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New functionalities on the *BioPharmaceutiques* website!

A number of new functionalities are now available on the *BioPharmaceutiques* website, in order to help you search through the European deals listed in our summary tables. As with the Clinical Studies table (where searches can be performed by Phase (I, II, IIa, IIb, III), company, compound, disease or status (launch or result)), we now offer you the ability to select agreements by type: R&D, licence, production, commercialisation/distribution or marketing/promotion. Check it out at <http://www.biopharmaceutiques.com/en/tables/agreements/>

Editorial

Towards a sacred union

What are the prospects of development in the biotech field this year where the majority of stock markets are dominated for the most part by lethargy and pessimism? While the question is on everyone's lips within the sector, answers are in short supply, save among those who would play the oracle, with all the attendant risks. In other words, the clinical symptoms have been identified and the diagnosis made, but what remedy or rather remedies should the patient be given? As with most diseases, there is no single perfect cure and a variety of different solutions will be necessary involving the various actors within the health care chain. This week's news highlights a number of cures that have already proved successful, such as grants from patient associations for the development of new drugs, as illustrated by the AFM funding of Trophos, and the creation of dedicated venture capital funds by big pharma firms, in the image of the fledgling Merck Serono Ventures.

Anne-Lise Berthier

Industry and partners

More blows and heartache for Biotech firms

Talk of a difficult period for the economy in general and for biotech companies in particular now seems something of an understatement. Restructuring, drastically reduced spending and plans to close down completely have now become a reality for a number of European biotech companies. In Switzerland, Arpida currently finds itself in the eye of the storm following the FDA's refusal in January to authorise its antibiotic iclaprim. The demands of the US agency, which had requested additional clinical efficacy data, already prompted drastic reorganisation of the company's activities and stringent cost reduction measures. Today, the delays surrounding the US regulatory process regarding iclaprim could deliver a fatal blow. Arpida, which had funds of CHF 38.7 m (EUR 25.4 m) at 31 December 2008, has announced that it is "examining all possible options regarding its future", from merger with a partner and the sale of iclaprim and associated substances through to purely and simply selling up. The various solutions will be presented at the forthcoming general assembly on 7 May and the company's shareholders will be invited to indicate which solution they would prefer.

Clinical setbacks. Another struggling Swiss company, Cytos Biotechnology, is currently trimming its sails following disappointing results for its lead product, CYT006-AngQb. This therapeutic vaccine, developed to induce an immune system response to angiotensin II, is a candidate for treatment of hypertension. While an initial phase I/IIa study demonstrated the existence of a reversible dose-dependent antibody response (with a half life of around four months) and reductions in systolic pressure of 5.6 mm Hg and in diastolic pressure of 2.8 mm Hg, the first of the two phase II studies designed to confirm the efficacy of the drug has failed to achieve the study aim (See [Summary Table of Clinical Studies](#) and *BioPharmaceutiques* No 57). In this study using an unmodified formulation and a different therapeutic regimen, CYT006-AngQb was unable to significantly reduce ambulatory pressure. Although the titre of antibodies produced was higher, the antibodies themselves exhibited lower affinity for angiotensin. A detailed analysis of the study data is currently underway and Cytos Biotechnology is awaiting the results of its third phase II study, due in July. Until then, development of the drug has been suspended and the company has initiated cost-cutting and restructuring measures in order to devote its resources to other products for which the phase II study results are expected in 2009-2010 (CYT003-QbG10 for allergies, CYT004-MelQbG10 for melanoma, and CYT013-IL1bQb for type 2 diabetes) and to its partnerships with Novartis and Pfizer (see [Summary Table of Agreements](#)). Staff will be reduced by more than 42%, from 135 to 57 employees, while spending, initially estimated at CHF 40 to 44 m for this year, will be limited to CHF 36 m (EUR 23.6 m) for 2009 and to around CHF 25 m (EUR 16.4 m) for 2010.

Finally, the German company GPC Biotech, another firm currently struggling after running into difficulties with its key product, sartraplatin, last month opted to merge with US firm Agennix (see *BioPharmaceutiques* No 96). During the presentation of its 2008 results, down 31% at EUR 12.4 m, GPC Biotech, which had already initiated restructuring plans in 2007 and in 2008, announced further staff cuts (see *BioPharmaceutiques* No 43 and 74). Henceforth, its US site in Princeton will have only 31 staff instead of 39, although the payroll at the Munich facility (Germany) will remain unchanged at 11.

