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ArQule Makes Two Deals with Daiichi in Cancer

By Catherine Hollingsworth
Staff Writer

ArQule would receive \$75 million in up-front cash under two deals with Japan's Daiichi Sankyo Co. Ltd. – one to develop an anticancer compound and the other to discover a new generation of kinase inhibitors for cancer.

"We now have sufficient financial resources and provisions to implement our three-year business plan," Paolo Pucci, ArQule CEO said in a conference call. He was referencing the company's 10K report, in which ArQule stated that it hopes to have sufficient cash, cash equivalents and securities to last through the end of 2011.

Woburn, Mass-based ArQule and Tokyo-based Daiichi Sankyo will work to develop ARQ197 in cancer, as part of a development and commercialization agreement that would bring in \$60 million cash for the U.S. biotech.

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American Heart Association 2008

LDL Hypothesis Alive and Well; Other Biomarkers also Valuable

By Trista Morrison
Staff Writer

During a press conference at the American Heart Association's 2008 Scientific Sessions, which kicked off this weekend in New Orleans, Monash University's Andrew Tonkin said the "cholesterol hypothesis is well and truly still alive."

Tonkin's comments referred to data from the JUPITER trial, a randomized, double-blind, placebo-controlled study of the statin Crestor (rosuvastatin calcium, AstraZeneca plc) vs. placebo in nearly 18,000 patients.

Crestor resulted in a median 50 percent reduction in low-density lipoprotein (LDL) cholesterol levels ($p < 0.001$) and a 44 percent reduction in major cardiovascular events such as myocardial infarction or stroke ($p < 0.001$).

Yet the JUPITER trial was not designed to evaluate LDL

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Two New Studies Bullish on T Cells

Improved T-Cell Receptor Takes on all Corners of HIV Epitope

By Anette Breindl
Science Editor

In the Nov. 9, 2008, online edition of *Nature Medicine*, scientists reported on engineering an anti-HIV T-cell receptor that has two advantages over its natural parent: T cells bearing the receptor have a much stronger response to the epitope it targets, and the receptor recognizes all escape variants of that epitope, which goes by the name of SL9.

One of the big scientific challenges in treating HIV is that the virus mutates so rapidly. "There are no good epitopes that are completely conserved," corresponding author Bent Jakobsen told *BioWorld Today*.

But in their paper, Jakobsen and his colleagues showed that the T-cell receptor they have created is capable of recognizing all escape variants of the SL9.

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Biotech 2008

Moving from Licensing Talks to M&A can be a Tricky Step

By Donna Young
Washington Editor

PHILADELPHIA – More and more, licensing discussions between biotechnology firms and large pharmaceutical makers are morphing into merger and acquisition deals. And with an M&A environment that is rich for biotechs, those firms need to consider the best strategy that puts them on the offense rather than the defense, said Joseph Reiser, CEO of CureDM Inc.

Biotechs that have considered the potential for an M&A deal during talks about an anticipated licensing agreement fare far better than those that approach such a move from existing licensing relationships, Reiser argued Monday during a panel discussion at the Biotech 2008 conference, hosted this year by Pennsylvania Bio and BioNJ.

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OTHER NEWS TO NOTE

- **3SBio Inc.**, of Shenyang, China, said it filed for approval in China for NuLeusin in late-stage metastatic renal-cell carcinoma. The drug is a second-generation interleukin-2 agent and is genetically modified to improve biochemical properties over naturally occurring IL-2.

- **Accentia Biopharmaceuticals Inc.**, of Tampa, Fla., said it and its subsidiaries, including BioVest International Inc., filed voluntary petitions for reorganization in an effort to restore shareholder value and to pay secured and unsecured creditors. The firm plans to implement a series of initiatives designed to decrease operating expenses and financing costs and to focus cash and resources on drug development and other priority programs that will allow it to attract funding and partnering opportunities. Accentia said affiliates, including major shareholder Hopkins Capital Group LLC, have indicated a willingness to provide additional financing as part of the reorganization plan. Shares of Accentia (OTC PK:ABPI) plummeted 13 cents, or 59 percent, Monday to close at 9 cents.

- **Advinus Therapeutics Ltd.**, of Bagalore, India, has started its U.S. operations by incorporating a wholly owned subsidiary, Advinus Therapeutics Inc. The U.S. company will operate in Research Triangle Park, N.C. In addition, the company has appointed Eric Nelson as its global head of business development, marketing and strategy.

