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## BioAlliance Pharma Files For €30M IPO On Euronext In Paris

**By James Etheridge**  
**BioWorld International Correspondent**

PARIS – BioAlliance Pharma SA launched an IPO on Eurolist Compartment C of the Euronext stock exchange in Paris with the aim of raising €29.5 to €33.8 million and, in the words of its chairman and co-founder, Dominique Costantini, of “transmuting from a drug discovery company into a profitable pharmaceutical company.”

She explained that Paris-based BioAlliance was launching the IPO to fund the commercialization of its lead compound, Loramyc, which it has filed for marketing approval in Europe as a first-line local treatment for oropharyngeal candidiasis, an oral fungus commonly found in immunocompromised patients suffering from diseases such as cancer, HIV and diabetes.

BioAlliance, which was founded in 1997, has completed the development of this product in a relatively short time and at exceptionally low cost – only €10 million, Costantini

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## IDM Sells Infectious Disease Program To Pharmexa For \$12M

**By James Etheridge**  
**BioWorld International Correspondent**

PARIS – IDM Pharma Inc. entered into a definitive agreement with Pharmexa A/S for the sale of its infectious disease programs and other assets for \$12 million in cash.

For San Diego-based IDM Pharma, which came into being in August through the merger of Immuno-Designed Molecules, of Paris, and Epimmune Inc., of San Diego, the object is to focus its activities on its five clinical-stage anticancer agents, reduce its cash burn rate and strengthen its cash position.

Among the assets to be acquired by Pharmexa, of Copenhagen, Denmark, are the Padre and EIS (Epitope Identification System) technology platforms, and the companies plan to enter license agreements giving IDM continuing rights to use those technologies in its cancer programs.

In addition, Pharmexa will take over IDM’s current lease on the former San Diego research and production

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## Researchers Discover New Target For Schizophrenia

**By Sharon Kingman**  
**BioWorld International Correspondent**

LONDON – Scientists have identified a novel biochemical pathway underpinning the development of severe mental illnesses such as schizophrenia and bipolar disorder. The new pathway links an enzyme not previously known to have a role in mental illness with the product of a gene that had been linked to schizophrenia.

The enzyme belongs to the class known as phosphodiesterases. Drug designers already are targeting other members of that family with the aim of developing treatments for disorders such as asthma and chronic obstructive pulmonary disease, raising hopes that it may be possible to apply similar approaches to therapies for severe mental illnesses.

David Porteous, professor of medical genetics at the University of Edinburgh, told *BioWorld International*:

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## Innovata Emerges As Suitor That Approached SkyePharma

**By Nuala Moran**  
**BioWorld International Correspondent**

LONDON – Shares in drug delivery specialist SkyePharma plc fell 15 percent Friday after a smaller counterpart, Innovata plc, was revealed as its would-be suitor.

The market was hoping for an outright bid for SkyePharma after the company said earlier in the month that it had ordered a strategic review following an unsolicited approach from a third party.

It was Innovata that confirmed the “early stage discussions . . . regarding a possible combination of the two companies.” It emphasized that the talks were “preliminary in nature,” and said there can be no certainty a transaction would be concluded.

London-based SkyePharma’s position was weakened in October when CEO Michael Ashton announced he was retiring from the company next year as he launched a

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THOMSON



## Dundee University Forms Unit To Work On Tropical Diseases

By Nuala Moran

**BioWorld International Correspondent**

LONDON – Dundee University will pay industry-level salaries to attract staff to work on treatments for tropical diseases neglected by commercial companies, as it sets up a new unit to take targets discovered at the university through screening and optimization to be ready for clinical development.

That will mean paying rates 30 percent above academic salaries for eight medicinal chemists it wants to recruit, Mike Ferguson, one of the project leaders, told *BioWorld International*.

Ferguson and his colleagues have discovered targets in tropical diseases including African sleeping sickness, Chagas' disease and leishmaniasis, but have had no success in persuading industry to take them into discovery.

"The work we are planning to do would normally be carried out by industrial partners, but these are three of the most neglected diseases, where there is no travelers' market, and thus no commercial activity, or plans for any," he said.