Neovacs assumes a new dimension

As for its fellow French company Innate Pharma, 2009 promises to be a key year for Neovacs (see *BioPharmaceutiques* No 99). Within the space of a few short days, the firm has obtained two serious acknowledgements of interest in its Kinoid® technology to develop therapeutic vaccines against human cytokines.

IFN alpha Kinoid® figures in PNAS. This approach involving active immunisation using the company's IFN alpha Kinoid® has also formed the subject of an advance publication in the scientific journal PNAS (*Proceedings of the National Academy of Sciences of the USA*) **(1)**. The studies performed in a mouse model of lethal disseminated lupus erythematosus show that administration of the IFN alpha Kinoid® delays or prevent signs of this

autoimmune disease such as proteinuria, histological lesions and above all, death of the affected animals. "Half of the mice treated with IFN alpha Kinoid® survived," noted Neovacs director-general Guy-Charles Fanneau de la Horie. "Survival depended on the administered dose, but more particularly, half of the surviving animals no longer presented renal lesions and renal function had returned to normal." This study also showed that the induced immune response in fact consists of humoral response, with the production of transient neutralising antibodies, particularly immunoglobulin G, rather than a cellular response. "Neovacs is now conducting regulatory toxicity studies and is planning to begin phase I/II studies with IFN alpha Kinoid® by the end of the year," added the director.

TNF alpha Kinoid® lauded by Thomson Reuters. The second acknowledgement received by the company comes from Thomson Reuters, the professional information and finance group. Experts in the Thomson Pharma branch, who regularly prepare classifications of products with high potential based on public industrial and scientific information, have named Neovacs TNF-alpha Kinoid® as first among the most promising drugs now entering phase II. This Neovacs product, which is currently in phase I/II studies in patients with Crohn's disease, forms the core of the Tracker project for which Neovacs and its partner BioMedical Diagnostics were awarded an OSEO grant of EUR 7.9 m last autumn (see *BioPharmaceutiques* No 80). "We now plan to begin a phase II/III study by the end of the year in 200 to 250 rheumatoid arthritis patients who have become refractory to anti-TNF alpha," explained the director. "With two products in clinical trials this year and the results of our phase I/II study of TNF-alpha Kinoid® due in the next three months, Neovacs is on the point of obtaining validation of its approach and of being able to show that it offers an entirely credible alternative to monoclonal antibodies."

(1) IFN alpha kinoid vaccine-induced neutralizing antibodies prevent clinical manifestations in a lupus flare murine model. Daniel Zagury et al. PNAS. Published online before printing on March 11, 2009. This article may be consulted at the following web address: <http://www.pnas.org/content/early/2009/03/10/0900615106.full.pdf> . IFN alpha Kinoid® is an immunogenic complex that combines human interferon alpha with a carrier protein, KLH (keyhole limpet haemocyanin).

Cerep to set up in China

With the pharmaceuticals industry massively seeking to invest massively in R&D in the emerging markets, and above all in China, Cerep, which is this year celebrating its twentieth year in business, has decided to go down this road. The French firm specialising in providing drug profiling services has decided to test itself against fledgling Chinese companies on their own territory by setting up a drug screening and profiling laboratory in the Shanghai region. This unit will employ a maximum of 15 staff and should be operational by the fourth quarter of 2009. Cerep CEO Thierry Jean indicated that this strategy was in response to demand from a number of the company's big pharma clients, several of whom are already present in China. This "satellite" approach has already been adopted regarding the United States, with the company currently transferring part of its pharmacological screening and profiling know-how from its laboratory in Poitiers (France) to its Seattle facility in order to spare its customers the constraints of transatlantic shipment of compounds (see *BioPharmaceutiques* No 60).

