onyx Pharmaceuticals will hold worldwide development and marketing rights for this product currently in the final phase of preclinical development. The agreement between the two companies provides for payment of up to USD 320 m, with an initial downpayment for BTG of USD 13 m, and it also includes royalties on sales.

**Varisolve® soon to enter phase III.** Further upstream, the UK company is also seeking a commercial partner for its most advanced product, Varisolve® (polidocanol microfoam), which is being developed to treat varicose veins (see *BioPharmaceutiques* No 25). During the 22<sup>nd</sup> annual congress of the *American College of Phlebology*, the company presented the results of a phase II safety study conducted in the US in 82 patients and confirming the absence of treatment-related cerebral damage in patients presenting right-to-left cardiac shunt. Since polidocanol foam is administered intravenously, concern had been expressed regarding the risk of cerebral gas embolisation in this patient population whose arterial circulation could be affected by the presence of residual bubbles. Other preparatory studies are currently underway with a view to launching a pivotal phase III study in the US, possibly before the end of the first half of 2009.

### **German company Ascenion acquires shares in US Certus Pharmaceuticals**

Ascenion, a German intellectual property management consultancy firm, has decided to acquire shares in Certus Pharmaceuticals, a San Francisco-based US company specialised in the delivery of anti-cancer drugs. Ascenion now holds shares in 15 companies. With the exception of Swiss company AmVac, Ascenion had previously restricted its investment to fellow German companies, primarily companies funded by scientists from research institutes with which it is working (see *BioPharmaceutiques* No 48). The case of Certus is fairly similar, since the technologies underpinning the platforms for the Californian company's anti-cancer products were developed at the Max-Delbrück Centre (MDC), of which Ascenion is the exclusive partner for intellectual property management. Several weeks ago, the German company negotiated a licensing agreement with the US firm concerning technologies developed by the MDC and it is as part of this licensing agreement that Certus Pharmaceuticals shares were transferred to Ascenion. The technologies licensed by MDC to Certus are intended to improve the delivery of known anti-cancer drugs and to enhance their accumulation specifically within tumours. They have yielded two initial drugs, for which MDC selected the Californian company as its development and marketing partner. EmboSphere, designed to treat hepatic tumours, consists of microparticles carrying nanoparticles that contain an active anti-cancer agent (doxorubicin or carboplatin). These microparticles temporarily reduce blood flow at the tumour site and release nanoparticles, which then penetrate the tumour tissue before releasing the active substance. The other product derived from MDC technologies, TaxoSphere, uses as its active anti-cancer substance Taxol® (paclitaxel) and targets solid tumours, including those in which Taxol® has hitherto demonstrated little or no activity. Certus is currently preparing its first fund-raising roundtable in order to finance the continued development of these drugs.

## **Clinical trials**

---

### **Encouraging results for Tripep therapeutic vaccine against hepatitis C**

At the annual meeting of the American Association for the Study of Liver Diseases held last month in San Francisco, Swedish company Tripep presented promising preliminary results for its phase I/II study designed to evaluate its DNA vaccine ChronVac-C® in the treatment of infection with hepatitis C virus (VHX). This therapeutic vaccine works by activating patients' T cells, which then enter the liver and suppress hepatic cells expressing viral protein.

The clinical trial, initiated in October 2007 and being conducted at the Karolinska University Teaching Hospital, is to include a total of 12 treatment-naive patients infected with a strain of HVC genotype 1 and presenting a low viral load. The study protocol requires monthly administration over a 4-month period followed by 6 months of follow-up. The vaccine is administered using a Medpulsar® electroporation-based DNA delivery system from US company Inovio, with which Tripep signed a development agreement in January 2006. This is in fact the first time that an anti-infective DNA vaccine has been administered in humans using electroporation **(1)**. Different doses of vaccine are being evaluated. At present, 9 of the 12 patients scheduled to take part have completed treatment and no serious or unexpected adverse effects have been noted. An extremely marked reduction in viral load, respectively of up to 87 and 98%, was seen in two of the three patients on the intermediate dose, while in two of the three patients on the highest dose, respective reductions of 93 and 99.7% were noted. However, no reduction in viral load was observed with the lowest dose. An interim analysis, due to be completed this month, will allow selection based on these preliminary results of the most suitable dose in terms of safety, immunogenicity and efficacy. This is in fact the dose that will be given to the last three patients taking part in the study.