- **Arbor Vita Corp.**, of Sunnyvale, Calif., entered into a collaboration in women's health with **Becton, Dickinson and Co.**, of Franklin Lakes, N.J. The collaboration and license agreement initially will focus on development of a commercial diagnostics for cervical cancer. Financial terms were not disclosed. The new diagnostic is one of the first applications of AVC's PDZ platform, with organizes critical cellular processes including cell signaling and cell-cell contacts.

- **Arteriocyte Medical Systems Inc.**, of Cleveland,

said it was granted a \$1.95 million award from the Defense Advanced Research Projects Agency for the company's Nanofiber-based system (NANEX) technology for the Red Blood Cells project. Arteriocyte is developing NANEX to provide a continuous manufacturing system to enable the increased supply of universal donor red blood units. The development program is designed to deliver a novel RBC manufacturing technology to help alleviate the military's pressing need for constant supply of universal donor red blood units.

- **Azur Pharma Ltd.**, of Dublin, Ireland, said it entered an agreement to develop and commercialize once-daily formulations of clozapine using drug delivery technologies from **Elan Corp. plc**, also of Dublin. The deal includes the use of Elan's NanoCrystal technology. Under the terms, Azur will be responsible for the clinical development program, as well as the regulatory process and U.S. commercialization, with an option to extend its rights to countries outside the U.S. Elan will develop the formulation and manufacture the product and will receive payments from Azur upon the achievement of milestones, plus manufacturing fees and royalties on product sales. Specific terms were not disclosed.

- **Discovery Laboratories Inc.**, of Warrington, Pa., said the FDA has accepted for review its complete response for Surfaxin (lucinactant) for the prevention of respiratory distress syndrome in premature infants. The company received an approvable letter from the FDA in May.

- **Duska Therapeutics Inc.**, of La Jolla, Calif., and **DSM Pharmaceuticals Inc.**, of Parsippany, N.J., said they entered a preliminary agreement to collaborate on the manufacture of commercial batches of ATPace for Duska's planned pivotal Phase III trial in paroxysmal supraventricular tachycardia. Terms were not disclosed. Duska is in the process of modifying the proposed design for that trial and, if successful, plans to file a new drug application for ATPace, a stable liquid formulation of adenosine 5'-triphosphate for intravenous injection, under a 505(b)(2) submission.

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AHC Media LLC

Regulatory Hitch to Delay Solzira Filing, Milestone to XenoPort

By Jennifer Boggs
Assistant Managing Editor

Shares of XenoPort Inc. fell 14 percent after partner GlaxoSmithKline plc said it planned to withdraw its recently submitted new drug application for Solzira (gabapentin enacarbil) in restless legs syndrome (RLS) due to a data formatting issue involving one trial, delaying a \$23 million milestone payment that XenoPort had expected this quarter.

The Solzira NDA was filed by GSK in September, based on data from three Phase III studies, all of which met their primary endpoints of showing the drug's efficacy in RLS, a chronic condition characterized by burning, creeping, tugging or tingling sensations in the legs that forces movement to alleviate discomfort and often disrupts sleep. (See *BioWorld Today*, Sept. 17, 2008.)

XenoPort and GSK stressed that the NDA withdrawal was not related to the filing's data content. Instead, it relates to the database regarding a single trial – the XP060 long-term efficacy study – which involved “multiple variables of input” for the primary endpoint, Jackie Cossmon, spokeswoman for Santa Clara, Calif.-based XenoPort, told *BioWorld Today*.

She added that London-based GSK also will be going back and looking at other studies to make sure any formatting changes are incorporated into those as well. The firms have not provided a timeline for resubmitting the Solzira NDA, but Cossmon said they will move “just as quickly as possible.”

Despite those assurances, however, Wall Street sent shares of XenoPort (NASDAQ: XNPT) down \$5.12, or 13 percent, to close at \$34.44 Monday, the stock's second knock in less than a week's time.

Late last week, the company's shares fell \$1.86 to \$38.62 after its Japanese partner, Astellas Pharma Inc., dropped a Phase II study of the drug in painful diabetic neuropathy patients after an analysis indicated that the study was unlikely to reach statistical significance. (See *BioWorld Today*, Nov. 7, 2008.)