Research carried out over several years at Dundee has generated a dozen validated targets. Ferguson said they have not been patented because, "There isn't any money in this, but as we develop molecules to lead optimization, we may well start to patent."

The work will be carried out in a new Centre for Interdisciplinary Research completed recently at a cost of £20 million (US\$36 million). The project itself will cost £13 million over the next five years, most of which comes from a grant of £8.1 million from the research charity Wellcome Trust.

"Getting all the pieces together to carry out a serious drug discovery program in an academic environment is virtually unprecedented," Ferguson said. "This initiative aims to marry the best of drug industry practice with academic excellence."

The World Health Organization estimates that there are about 400,000 cases of African sleeping sickness per annum, more than 16 million people have Chagas' disease, which is endemic in central and south America, and more than 12 million have leishmaniasis, a range of diseases found in the tropics and subtropics.

One of the first industry recruits is Julie Frearson, who has joined from BioFocus plc in Cambridge, to set up and oversee the compound screening facilities. In addition to eight medicinal chemists, Ferguson wants to recruit seven other staff with skills in high-throughput screening and target biology to complement the 60 existing academic staff and establish the skills and resources more usually found in a small biotechnology company. ■

## OTHER NEWS TO NOTE

- **Acambis plc**, of Cambridge, UK, said it started a U.S. Phase I trial of its vaccine against *Clostridium difficile* in healthy elderly subjects. That follows an initial trial in healthy young adults. The new trial is designed to test safety, tolerability and immunogenicity of different dose levels. The aim is to develop a preventive vaccine against the disease, which is endemic in many hospitals and nursing homes.

- **Allergy Therapeutics plc**, of Worthing, UK, said it completed recruitment of 228 patients in the Phase III trial of its ragweed allergy vaccine. Preliminary results are expected in the first quarter of 2006.

- **Biotec Pharmacon ASA**, of Tromsø, Norway, will initiate a clinical trial in the first half of 2006 of its formulation of soluble beta glucan (SBC) in combination with Herceptin in breast cancer patients. The study will be conducted in collaboration with the Department of Oncology at Ullevål University Hospital in Oslo. Biotec already is engaged in cooperative cancer program involving other cancer antibodies with Memorial Sloan-Kettering Cancer Center in New York.

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**THOMSON**



## Actelion's Tracleer Falls Short In Pulmonary Fibrosis Studies

By Cormac Sheridan

*BioWorld International Correspondent*

Shares in Actelion Ltd. dropped 12.1 percent Monday on the Swiss Stock Exchange, on news that its endothelin receptor antagonist bosentan (Tracleer) failed to meet primary endpoints in two Phase II/III trials in pulmonary fibrosis.

However, the company reported a positive mortality/morbidity trend in one of the studies, involving patients with idiopathic pulmonary fibrosis, and it intends to pursue a confirmatory Phase III clinical trial in that indication.

Bosentan already is approved for treating pulmonary arterial hypertension but, with competition from several new products looming in 2006, Allschwil, Switzerland-based Actelion has sought to lessen its dependence on that franchise by building line extensions to the product.

Although it said it had a scientific rationale underpinning a possible role for the product in treatment of pulmonary fibrosis – a progressive set of conditions characterized by irreversible scarring of lung tissue – in the absence of definitive efficacy data, it decided to first assess bosentan's efficacy in a relatively small patient population using what Isaac Kobrin, head of clinical development, called a "softer endpoint," that of performance in a six-minute walk test. It also looked at several secondary endpoints, including morbidity, as measured by several criteria, and mortality, but the studies were not powered to provide conclusive evidence of efficacy with respect to those parameters.

It conducted double-blinded, randomized, placebo-controlled studies on 163 patients with pulmonary fibrosis secondary to the connective tissue disorder scleroderma, and on 158 patients with idiopathic pulmonary fibrosis, that is pulmonary fibrosis of unknown origin. The former condition is characterized by slow progression, with death occurring on average 10 years after diagnosis. The latter progresses more rapidly – death occurs within an average of three years after diagnosis.