Refocusing programme complete. The company, which sold its programme for a treatment for type 2 diabetes to Sanofi-Aventis and its LFA-1 receptor antagonist to Théa, has finally decided to seek a buyer for its oncology programme (see *BioPharmaceutiques* No 91). According to Cerep, a number of companies have expressed interest in the programme, but they have all requested additional information, including clinical data. This decision has resulted in a EUR 4.87 m reduction in the net result of all activities either abandoned or sold. The company posted a net loss of EUR 4.06 m as of 31 December 2008. Overall, the group's 2008 result showed a deficit of EUR 2.15 m as against a profit of EUR 9.16 m in 2007. Sales for service activities, which stood at EUR 30.8 m in 2008, were down 1.7 % in relation to 2007. While the company increased its customer base (466 in 2008), the industry-wide tendency to freeze certain subcontract budgets took its toll on the firm's results. Henceforth, Cerep intends to concentrate its commercial efforts on small biotech companies. Given the current climate of uncertainty over the future, the company has refused to make forecasts

for 2009 and has simply indicated that it does not expect any growth in revenue. It nevertheless hopes to increase its number of customers and conclude a dozen or so consultancy contracts thanks to its BioPrint® database, which is used to predict the adverse effects and toxicity profile of candidate drugs through the interpretation of *in vitro* profiling data.

TopoTarget plans to cut losses in 2009

Following last month's announcement of the doubling of sales of its leading product Savene®/Totect® (desrazoxane - topoisomerase II inhibitor), Danish firm TopoTarget last week published its complete results for 2008 (see *BioPharmaceutiques* No 99). Pre-tax losses were very slightly down (-0.7%) at DKK 212.6 m (EUR 28.5 m), in line with forecasts. Given the extent of operations conducted in 2008, the company's management feels this result is satisfactory. As planned, in late 2008 the company began recruiting patients for its pivotal study with the most advanced product in its clinical portfolio, the histone deacetylase inhibitor belinostat, in the treatment of peripheral t-cell lymphomas after obtaining FDA approval in September as part of an evaluation procedure for a special protocol (see *BioPharmaceutiques* No 76). The study will be conducted primarily in North America and Europe. TopoTarget recently presented preliminary data for 53 patients treated with its product in a phase II study in T-cell lymphoma, supporting the initial results published last June (see [Summary Table of Clinical Studies](#)). Eighteen clinical trials are currently underway with belinostat in various indications involving solid and haematological tumours, with over half being funded by the US *National Cancer Institute*.

One year of funds. The development costs of the product had a greater impact than envisaged on the firm's cash flow and R&D spending, with the company having recovered all rights to belinostat following the withdrawal of its US partner CuraGen last spring (see *BioPharmaceutiques* No 64). In response to these excess costs and in anticipation of the consequences of the financial crisis, in 2008 the company began restructuring operations that led to the layoff of 60% of staff. Thanks to the savings generated as well as optimism concerning growth of Savene®/Totect® sales, TopoTarget is forecasting a considerable reduction in pre-tax losses, which in 2009 should be between DKK 120 and 140 m (EUR 15 to 18 m). With DKK 108 m (EUR 14.5 m) cash available on 31 December 2008, the company has only one year's funds to finance its activities, which will henceforth be focused on the development of belinostat. It is now more urgent than ever to sign a new partnership agreement for this development in 2010 and beyond.

ESBATEch making headway with its anti-TNF in ophthalmology

Swiss firm ESBATEch is off to a roaring start in 2009 with the launch of three clinical trials during the first quarter for its most advanced product, ESBA105. A spin-out of the University of Zurich, the firm develops human single-chain antibody fragments produced using its Imuna® screening technology. Its key product, a recombinant human antibody fragment directed against TNF (tumour necrosis factor) alpha and administrable by instillation of eyedrops, is currently being developed in three indications, two of which are in ophthalmology. Since early February, ESBA105 has been investigated in a single-centre phase I/II clinical trial in Switzerland in patients faced with imminent surgical treatment for cataract. At the end of February, the company launched a multicentre phase IIa study in the treatment of acute anterior uveitis (ocular inflammation of the iris or ciliary body).