Analyst Katherine Xu, of Credit-Suisse Securities, said news of the NDA withdrawal is “frustrating” given that the companies provided limited details and “uncertainty remains as to whether there are other problems with the filing,” but maintained in a research note that, to date, Solzira data have “demonstrated a combined efficacy and safety profile that could provide an important alternative” to patients with RLS.

If approved, Solzira, a transported prodrug of gabapentin, would be the first gabapentin drug marketed for RLS, a condition believed to affect roughly 12 million people in the U.S. Existing drugs include dopamine agonists Requip (ropinirole, GSK) and Mirapex (pramipexole,

Boehringer Ingelheim GmbH), while other programs coming down the development pipeline include Brussels, Belgium-based UCB SA's dopamine D2 agonist Neupro (rotigotine transdermal patch), which recently gained a positive opinion from European regulators, and Branford, Conn.-based Neurogen Inc.'s aplindore (a dopamine D2 partial agonist), which demonstrated positive results in a Phase II trial last month. (See *BioWorld Today*, Oct. 15, 2008.)

But analysts have suggested that Solzira might have an edge over the dopamine agonists in terms of its safety profile and its sleep benefit.

Xu said the setback likely means a launch of Solzira will be pushed back from October 2009 to March 2010.

XenoPort partnered Solzira (also known as XPI3512) in Japan and five other Asian countries with Tokyo-based Astellas in a late 2005 deal worth about \$85 million. Meanwhile, GSK holds the co-development and commercialization rights to the drug in all other regions under a February 2007 deal valued at up to \$640 million. (See *BioWorld Today*, Dec. 2, 2005, and Feb. 9, 2007.)

Upon FDA's acceptance of the Solzira NDA, XenoPort is entitled to a milestone payment from its partners totaling \$23 million. That money had been expected this quarter. However, the filing glitch means a delay in that payment, though Cossmon said that delay is not expected to affect any of XenoPort's ongoing activities.

Earlier in its pipeline, the company has XPI9986, a transported prodrug of baclofen, which recently finished enrolling patients in a Phase II trial in gastroesophageal reflux disease, with top-line results expected by year-end. XenoPort also plans to start a Phase II study of that drug in patients with acute back spasms of neuromuscular origin later this year.

In Phase I development, the firm has XP21279 for Parkinson's disease. An ongoing study is comparing the product, a transported prodrug of levodopa, with oral L-Dopa, and data are expected in the first quarter of 2009.

XenoPort reported a net loss of \$24.1 million, or 96 cents per share, in its third-quarter earnings. As of Sept. 30, its cash position totaled about \$125.1 million. ■

OTHER NEWS TO NOTE

• **Geron Corp.**, of Menlo Park, Calif., said preclinical data on TAT2, a small-molecule telomerase activator, has been published online in advance of the Nov. 15, 2008, issue of the *Journal of Immunology*. The studies showed that human CD8+ T-cells from HIV-infected donors exposed to TAT2 exhibited increased telomerase activity, resulting in retardation of telomere shortening, an increase in T-cell proliferation and enhancement of critical antiviral functions against HIV-1.

ArQule

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"We view the deal as favorable for ArQule given the current market conditions, and validates ARQ 197 c-Met approach for cancer," Standford Group analyst Han Li wrote in a research note. He said the compound, a c-Met inhibitor, currently is in Phase II studies for pediatric sarcoma, lung cancer and pancreatic cancer, with interim data in pediatric sarcoma expected in mid-2009 at the American Society of Clinical Oncology meeting.

Under a binding letter of intent, the two companies have agreed to share equally the costs of Phase II and III studies, with ArQule's share of Phase III costs payable solely from milestone and royalty payments by Daiichi Sankyo. If the Phase III costs exceed the amount in milestone payments and royalties, ArQule would not be on the hook for those costs beyond what it would receive in payments under the deal, Peter Lawrence, ArQule president and chief operating officer, told *BioWorld Today*.

If all goes well, the plan is to eventually launch ARQ197 in the U.S., Europe, South America and other parts of the world. However, Kyowa Hakko Kirin Co. Ltd. would have exclusive rights to develop and commercialize the product in China, South Korea and Taiwan. ArQule licensed ARQ197 rights to Tokyo-based Kyowa Hakko for those Asian markets in April 2007 for \$30 million up front.