In the scleroderma patient study, called Build-2, no effect was observed on either primary or secondary endpoints. The six-minute walk test, Kobrin said, may not have been an appropriate primary endpoint. "It is possible the disease is progressing too slowly for detecting a difference on secondary endpoints," he told a conference call audience. CEO Jean-Paul Clozel said the company has no further plans to pursue that indication.

The idiopathic pulmonary fibrosis study, called Build-1, yielded more promising data. Although bosentan again failed to meet its primary endpoint, it demonstrated a positive trend in several predefined secondary endpoints related to morbidity and mortality. It disclosed data on one endpoint – combined incidence of death or treatment fail-

ure at 12 months. That occurred at a rate of 36.1 percent in the placebo group, whereas in the bosentan group, the equivalent figure was 22.5 percent.

"I would like to emphasize that these results have been obtained without any subgroup analysis. This is the full evaluation of all the patients included in Build-1," Clozel said. "Looking at these data now, we have a very strong rationale for pursuing a morbidity/mortality Phase III confirmatory trial in idiopathic pulmonary fibrosis," he added.

The response to the news was mixed, particularly as the market, according to a research note from Canaccord's London office, had priced expectations of a positive outcome into the stock.

"In the short term, of course, the disappointment is greater than the enthusiasm you can see in a potential drug for idiopathic pulmonary fibrosis," said one Swiss analyst who declined to be named. But the scleroderma indication could be revisited, he said, if the idiopathic pulmonary fibrosis program were successful. "For me, if it works in idiopathic pulmonary fibrosis, there's no reason why it shouldn't work in scleroderma," he said. ■

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## OTHER NEWS TO NOTE

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- **Crucell NV**, of Leiden, the Netherlands, signed a nonexclusive license agreement allowing Ireland-based **Tibotec Pharmaceuticals Ltd.** to use its PER.C6 cell line for research in virology. Tibotec will pay a research license fee, annual maintenance fees and milestone payments. Further financial details were not disclosed.

- **CyGenics Ltd.**, of Sydney, Australia, intends to investigate the listing of its tissue banking business, predominantly held under its subsidiary, CordLife Pte. Ltd., on an Asian stock exchange. The listing seeks to raise additional funds for both investment and working capital and would create a second equity position for existing and potential shareholders, the company said. CordLife is a regional cord blood bank that operates a facility in Singapore and a separate facility in Hong Kong.

- **Enzon Pharmaceuticals Inc.**, of Bridgewater, N.J., and **Micromet AG**, of Munich, Germany, agreed to end their collaboration to identify and develop antibody-based therapeutics for the treatment of inflammatory and autoimmune diseases. Enzon is redirecting its investments to other projects, including one focused on cancer. Enzon will make a final payment to Micromet, which retains rights to the lead compound, MT203, for which Enzon would receive royalties. The termination does not affect either the cross-licensing agreement between the companies, or a marketing agreement under which Micromet exclusively markets the companies' combined intellectual property estate in the field of single-chain antibody technology.

## BioAlliance

*Continued from Page 1*

said. That is because the company's strategy largely is focused on reformulating existing compounds for administration through proprietary delivery systems, giving it the opportunity to exploit off-patent products and improve their bioavailability.

The IPO is designed to carry the company through the next two or three years, since it expects to move into profit in late 2008. BioAlliance Pharma is offering more than 2.1 million shares to institutions in France and other European countries and to private investors in France, plus an overallotment option of 317,000 shares.

The indicative price range is set at €12.40 to €14.20 per share, valuing the company at between €75 million and €85 million. The offering opened Nov. 23 and will close Dec. 6. The price is expected to be announced Dec. 7, with trading to begin the next day.

Besides the public offering, 587,011 new shares are being issued in a capital increase reserved for holders of the €7 million of convertible bonds the company issued in May 2004. All its existing shareholders subscribed to those bonds and none is using the IPO to exit, according to BioAlliance Pharma's chief financial officer, Piers Morgan.

Private equity funds currently control 86.7 percent of the company, the largest investors being Auriga Ventures II, of Paris (20.78 percent); ING Belgique, of Brussels (20.8 percent); and FCPR-FCJE, of Paris (13.2 percent).