**(1)** Electroporation allows DNA to be introduced into cells by creating pores in cell membrane by means of electrical shocks.

## Vaccines

---

### Therapeutic West Nile Virus vaccine

West Nile Virus (WNV), present in the US since 1999 and transmitted to man by animals, is a regular cause of major epidemics in the region (more than 24 000 cases of infection and 926 deaths were reported in the US from 1999 to 2006). The disease also reappears regularly in Europe and a number of cases of human infection have recently been identified in certain Central European states. There are as yet no vaccines available against infection with this virus in man, although several candidate vaccines are currently in the clinical development stage, including ChimeriVax® (live attenuated flavivirus) from UK company Acambis, which was purchased this summer by the French group Sanofi Pasteur (see *BioPharmaceutiques* No 74).

Although the most advanced projects are based primarily on the use of killed or attenuated viruses, a number of research teams throughout the world are seeking to develop a DNA-based vaccine, which is considered safer from a biological standpoint. Researchers at the Fraunhofer Institute for cell therapy and immunology (IZI) in Leipzig have adopted this approach in order to develop an initial vaccine against WNV that is both preventive and therapeutic and is intended for use in man and certain "high-value" animals such as horses. The vaccine proposed by this team, for which a patent is currently being filed, uses a plasmid expression vector containing various different viral antigens able to stimulate antibody production in the recipient. Naked DNA plasmids are associated with nanoparticles containing specific antigens that facilitate entry of the vaccine into cells. The IZI research team hopes to complete the preparatory phases in the development of their vaccine by 2009 before initiating preclinical and clinical studies.

## United Kingdom

---

### Royal approval for new UK bioethics legislation

Updating of the bioethics law in the United Kingdom has now completed the legislative process. The recent *Human Fertilisation and Embryology Act* has just received royal approval, although this was a simple administrative formality, since the text had already been passed by the House of Lords at the start of the year and by the House of Commons last month. The HFEA (*Human Fertilisation and Embryology Authority*), the UK's higher authority responsible for medically assisted procreation and embryological research, is delighted with this outcome since the new law embodies a number of the policies embraced by the authority, including that of the creation of hybrid embryos for research purposes. In September 2007 the HFEA had in fact pronounced in favour of the possibility of creating

such embryos by the transfer of a human somatic nucleus into an enucleated animal oocyte. It then approved three research projects aimed at the creation of hybrid embryos (see *BioPharmaceutiques* No 50). The third of these projects, authorised in June, concerns the creation of human embryonic cells through the transfer into enucleated porcine oocytes of human skin cells containing a mutation specific to a cardiac disease.

The key elements of this new law, which concern embryonic research, will come into force in October 2009. The text stipulates in particular that the creation, storage and use of hybrid embryos, referred to as *admixed embryos*, shall be regulated by the HFEA. These new measures will ensure that the United Kingdom is well-placed to retain its position as European leader in the field of embryonic stem cell research. In the United States too, conditions seem set to develop favourably in this research domain. Senator Obama has reiterated his position in favour of federal funding for human embryo-derived stem cell research, while George W Bush remains firmly opposed. In the wake of his presidential appointment, Barack Obama has confirmed his commitment and the removal of restrictions blocking access to public funding could be one of his first decisions in office. Pfizer has anticipated such a development by announcing the creation of a new regenerative medicine research unit (which will use stem cells to develop innovative treatments) at two sites on each side of the Atlantic, one in Cambridge, Massachusetts, and the other in Cambridge, England.

## France

---

### New scientific leads in treatment of obesity

Following the decision by Merck&Co, Sanofi-Aventis, Solvay and Pfizer one after another to abandon their anti-obesity products in the final development stage, or even after market launch, academic research laboratories continue to investigate innovative therapeutic approaches. On 5 November, two French scientific teams published promising results for anti-obesity treatment obtained in murine models in the journal *Cell Metabolism* **(1)**.