Upon commercialization, ArQule will receive tiered royalties from Daiichi Sankyo on net sales of ARQ 197. ArQule retains the option to participate in the commercialization of ARQ 197 in the U.S.

The final contract for the ARQ 197 agreement is expected to be signed in December, at which time the \$60 million up-front payment would be provided, pending a waiting period for antitrust clearance.

Preclinical data have demonstrated that ARQ 197, ArQule's lead product, inhibits c-Met activation in a range of human tumor cell lines, including clear cell sarcoma, and shows antitumor activity against several human tumor xenografts. When abnormally activated, c-Met plays multiple roles in aspects of human cancer, including cancer cell growth, survival, angiogenesis, invasion and metastasis, according to ArQule.

In clinical studies to date, treatment with ARQ 197 has been well tolerated and has resulted in tumor responses and prolonged stable disease across broad ranges of tumors and doses, the company said.

The second deal with Daiichi Sankyo involves the use of ArQule's kinase inhibitor platform (AKIP) to develop a new generation of highly selective, anticancer compounds. The agreement defines two such kinase targets, and Daiichi Sankyo will have an option to license compounds directed to those targets following the completion of certain pre-clinical studies. Under that deal, ArQule would receive a \$15 million up-front payment. In addition, the company would get undisclosed payments in research support for the first

and second years of the collaboration, licensing fees for compounds discovered as a result of the research, milestone payments related to clinical development, regulatory review and sales, and royalty payments. ArQule retains the option to co-commercialize licensed products in the U.S.

ArQule's other clinical-stage program includes compounds that activate the cell's DNA damage response mechanism mediated by the E2F-1 transcription factor.

According to the company's earnings results, ArQule had about \$136.25 million in cash, cash equivalents and long-term marketable securities at the end of September. That figure includes \$46.05 million drawn down during the third quarter under a line of credit collateralized by the company's auction rate securities. However, that total does not include the \$75 million in cash up-front payments that would come from the two deals with Daiichi Sankyo.

Net use of cash in 2008 is expected to range between \$57 and \$62 million, compared with previous guidance of between \$55 and \$60 million. The net loss is expected to range between \$51 and \$56 million.

ArQule expects to end the year with between \$145 million and \$150 million in cash, cash equivalents and long-term marketable securities, net of its loan collateralized by its auction rate securities, compared with previous guidance of between \$75 million and \$80 million.

Shares in ArQule (NASDAQ:ARQL) fell 31 cents or 12.5 percent, closing at \$2.18. ■

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AHA

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lowering effects. In fact, the trial enrolled patients with low to normal baseline LDL but elevated levels of high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation that has been associated with an increased risk of atherosclerotic cardiovascular events.

Paul Ridker, of Harvard Medical School and Brigham & Women's Hospital, explained that the study was designed to address the fact that "half of all heart attacks and strokes that do occur are among individuals that simply don't have overt hyperlipidemia" – i.e. high LDL levels. A CRP blood test may be able to identify patients with lower LDL who are still at risk.

Tonkin argued that "we do not know from the data whether LDL lowering is most important . . . and to what extent CRP is important."

But at least the JUPITER data may help ease any fears from the ENHANCE study, which previously showed that while the statin combo drug Vytorin (ezetimibe/simvastatin, Schering-Plough Corp. and Merck & Co. Inc.) significantly lowered LDL more than simvastatin alone, the effect did not translate to a benefit in arterial plaque reduction. The data led some to question the validity of LDL as a biomarker. (See *BioWorld Today*, April 1, 2008.)

In addition to the JUPITER trial, results of the 12,000-patient SEARCH trial, which compared low- and high-dose statin treatment, pointed to the correlation between reductions in LDL and reductions in cardiovascular risk.

Even so, Emory University's Peter Wilson questioned whether the industry should "go beyond LDL" to look at CRP and other biomarkers such as apolipoprotein B (apoB). Wilson also argued that future lipid-lowering trials should replace the placebo arm with a standard-of-care statin arm.

That design is already the norm for biotechs like Aegerion Pharmaceuticals Inc. and Isis Pharmaceuticals Inc., both of which are in Phase III with drugs designed to lower LDL levels on top of the statin effect. Aegerion's AEGR-733, a microsomal triglyceride transfer protein (MTP) inhibitor, is being evaluated on top of existing treatments, such as high-dose statins, in a Phase III study in patients with homozygous familial hypercholesterolemia. Initial data released last week showed LDL reductions of more than 50 percent on top of the effects of the background treatments in most patients who had reached the maximum AEGR-733 dose of 60 mg per day. (See *BioWorld Today*, Nov. 7, 2008.)