The co-lead managers and bookrunners of the offering are the Paris office of Bryan, Garnier & Co. and ING, of Amsterdam.

BioAlliance Pharma has raised €18 million in three private financings since it was founded in 1997, the last of which netted it €12 million in August 2004. It had cash reserves of €4.3 million as of Sept. 30.

Loramyc, known as miconazole Lauriad up to now, is a 50-mg formulation of miconazole as a once-a-day, bioadhesive, buccal tablet. Two Phase III trials of the product in the indication of oropharyngeal candidiasis, one in HIV patients and one in patients who had undergone radiotherapy for head or neck cancer, were completed earlier this year.

The company is hoping to obtain approval for Loramyc in France before the end of 2006 and to launch the product there in the first quarter of 2007. It anticipates signing distribution agreements for the other main European countries in the second quarter of 2007.

In addition, BioAlliance has plans for partnering out the development and commercialization of the product in the U.S. and Japan. The FDA has approved an investigational new drug application filed by BioAlliance earlier this year for the conduct of a pivotal Phase III trial in the U.S. in HIV-positive patients suffering from oropharyngeal candidiasis.

BioAlliance now is in negotiations with possible American partners and expects to sign a license agreement in the second quarter of 2006. BioAlliance also intends to

partner out the product in Japan in 2008.

Lauriad is one of two drug delivery systems developed by BioAlliance, which is focusing on therapeutics for overcoming drug resistance in cancer, HIV and other severe infections. Besides its Lauriad platform, which ensures early and prolonged release of therapeutic agents at the site of the disease, it has developed a nanoparticle technology called TransDrug, which is designed for intracellular targeting and also ensures prolonged release of the active ingredient.

The second product in BioAlliance's pipeline is another Lauriad formulation of a known compound, acyclovir. A recently completed Phase I clinical trial of acyclovir Lauriad in Europe for the treatment of oral herpes established the product's ability to deliver a high level of concentration to the target zone.

BioAlliance's third most advanced product is doxorubicin Transdrug, which is undergoing a Phase I/II clinical trial in Europe in the indication of primary liver cancer. That compound has been granted orphan drug status in both the U.S. and Europe.

One of the merits of the Transdrug delivery system is that it can be administered through different channels – inter-arterial infusion (the form being tested in the clinical trial), intravenous injection or orally. The preliminary results of the trial are encouraging, said BioAlliance, which expects to have the final results in the second quarter of 2006 and to initiate a Phase II/III trial in the third quarter.

BioAlliance has a third string to its bow, and that is a program aimed at discovering and developing drugs in oncology and HIV. It has a number of drug candidates in the pipeline, including an anti-HIV integrase inhibitor and two anticancer agents. The former is likely to be tested in a Phase I trial starting in the second quarter of 2007.

Earlier in its short history, BioAlliance developed a predictive phenotyping assay that measures resistance to HIV drugs. Called Phenoscript, the product was launched in both Europe and the U.S. 2002 and was marketed in both regions by a wholly owned subsidiary of BioAlliance, VIRalliance. At the beginning of November, however, BioAlliance agreed to sell the business and assets of VIRalliance, including Phenoscript, to Eurofins Scientific Inc., of Memphis, Tenn., a wholly owned subsidiary of another French company, Eurofins Scientific, of Nantes. ■

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## OTHER NEWS TO NOTE

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• **ExonHit Therapeutics SA**, of Paris, said preclinical data published in the *Journal of Biological Chemistry* showed that EHT 0206, one of its drug candidates, has potential in treating Alzheimer's disease. Specifically, data have shown that EHT 0206 may decrease the formation of senile plaques, meaning it has the potential not only to slow down its progression but also to change the course of the underlying disease.

## Pharmexa Raises \$11.4M To Fund Acquisition From IDM

By Cormac Sheridan

*BioWorld International* Correspondent

Pharmexa A/S raised gross proceeds of DKK72 million (US\$11.4 million) in a private placement to fund its \$12 million cash acquisition of infectious disease and other assets from IDM Pharma Inc., of San Diego.