**SIRT1, a new therapeutic target.** A research team at the IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire - *Institute of Genetics and Molecular and Cellular Biology*) in Illkirch, Alsace, has begun studying deacetylase SIRT1, an enzyme involved in the regulation of certain cell energy mechanisms. It has been postulated that activation of this enzyme may prevent food-related obesity and associated deregulation. This concept has been validated in mice treated with resveratrol, a natural ingredient of red wine able to activate SIRT1 and AMP-activated protein kinase (AMPK). In order to determine the degree of efficacy associated specifically with SIRT1 activation, the IGBMC researchers used mice to test the effects of a small molecule specifically targeting the SIRT1 pathway, SRT1720, developed by US company Sirtis Pharmaceuticals, a partner of IGBMC since 2004 **(2)**. The results of the experiments conducted by the Alsace research team in collaboration with Sirtis show that administration of SRT1720 protects against obesity associated with a fat-rich diet by raising oxidative metabolism in skeletal muscle, liver and brown adipose tissue. By restoring sensitivity to insulin, leading to improved glucose homeostasis, the molecule also exerts antidiabetic effects. While these studies support the use of SIRT1 enzyme as a therapeutic target in the treatment of obesity, further animal studies are required before the clinical phase of development of SRT1720 may be initiated.

**Apelin provides a safety valve.** Independently, researchers at with Inserm (Institut national de la Santé et de la Recherche médicale - *French Institute of Health and Medical Research*) in Toulouse, France, have investigated regulation of glucose homeostasis dependent on apelin. This peptide, secreted in particular by adipose tissue cells, is overexpressed in obese subjects presenting hyperinsulinaemia. Under normal physiological conditions, insulin, the key regulator of blood glucose levels, also controls apelin production. In the event of insulin pathway deficiency, and in particular insulin resistance, activation of the apelin pathway could restore glucose regulation. The researchers tested this hypothesis in mice. In healthy animals, intravenous injection of apelin reduces blood glucose levels and increases its utilisation by skeletal muscle. This finding is also seen in obese insulin-resistant mice, in which administration of apelin restores glucose tolerance. Authorisations are pending to begin preliminary studies of apelin administration in man, first in healthy volunteers and then in subjects with type-2 diabetes. A synthetic molecule

capable of activating the apelin pathway is currently being developed.

(1) J.N. Feige *et al.* (2008) *Cell Metabolism* 8, 347-58 and C. Dray *et al.* (2008) *Cell Metabolism* 8, 437-45

(2) Following submission of the article, Sirtis Pharmaceuticals was purchased by GSK in the first half of 2008.

## In brief

---

### IGEM 2008

Slovenian students once again shone in the 2008 edition of the iGEM (*International Genetically Engineered Machine*) competition, a synthetic biology competition organised by MIT (*Massachusetts Institute of Technology*) (see *BioPharmaceutiques* No 80). After winning the Grand Prize in 2006 and first prize in the "Health and medicine" category in 2007, the research team from the National Chemistry Institute in Ljubljana pulled off another double this year by winning the Grand Prize and first prize in the "Health and medicine" section with a project involving a vaccine against *Helicobacter pylori*, the bacteria responsible for infectious ulcers of the stomach and duodenum. The vaccine is based on a transmembrane fusion protein combining elements needed to activate both innate immune response (TLR5 signalling pathway) and adaptive (antigen-dependent) immune response. Preliminary animal studies have already been performed.

### GSK and Addex: the sequel

SR One, the venture capital arm of GSK, continues to build up its stake in the Swiss firm Addex Pharmaceuticals. Barely one month after increasing its holding to 3% of the biotech company's capital, SR One has raised its stake to 5% and now holds 293 125 Addex shares (see *BioPharmaceutiques* No 79).

### Zevtera® authorised in Switzerland

Following approval of the drug in Canada this summer, the Swiss authorities have now granted marketing authorisation for Zevtera® (ceftobiprole medocaril), a broad-spectrum cephalosporin developed by Basilea Pharmaceutica (see *BioPharmaceutiques* No 72). This antibiotic, intended for the treatment of complicated skin and soft tissue infections, including diabetic foot infections, will be marketed in Switzerland by the company's partner Janssen-Cilag.

### Solvay and Innogenetics

Following the third period of its proposal to purchase Innogenetics \*, Solvay Pharmaceuticals is to acquire an additional 690 000 shares, taking the group's stake to 95.33% of its fellow Belgian company's capital, and it will seek to delist Innogenetics, which should be effective by mid-December 2008.

### From Acambis to Vernalis

As of next month, UK firm Vernalis will have a new managing director in the person of Ian Garland, previously at the helm of Acambis, a company specializing in vaccines acquired in September by Sanofi-Aventis (see [Summary Table of Acquisitions](#)).