Isis Pharmaceuticals Inc.'s mipomersen, an antisense compound-targeting apolipoprotein B-100, is in two Phase III trials for homozygous and heterozygous familial hypercholesterolemia. Phase II data showed that the drug can decrease apoB levels by 42 percent and LDL cholesterol levels by 48 percent beyond what statins can achieve alone.

VIA's VIA-2291 Inhibits Leukotrienes in Phase II

Also during the AHA conference, VIA Pharmaceuticals Inc. presented data from two Phase II trials showing that

VIA-2291 inhibited leukotrienes associated with vascular inflammation.

The news sent shares of San Francisco-based VIA (NASDAQ:VIAP) up 40 percent in early trading before closing at 56 cents, a loss of 3 cents for the day.

In a trial of 191 patients with acute coronary syndromes (ACS) who recently had a heart attack or unstable angina, VIA-2291 met its primary endpoint by significantly inhibiting Leukotriene B4 (LTB4) production at all doses tested ($p < 0.001$). Significant reductions in hs-CRP levels were not observed in the overall ACS trial, which VIA attributed to variability at baseline, but reductions were seen in a subgroup treated for a longer period of time.

The second trial, in 50 patients scheduled for elective carotid endarterectomy (CEA), missed its primary endpoint of reducing the percentage of macrophage inflammatory cells in plaque tissue. However, the drug reduced LTB4 production ($p < 0.001$) and hs-CRP levels ($p < 0.01$)

VIA-2291 was generally well tolerated in both studies. A third Phase II trial is under way.

VIA-2291, exclusively licensed from Abbott in 2005, is a reversible inhibitor of 5-lipoxygenase, an enzyme involved in the biosynthesis of leukotrienes. Marketed asthma drug Zflo (zileuton, Critical Therapeutics Inc.) also inhibits 5-lipoxygenase and also originated at Abbott, of Abbott Park, Ill. Yet while Zflo is intended to treat the inflammation, swelling and bronchoconstriction in asthma, VIA-2291 is designed to target the inflammation in atherosclerotic plaques that can increase the risk of heart attack or stroke.

In other AHA news:

- **Celladon Corp.**, of La Jolla, Calif., said Mydicar (AAVI/SERCA2a) demonstrated an acceptable safety profile in the first nine patients treated in a Phase I heart failure trial. Some patients also showed improvements in symptoms, function, biomarker levels and other measures. The open-label, Phase I dose-escalation study will be followed by a randomized, double-blind, placebo-controlled, dose-ranging Phase II study. Mydicar is a recombinant adeno-associated viral (rAAV) vector that transfers the SERCA2a gene into heart muscle cells with the goal of restoring SERCA2a enzyme activity.

- **Cytokinetics Inc.**, of South San Francisco, reported interim data from a Phase IIa trial showing that CK-1827452 significantly improved systolic ejection time, fractional shortening and stroke volume in stable heart failure patients. The data also showed a dose-dependent effect on cardiac output, heart rate and left ventricular end-systolic volume. CK-1827452, a cardiac myosin activator, also is being studied in Phase IIa trials for ischemic cardiomyopathy with angina and for stable heart failure patients undergoing coronary angiography, as well as in several Phase I trials.

- **Johnson & Johnson Pharmaceutical Research & Development LLC**, of New Brunswick, N.J., reported that the anticoagulant rivaroxaban was associated with a 21

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T Cells

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The authors began by isolating T cells from a patient who naturally mounted an immune response to the epitope in question, and engineered the T cell receptor, “a bit like you would engineer an antibody,” to improve its binding strength to SL9 several hundred-fold.

The resulting high-affinity T-cell receptor, the authors wrote in their paper, “bound with a half-life in excess of 3 [hours], retained specificity, targeted HIV-infected cells and recognized all common escape variants of this epitope.”

T cells that were transfected with the receptor were able to control the spread of HIV in cell culture.