The Hørsholm, Denmark-based company is taking over a 27-person R&D facility in San Diego, which had belonged to Epimmune Inc., prior to its merger earlier this year with Immuno-Designed Molecules SA, of Paris, to form IDM Pharma.

ING, of Amsterdam, the Netherlands, underwrote the sale of 3.4 million shares to 18 European institutional investors, including specialist life sciences investors Puilaetco, Dexia, KBC, Reabourne and Edmond de Rothschild. The shares were priced at DKK21.45 per share, a 6.3 percent discount to the stock's closing price of DKK22.90 on the day before disclosure of the transaction. Included in the deal with IDM is a pipeline of clinical and preclinical immunotherapy projects for treatment and prophylaxis of infectious disease, as well Epimmune's immunostimulatory, T-cell epitope platform Padre and its Epitope Identification System (EIS). Pharmexa has also taken over the Epimmune name and trademark, and it is establishing a U.S. subsidiary in San Diego, which will be called Pharmexa-Epimmune Inc.

"Pharmexa has known Epimmune for quite a while, since 2000, and we have had a license agreement on the Padre technology for five years, so it's a company we know quite well," Pharmexa CEO Jakob Schmidt told *BioWorld International*. "They've always been top of our wish list from the point of

view of technology we'd like to own. You could say we are buying back future royalties on the Padre technology. That alone would justify the value of what we're paying here."

But it has also acquired clinical-stage projects in HIV and hepatitis B virus therapy, as well as preclinical projects in malaria, influenza, human papillomavirus and hepatitis C virus. The HIV project work is supported by funding from the National Institutes of Health, while the HBV, HCV and HPV projects are the subject of an agreement with Innogenetics BV, of Ghent, Belgium, which recently was extended to the end of March 2006.

Pharmexa reported cash, cash equivalents and marketable securities totaling approximately \$60 million at the close of the third quarter, and therefore, the extra operational costs will not impose a significant burden on the company. "It's an additional cash burn of a few million dollars in the next two or three years," Schmidt said. For that expenditure, Pharmexa is teaming up with what Schmidt called "a world class group of people."

The acquisition follows its takeover earlier this year of Norwegian cancer immunotherapy firm GemVax A/S, through which it gained a peptide cancer vaccine that is about to enter two Phase III trials. The trials will involve about 1,400 patients in total, which, Schmidt said, will make the program one of the largest to date in the immunotherapy field. "We hope to be able to start them in the next three to six months."

The field, he said, has been slow to deliver on its promise, and its development has been hampered by poor target choices and inadequately designed clinical programs. But Schmidt sees more grounds for optimism at present. "There is more interest from big pharma, and there is more interest from investors; but it's a slow process, and it's going to be a few more years." ■

### IDM

*Continued from Page 1*

facility of Epimmune, as well as the 27 employees who work there. In that regard, Pharmexa will supply certain services that IDM requires for the ongoing clinical trials of its EP-2101 therapeutic vaccine for non-small-cell lung cancer. IDM retains all rights to its cancer programs.

The deal is scheduled to close around Dec. 31, subject to the usual closing conditions. IDM Pharma will retain its research and production facility in Irvine, Calif., with a staff of about 30, as well as its original center in Paris, which employs about 70 people. As well as an injection of cash, the deal is expected to reduce IDM's annual burn rate by \$3 million, from around \$20 million at present.

IDM Chairman and CEO Jean-Loup Romet-Lemonne told *BioWorld International* that the company was not large enough to develop two families of products and that it needed to concentrate its resources on its most advanced activities, which are its cancer programs.

In particular, he said, it intended to file its lead compound, Junovan, for regulatory approval in both the U.S.

and Europe in mid-2006 and needed to start making preparations for the commercialization of the product in 2007. Known as Mepact throughout its clinical development phase, Junovan is a liposomal muramyl tripeptide phosphatidyl ethanolamine-based immune system stimulant designed to promote the destruction of cancer cells by activating macrophages present in the body.

IDM was granted orphan drug status for the product in the treatment of osteosarcoma in the U.S. in 2001 and in the European Union in 2004, and Junovan completed a Phase III trial in that indication in the U.S. earlier this year.