New results in monkeys. Finally, ESBATEch this week presented preclinical results for the ophthalmological indication of choroidal neovascularisation **(1)**. In this indication characterised by abnormal development of blood vessels in the central part of the retina, and which constitutes the main sign of exudative age-related macular degeneration (ARMD), currently available treatments target vascular endothelial growth factor (VEGF). The study, performed in a primate model, has apparently demonstrated the ability of topically administered ESBA105 to significantly reduce choroidal neovascularisation and suggests that the TNF alpha could have an important role to play in a wide range of neovascular diseases involving the eye. However, ESBATEch is also continuing to focus on the anti-VEGF route with the development of another single-chain antibody fragment, ESBA903, directed against this growth factor. Like ESBA105, this drug has the advantage of being suitable for

administration in eye-drops, while the anti-VEGFs currently available for ophthalmic indications require injection. The Swiss firm's ambitions go beyond ophthalmology, and it is also seeking to exploit the potential of its leading product in another inflammatory indication, osteoarthritis. A multicentre phase I/II study was begun in Switzerland at the start of January to evaluate ESBA105 in the treatment of pain associated with knee osteoarthritis. It should be recalled that ESBATech is able to finance its activities using funds of CHF 23 m (EUR 14 m) raised in August 2008, in addition to a series B round table worth CHF 50 m (EUR 31 m) concluded in 2006 (see [Summary Table of Fundraising](#)).

France

I-Stem begins screens using stem cells

In France, I-Stem (the Institute for Stem Cells in the Treatment and Study of Monogenic Diseases) has just performed its first therapeutic screening programmes using human embryonic stem cells to identify substances active on the most common form of adult myopathy, namely type 1 muscular dystrophy. This result is the outcome of two series of studies conducted simultaneously; on the one hand the development of a line of embryonic stem cells used for this screening, and on the other, automation of the studies required to enable this development. The line used in this case is a line of embryonic stem cells carrying the mutation responsible for this monogenic disease. The studies conducted by I-Stem first showed that this line presents the cellular and molecular anomalies characteristic of the disease, namely the presence of aggregates of mutant RNA and cellular proteins, termed RNA foci, thereby confirming the relevance of the cell source for this particular study programme.

HTS and HCS screening. The high throughput screening system (HTS) and the high content screening system (HCS) developed by I-Stem in partnership with Velocity11, Prestwick Chemical and Discngine were used to test a collection of compounds from Prestwick Chemical comprising 1120 FDA-approved molecules on this line, as well as 50 small interfering RNAs developed by research teams at the Institute. In the first case, the purpose was to identify potential hits capable of destroying foci. In the second case, the aim was rather to identify switched-off genes and gain a better understanding of the disease. To date, the initial screening has resulted in identification of five molecules with activity against foci and in-depth analysis has resulted in the retention of only one potential hit on which studies are being continued. While this research programme demonstrates the feasibility of this screening method, new larger-scale studies are scheduled this year, with continuation of studies of type 1 muscular dystrophy on the one hand, and on the other, the initiation of a programme concerning Huntington's chorea.

Orphan drugs

AFM finances pivotal study of Trophos orphan drug

In these particularly lean times, every piece of help from associations is welcome. The aid recently extended by the French Muscular Dystrophy Association (AFM) to Trophos totals EUR 6.7 m over three years to allow continued development of olesoxime (TRO19622) in spinal muscular atrophy. This French firm, based in Marseille, already received AFM funding in 2007 to the tune of EUR 8.5 m to develop olesoxime in a number of indications (see [Summary Table of Fundraising](#)). Although Trophos has finally given up on developing its drug in non-alcoholic steatohepatitis and diabetic neuropathic pain, it is continuing to work on chemotherapy-related neuropathies, with a phase IIa study beginning in France in February, and on two rare diseases, amyotrophic lateral sclerosis and spinal muscular atrophy (see *BioPharmaceutiques* No 90). In these two indications, olesoxime enjoys orphan drug status in Europe and the United States. The FDA finally awarded orphan status to this drug in spinal amyotrophy only in the last two weeks, despite the fact that it was granted in the EU in 2005.

Only one study before MA submission? Olesoxime, an oral drug derived from cholesterol, acts through a mitochondrial mechanism of action to enhance neuronal functioning and survival. The results of a phase Ib study initiated in 2007 and conducted in

four French centres will be presented in April in Seattle at the Annual Meeting of the American Academy of Neurology (see [Summary Table of Clinical Studies](#)). The drug was shown to be safe and well tolerated in the eight patients (children and young adults) recruited to the study. The AFM funding will enable Trophos to begin a phase II study in Europe at the end of the year. The protocol for this study is currently being examined by the EMEA. The company is banking on olesoxime's orphan drug status to ensure that a single European pivotal study will suffice for the MA submission file. Discussions are also ongoing with the FDA to determine whether an additional study on the other side of the Atlantic will be needed to register the drug in the US for spinal muscular atrophy.