Clinical application of the results, Jakobsen said, would entail taking a blood sample from HIV-infected patients, transfecting the T cells with the engineered receptor and re-infusing them into the patient. As such, the approach is fairly elaborate, though not so elaborate as to make it a pipe dream. “It takes cellular facilities to handle this,” Jakobsen said. “But those are becoming more widespread.”

Jakobsen said that for its utility in HIV, the most important aspect of the engineered receptor probably is its ability to recognize escape variants.

But, he added, its much improved binding strength bodes well for the use of T cells in an area where they have, to date, racked up mainly failures: cancer immunotherapy.

The immune system response to cancer is much greater than that to infectious disease, and so strengthening the T-cell response is seen as more critical for cancer immunotherapy. But the work published in *Nature Medicine* showed that “we can improve even an antiviral immune response, at least in the laboratory,” Jakobsen said. And that fact gives his team “high hopes” that the technology ultimately will lead to an effective anticancer T-cell therapy as well.

The authors on the paper hail from British biotech start-up Adaptimmune Ltd., as well as Immunocore Ltd., the University of Pennsylvania and Cardiff University.

Jakobsen is one of three employees at start-up Adaptimmune, which plans to pursue both infectious disease and cancer applications of engineered T-cell receptors. Adaptimmune was founded officially in July 2008, and continues to have “a close relationship” with its parent company Immunocore – where, indeed, Jakobsen is chief scientific officer. Immunocore is a spinout of German company MediGene AG, and ultimately descended from Avidex Ltd. (See *BioWorld Today*, Oct. 2, 2008.)

The plan is for Immunocore to pursue the uses of engineered T-cell receptors that are more antibody-like, while Adaptimmune plans to pursue the cellular therapies coming out of the approach.

Adaptimmune plans on starting a clinical trial in HIV – which will be conducted by the University of Pennsylvania – by next summer. The cancer work, Jakobsen said, is “about nine months behind.”

A separate study, published in the Nov. 9, 2008, online

edition of *Nature* also brings good news about the use of T-cell-based therapeutic vaccines for HIV. The concept suffered a major setback in 2007 with the failure of Merck and Co’s V520. But in their paper, researchers showed that when they used different viral vectors for delivery of the monkey version of the same protein used in V520, rhesus monkeys were able to fend off simian immunodeficiency virus – the monkey equivalent of HIV.

The work is not directly applicable to humans for several methodological reasons. But the authors concluded that “despite current controversies about . . . vaccines for HIV-1, our data have important implications for the development of next-generation T-cell-based vaccines by the proof-of-concept demonstration that durable partial immune control of a pathogenic SIV challenge can be achieved.” ■

AHA

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percent reduction in risk of death, myocardial infarction, stroke or severe recurrent ischemia in a Phase II trial, although the result was not statistically significant ($p = 0.1$). The drug was also associated with higher rates of bleeding, although no arms of the 3,500-patient dose-ranging trial were halted due to bleeding. J&J plans to begin a Phase III trial in December with the direct Factor Xa inhibitor.

• **Molecular Insight Pharmaceuticals Inc.**, of Cambridge, Mass., said data from a Phase IIb trial of Zemiva (Iodofilic acid I 123) – a fatty acid analogue intended to detect cardiac ischemia – found that conducting SPECT imaging along with Zemiva helped identify patients at risk of acute ACS. Data from a second ongoing Phase II study are expected by year-end. ■

OTHER NEWS TO NOTE

• **Insmed Inc.**, of Richmond, Va., said South San Francisco-based **Genentech Inc.** and **Tercica Inc.** (now part of Paris-based Ipsen SA) signed a letter of intent to amend the court-ordered settlement regarding IPlex, Insmed’s disputed IGF-1/IGFBP3 product, to allow Insmed to supply the drug in named-patient amyotrophic lateral sclerosis programs worldwide on a royalty-free basis. Tercica/Ipsen and Insmed also said they plan to enter negotiations concerning the development of IPlex in ALS, subject to analyzing the data from the ALS patients in Italy who have received IPlex, and the satisfaction of any applicable regulatory requirements. IPlex was the subject of a patent dispute over IGF-1 deficiency drugs that, which resolved last year with Insmed agreeing to remove IPlex from the market in that indication. Shares of Insmed (NASDAQ:INSM) gained 11 cents, or 23 percent, to close Monday at 59 cents. (See *BioWorld Today*, March 8, 2007.)