In June, IDM Pharma concluded an exclusive marketing agreement with Cambridge Laboratories Ltd., of Cambridge, UK, for the distribution of Junovan in the United Kingdom and Ireland. As regards mainland Europe and the U.S., however, Romet-Lemonne said IDM "would like to develop its own sales force, but we might decide to focus on the U.S. and look for a distributor in Europe."

With the additional cash in the bank and its reduced burn rate, the company can fund its activities until mid-2007 at least, Romet-Lemonne said, when having a product on the market would make it easier to raise capital. ■

## SkyePharma

*Continued from Page 1*

heavily discounted rights issue at 30 pence per share to raise £35 million (US\$61 million) to pay for Phase III trials of flutiform, a combination asthma product.

The market reacted negatively, as the company had said previously that it would find a partner to pay for the trial. In April it announced heads of agreement on a deal with a headline value of £160 million, before pulling out in September when another potential partner appeared.

SkyePharma's shares perked up initially when news of the approach and the appointment of Lehman Brothers to give advice was announced Nov. 14. Friday's fall to 47.5 pence valued the company at about £360 million. SkyePharma did not comment on Innovata's announcement.

Innovata said it was in expansion mode following its formation in March from ML Laboratories plc and Quadrant Technologies Ltd. The business was created after Kieran Murphy was appointed CEO of ML Labs and set about a root and branch restructuring, closing six ML Labs business units. After acquiring Quadrant for £46.7 million, the company was renamed Innovata and moved into Quadrant's headquarters in Nottingham.

Following its formation, Innovata has narrowed its focus to the pulmonary delivery of existing and novel compounds, based on delivery devices from the ML Labs

business and formulation technology from Quadrant. At the time, Murphy said that following the acquisition of Quadrant, the company would have the devices and stabilization and formulation technologies to take a more creative approach to pulmonary delivery, moving beyond asthma and chronic obstructive pulmonary disease treatments that currently are administered by this route, to the delivery of antibodies, proteins and peptides.

Innovata has not published any financial results since its creation. In the six months to the end of March, ML Labs' turnover was £6.4 million, and Murphy promised at the time of acquiring Quadrant that the merged entity would be profitable once the merger was completed in October. Innovata's share price rose by 3 percent to 25.75 pence when it said it had approached SkyePharma.

Although SkyePharma has interests in pulmonary delivery, most notably in flutiform, the company has a range of other technologies for oral, injectable and topical delivery, supported by solubilization capabilities. They are in use in a number of marketed products, including an extended-release formulation of morphine and the controlled-release version of GlaxoSmithKline plc's Paxil.

In the six months ending in June, SkyePharma had revenues of £36 million and a loss of £9.3 million. At that point, it had net cash of £19 million. ■

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## OTHER NEWS TO NOTE

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• **Galapagos NV**, of Mechelen, Belgium, entered into a two-year collaboration worth up to \$2.5 million with **Idenix Pharmaceuticals Inc.**, of Cambridge, Mass., on selected hepatitis and HIV infectious disease programs. BioFocus, a division of Galapagos, will supply its SoftFocus chemical compound collections to Idenix and provide expertise in the design and synthesis of biologically directed compound collections. BioFocus also will provide hit-to-lead and lead optimization services.

• **Immatics Biotechnologies GmbH**, of Tuebingen, Germany, has added Klaus Stoeckemann to its supervisory board. Stoeckemann is a partner with the venture capital firm 3i and a supervisory board member at recent IPO firm Jerini AG, of Berlin, and two other companies. Immatics is a drug discovery and development company concentrating on cancer immunotherapy. In German corporate governance, the supervisory board has responsibility for general oversight, while a management board runs day-to-day operations.

• **Immutep SA**, of Orsay, France, initiated a Phase I trial of its lead product, ImmuFact IMP321, in metastatic renal

cell carcinoma. ImmuFact IMP321 is a natural human T-cell immunostimulatory factor designed to amplify the T-cell immune response through activation of dendritic cells and more efficient antigen presentation to T cells. It is a single-center, open-label, escalating-dose study.