Agreements

Biovitrum and Karolinska Development join forces against leukaemia

Biovitrum will no longer be working alone on its leukaemia R&D programme. The Swedish company has just entered an alliance with investment firm Karolinska Development to create a joint company that will develop specific inhibitors of tyrosine kinase FLT3. These patented products, belonging to the Biovitrum portfolio, are low molecular weight compounds. In around a quarter of patients presenting the most common form of leukaemia, namely acute myeloid leukaemia, this kinase is impaired and constitutively active, enhancing proliferation of haematopoietic cells. Karolinska Development specialises in companies developing innovative solutions for diseases in which there are considerable medical needs. It is the largest investor in all 37 companies in its portfolio, mostly Swedish and many of whom it has in fact set up.

Refocusing strategy. The new company created with Biovitrum, Akinion Pharmaceuticals AB, will be owned 80.1% by Karolinska Development and 19.9% by the biotech company. To start with, the financial support provided by the investment company for development of FLT3 inhibitors will total no more than SEK 10 m (EUR 0.9 m). Although preclinical proof of concept has not yet been established, Biovitrum has already carried out *in vitro* and *in vivo* studies demonstrating the cytotoxic activity of one of its components with regard to tumoral blood cells. The results of these studies were presented last June at the 13th Congress of the European Haematology Association. In addition to this financial support, Karolinska Development will provide the new entity with assistance from its network of professionals in the pharmaceuticals field. For its part, Biovitrum may receive royalties on sales of products developed under this programme. This externalisation move forms part of the Swedish company's strategy of refocusing on biodrugs (see *BioPharmaceutiques* No 93). This strategy also involves strengthening the company's profile and its partnerships in this field. Biovitrum has thus signed an agreement with fellow Swedish company Affibody providing it with access to the latter's albumin-binding technology. This technology improves the efficacy of biomolecules by increasing their half life in the bloodstream. The two companies will work together to develop new therapies targeting inflammatory and autoimmune diseases.

GSK sets its sights on amyloidosis

Pharmaceuticals group GSK has just created a partnership with Pentraxin Therapeutics, a spin-out company from University College London (UCL), to develop a compound combining an antibody and a small molecule for the treatment of amyloidosis. This generic term covers a number of diseases, including Alzheimer's disease and type 2 diabetes, with the common feature of tissue accumulation of amyloid substance resulting in dysfunctions of varying severity according to the location and size of these deposits. The two partners will work together on a conjugate developed by the UK biotech firm combining a murine antibody and CPHPC. This small molecule initially identified at UCL by Pentaxin Therapeutics founder, Mark Pepys, was subsequently developed in partnership with Roche. It is now fully owned once again by the UK company following Roche's decision to hand back the exclusive rights in January. Studies conducted with GSK are aimed initially at humanising the antibody used in the conjugate.

The stock market, fundraising and milestones

Creation of Merck Serono Ventures

Novartis, Roche, Amgen, GSK and Merck&Co are just some of the major pharmaceutical companies to have created strategic venture capital funds to invest in innovative young companies in the health sector. Today they are joined by German firm Merck KgaA, which intends to form such a structure through the creation of Merck Serono Ventures.

With an initial capital of EUR 40 m for the coming five years, this fund will be seeking to support biotech start-ups active in the group's main therapeutic areas (degenerative diseases, oncology, autoimmune and inflammatory diseases). However, the German group has no intention of limiting itself to these medicines and has demonstrated an interest in companies developing innovative technologies capable of discovering and developing new products within the therapeutic domains of interest to the group. While the funds available may appear modest, the initiative will nevertheless be welcome in the current economic and financial environment. Companies wishing to submit a project or who would like to receive further information about the fund can contact Merck KgaA via the group's website, where a special page has been set up specifically for [Merck Serono Ventures](#).

A new milestone for Flamel

Flamel Technologies has just received a further staggered payment of USD 4 m (EUR 2.9 m) from GSK as part of the licensing agreement for the development of Coreg CR®, a single daily-dose formulation of carvedilol that uses the French company's Micropump® controlled-release technology. This product, launched by GSK in 2007, is manufactured at Flamel's production facilities in Pessac (France).

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