Biotech 2008

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Driving the acquisitions of biotechs in recent years are the patent expirations of blockbuster drugs, Reiser said, noting that the worth of brand-name drug patents lost in 2008 is about \$20 billion.

In addition, big pharma's innovation and productivity pipeline has been on the verge of drying up.

Big pharma's need for new products has put that industry in the position of being willing to pay a premium for products that are perceived to be potential blockbusters and has forced large drugmakers to make M&A decisions more aggressively than they otherwise would have a decade or even five years ago, said Paul Medeiros, principal of the BioTransactions Group, a business development consultant company.

"Pharma is making decisions on what they need to do rather than want to do," Medeiros said. The current competitive atmosphere from big pharma for small biotechs has resulted in terms that are "increasingly favorable to the biotech side," he said.

The other big driver for M&As has been the lacking in the valuation of IPOs in recent years, Reiser said. The majority of venture capital investors prefer M&As over IPOs as an exit strategy, he contended. "That's not hard to imagine when you consider the valuation issues and the certainty of the high value of an M&A exit," Reiser said.

But biotechs need to plan ahead for M&A, and those that consider the strategy as part of licensing deal talks come out ahead of those that make it part of a later strategy, Reiser said. Firms that out-license their "crown jewels" early on are put on the defense when it comes time to talk M&A because they have potentially limited their options under their earlier contracts, he said, noting that the big pharma partner in the licensing deal has the advantage of being in the "driver seat."

Out-licensing early stage products also puts limitations on funding because existing partners may be a competitive deterrent for VC investors or other potential future partners, Reiser said.

While the licensing deals used to be seen as giving validation to a biotech's technology and provided the company with nondilutive capital to advance its pipeline, most venture capitalists nowadays "generally shy away" from licensing transactions, and prefer to be up front with a potential buyer that they are interested in M&A and not interested in licensing, said Todd Brady, principal of venture capital firm Domain Associates Inc.

It may make sense for some biotechs with broad platforms to do some licensing deals, as long as they are not "giving away the whole store. But, Brady said, licensing deals are a "bad idea" as an exit strategy.

The biotech company that considers M&A during licensing agreement discussions rather than later with an existing licensing partner tends to gain the option of more flexibility and has more room for negotiation of better

terms, Reiser said. "It's a nice place to be if you can get there and are in such a position," he said.

When licensing discussions morph into M&A talks, biotech sellers need to ensure that they have the "full buy-in" from all key decision makers, Reiser said. "There's nothing worse than going down the path of anticipating such an event, only to find out that there's another layer of buy-in, another person who hasn't blessed this deal," he warned.

Terms must be presented only after an honest discussion has occurred, he emphasized. "You need to look people in the eye," Reiser said. "This is all part of assuring the process, and that you are, in fact, not getting surprised."

In the negotiating process, small biotechs on the sell side must realize that bigger companies have different needs, he said. "Be flexible," Reiser said. "It has to be win-win if this is going to work."

Also important is not to "sell" the M&A internally to your company until all terms have been finalized with the acquiring firm.

Biotechs on the sell side also need to be prepared for a "no-go," with a backup strategy in place, such as discussions with another company.

The considerations that ultimately drive the "buy side" company's M&A decision, Medeiros said, include the relation of the deal's opportunities to that firm's overall business strategy and the unique characteristics presented by the biotech's products. For instance, he said, a large pharmaceutical firm is going to weigh whether the biotech's product platform would provide entry into a space that the acquiring company wants to pursue.

Big pharma are most interested in platforms that have broad applicability in several disease areas over those that have limited utility, Medeiros maintained. The buyer also will consider whether an acquisition will expand its technical competence or bring new intellectual capital into the company, he added.

What all firms in M&A deals need to keep in mind, said Barbara Dalton, vice president of Pfizer Venture Capital, is that while transactions are ultimately between companies, those deals are made by people who take credit for the success or can be a major impediment and the reason a deal fails. "The egos of the people involved cause problems," she declared.

Senior managers have often been known to want to tweak the final terms of a transaction that has been in the works for several months, which could cause problems in a deal, Dalton said. Deals involving biotechs that are backed by several VC investors can get very complicated because it is not transparent what all of the parties are ultimately expecting from the M&A, she noted.