• **Life Therapeutics Ltd.**, of Sydney, Australia, started an early stage project to develop a specialty immune globulin for influenza. It is a multiyear program to immunize selected donors with the flu vaccine and collect their hyperimmune blood plasma for use in a therapeutic drug to combat infection caused by the influenza virus. The company expects that a new supply of influenza hyperimmune will be produced each year to combat the latest influenza strain.

• **Macrozyme BV**, of Amsterdam, the Netherlands, entered an exclusive collaboration with **Genzyme Corp.**, of Cambridge, Mass., to explore the applications of Macrozyme's library of small molecules as new inhibitors of glucosylceramide synthase in diabetes and insulin resistance, along with other possible indications. Its library of compounds is understood to inhibit the glycosphingolipid biosynthesis pathway, and high levels of glycosphingolipid are known to be associated with insulin resistance and diabetes. In return, Macrozyme is entitled to research funding, milestone payments and royalties.

## Schizophrenia

*Continued from Page 1*

"This discovery sheds light on a very poorly understood subject, and one that is of huge importance because schizophrenia and bipolar disorder affect one in 50 of the population worldwide. We may be some way off from a cure, but we are now a lot closer to understanding the underlying problem, which gives us a much better chance of developing more effective and safer treatments."

Porteous, together with colleagues in Edinburgh, and collaborating teams in Glasgow, Paris and Edinburgh, and at Merck Sharp and Dohme Ltd. in Harlow, reports the findings in the Nov. 18, 2005, issue of *Science* in a paper titled, "DISCI and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling." J. Kirsty Millar and Benjamin S. Pickard are the joint first authors of the paper.

Five years ago, Porteous and his colleagues discovered that the gene they called DISCI (for disrupted in schizophrenia) appeared to play a role in schizophrenia. An abnormal version of the gene was inherited by affected members of a large Scottish family, several of whom had schizophrenia, bipolar affective disorder or recurrent major depression. But no one knew how or why DISCI, when faulty, caused those conditions.

The group set out to find out. "Our investigations showed that the protein produced by DISCI was probably a 'scaffold' protein to which other proteins attach, forming a functional complex," Porteous said. "We did biochemical studies to find out what those other proteins were, and one of them turned out to be a specific phosphodiesterase."

The phosphodiesterase in question was called PDE4BI. It was already known to be important in regulating the level of the key signaling molecule cyclic adenosine monophosphate (cAMP). Experiments showed that DISCI binds PDE4BI. When cAMP levels rise, DISCI and PDE4BI dissociate and PDE4BI becomes activated.

Although PDE4BI had never previously been associated with mental illness, some studies in animals did point to a neurological role. For example, mutations in the equivalent gene in *Drosophila* result in learning and memory defects. In mice, animals lacking functional PDE4BI behave as they do when they have been treated with antidepressants. In addition, PDE4 is the physiological target for the antidepressant rolipram.

What clinched the role of PDE4BI for Porteous and his colleagues, however, was the discovery that, in patients with schizophrenia, the gene encoding that protein was sometimes damaged.

Porteous said, "We then had a link between the two proteins at the functional level — they interacted and regulated each other's activity — and we had the evidence from family studies that damage to either DISCI or PDE4BI was

associated with an elevated risk of major mental illness."

The finding confirmed yet again, he added, that DISCI is a "really important player" in terms of genetic risk of mental illness.

Being an enzyme, PDE4BI could be an ideal therapeutic target. "This is a well-known class of proteins," Porteous said. "There are already drugs being developed that modulate the activity of other members of the phosphodiesterase family, for the treatment of asthma and stroke, for example. This gives us hope that the pharmaceutical industry may be able to adapt its work in related areas to bear intelligently on the area of mental illness."

Future work for the group will include working out exactly how DISCI and PDE4BI interact in the cell, and what the cellular consequences are. "We will also look at ways of modifying this interaction, with a view to being able to correct the biochemical imbalance that is found in patients with schizophrenia or bipolar affective disorder," Porteous said. ■

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## OTHER NEWS TO NOTE

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• **Neuren Pharmaceuticals Ltd.**, of North Sydney, Australia, executed a memorandum of understanding with the Henry M. Jackson Foundation for the Advancement of Military Medicine for inclusion of U.S. Army hospital sites in the company's forthcoming Phase III trial of Glypromate to prevent neurocognitive decline following coronary artery bypass grafting surgery. The trial is scheduled to start next year. The Jackson Foundation will coordinate and review the clinical trial plans and negotiate agreements for the participation of U.S. Army hospitals.

• **NicOx SA**, of Sophia Antipolis, France, said New York-based **Pfizer Inc.** selected a development candidate from the companies' collaboration focusing on nitric oxide-donating compounds in ophthalmology. Under the terms, Pfizer will pay €2 million (US\$2.3 million) to NicOx, in exchange for an exclusive worldwide license to NicOx compounds. Including the recent payment, NicOx has received a total of €4 million in connection with this agreement, and stands to receive an additional €33 million, plus royalties.

• **PharmaMar SA**, of Madrid, Spain, said data from two research projects show that patients with a defined pattern of tumor DNA repair efficiency have a higher probability of better survival, which is expected to affect the optimization of Yondelis in studies in solid tumors. Results also showed molecular evidence that correlates extreme in vitro sensitivity to Yondelis with mutation of the p53 gene. Yondelis is a marine-derived compound in development to treat soft-tissue sarcomas and ovarian cancer. The data were presented at the 11th annual Connective Tissue Oncology Society meeting in Boca Raton, Fla.

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## OTHER NEWS TO NOTE

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• **Pharmaxis Ltd.**, of Sydney, Australia, said the first patients have been dosed in a Phase II trial of Bronchitol, a mucus-clearing agent, in cystic fibrosis. After the first two weeks of treatment, patients will be randomized to begin testing different doses of the product, with changes measured according to respiratory function, quality of life and general health of the patient at each dose. The study's objective is to determine a suitable dose of Bronchitol for Phase III trials expected to begin mid-2006.

• **Sinovac Biotech Ltd.**, of Beijing, said the China State Food and Drug Administration approved the start of clinical trials for its pandemic influenza (H5N1) vaccine. The regulatory authority fast-tracked Sinovac's application in October in response to a potential avian flu pandemic, and cut the clinical trials process from three to two. Building on safety data from preclinical testing, scientists will use clinical trials to further examine safety and immunogenicity in humans, and to establish the ideal dosage and immunization schedule. Preliminary testing for the first clinical stage is expected to take about three months.

• **Spear Therapeutics Ltd.**, of London, said venture capital firm Advent International invested \$8.5 million, enabling it to move its lead product into clinical trials by the end of 2006. The company is developing chemotherapeutics based on prodrugs that are activated by enzymes that occur in tumor cells only. The technology is based on work carried out at De Montfort University and the Gray Cancer Institute, and funded by Cancer Research UK. The

most advanced products are applicable to any tumor expressing the enzyme CYP1B1, which includes breast, lung and prostate cancers.

• **Survac ApS**, of Copenhagen, Denmark, is being acquired by **Merck KGaA**, of Berlin, for €11 million. The deal, which is expected to be completed before year-end, will give Merck access to Survac's technology for identifying and modifying peptides for use as therapeutic cancer vaccines. Survac's intellectual property portfolio also includes proteins involved in cancer cell survival, which have potential as therapeutic targets. Survac, which was established in 2003 with funding from a consortium of Danish venture capital funds, had operated on a virtual basis, via collaborations with several European academic institutes and clinics.

• **Switzerland** is set to impose a five-year ban on commercial cultivation of genetically modified crops, following a referendum on Sunday in which 55.6 percent of voters supported the initiative. The ban will run until Nov. 27, 2010. EuropaBio, the Brussels, Belgium-based European biotechnology lobby group, said that although the ban affects only commercial cultivation, experience from the de facto moratorium in the European Union indicates that the "impact will be acutely felt in terms of research and innovation."

• **VASTox plc**, of Oxford, UK, said it started a fourth drug discovery program focusing on the bone morphogenetic signaling pathway, and in particular, its role in osteoarthritis. The company will use its zebrafish embryo functional genomics platform to screen for small molecules that perturb the pathway, which is well conserved between zebrafish and humans.

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