The VCs, Dalton said, often have in the back of their minds a number that is acceptable for this transaction to go through. "Obviously, if it is a large multiple, everyone is going to be happy," she said. But when it gets down to the tougher times, it is often not clear what is going to be sufficient to make the transaction worthwhile, she said, adding that "the VC is not always straightforward with its investing companies." ■

OTHER NEWS TO NOTE

• **Kamada Ltd.**, of Ness Ziona, Israel, said it signed a long-term supply agreement with a multinational company for the raw material required to manufacture AAT (alpha-1-antitrypsin), the company's flagship product, in development as an intravenous or inhaled treatment for severe respiratory diseases such as alpha-1-antitrypsin deficiency, cystic fibrosis and bronchiectasis. Terms were not disclosed.

• **Lorus Therapeutics Inc.**, of Toronto, said it successfully completed toxicology studies for lead small-molecule drug, LOR-253, a cancer drug designed to induce the tumor suppressor factor KLF4. Data from maximum tolerated dose and repeat-dose studies in rodents and nonrodents have established a toxicity profile for LOR-253 that will be supportive of Phase I testing in cancer patients.

• **NanoViricides Inc.**, of West Haven, Conn., reported that Feinstein Institute of Medical Research scientists presented the company's study on topical nanoviricides in a rabbit model of epidemic kerato-conjunctivitis at the annual meeting of the Ocular Microbiology and Immunology Group in Atlanta. Two broad-spectrum nanoviricides were found to be clinically highly effective against adenoviral EKC. Both significantly reduced conjunctival injection (severe redness of the eye) as well as stickiness, swelling and furriness. One of the nanoviricides was more effective in rapidly resolving the pathology, than the other one. NanoViricides previously announced the study's preliminary findings as they were received by the company.

• **Orexigen Therapeutics Inc.**, of San Diego, said CEO Gary Tollefson is taking a leave of absence and current nonexecutive board Chairman Eckard Weber will serve as executive chairman and interim CEO. Tollefson is expected to remain a member of the board, which will begin recruiting a permanent CEO.

• **Profectus BioSciences Inc.**, of Baltimore, has entered an assignment and license agreement with **Wyeth Pharmaceuticals**, of Madison, N.J., for Profectus therapeutic and prophylactic vaccine programs for HIV, hepatitis C, human papilloma virus and herpes simplex virus. Those programs combine Wyeth technologies in the fields of DNA and vectored vaccines used alone and in a prime-boost strategy to prevent and treat infections. The agreement also provides Profectus with access to a portfolio of intellectual property, research reagents, equipment, governmental funding and clinical trial products.

• **ProtoKinetix Inc.**, of Vancouver, British Columbia, said that it has received results of tests conducted in France to determine the biological activity of anti-aging glycoproteins on the selectin inflammation pathway. The highly specific tests conducted on selectin showed 100 per-

cent adhesion inhibition. Diseases such as Alzheimer's, Crohn's, diabetes, arthritis, cancer and cardiovascular problems are among the many life-threatening conditions treated with anti-inflammation and selectin inhibition therapies.

• **Raptor Pharmaceuticals Corp.**, of Ovato, Calif., has entered into an agreement with the Centre Hospitalier Universitaire d'Angers of France to evaluate Raptor's delayed-release cysteamine bitartrate in a Phase II trial in patients with Huntington's Disease. CHU d'Angers has received a French grant to fund the two-year, multicenter Phase II trial. Under the terms of the agreement, Raptor will provide clinical supplies of DR Cysteamine for the trial.

FINANCINGS ROUNDUP

• **Array BioPharma Inc.**, of Boulder, Colo., has filed a shelf registration statement with the Securities and Exchange Commission that will allow it to raise up to \$150 million through the sale of securities. Specific terms and prices will be determined later.

• **Critical Pharmaceuticals**, of Nottingham, UK, has closed a third round of investment totalling £650,000 (US\$1 million). The funding was fully supported by existing shareholders. The company has now raised more than £2 million since its formation in 2004 as a spinout from Nottingham University. The funds will be used to advance its pipeline and delivery technologies, secure its intellectual property portfolio and to help secure partnerships with pharmaceutical and biotechnology companies.

• **Precision Therapeutics Inc.**, of Pittsburgh, said it secured \$43 million in additional funding to expand the development and commercialization of ChemoFx, a diagnostic test aimed to help physicians select the most effective chemotherapeutic regimen for cancer patients. The round was led by new investor Longitude Venture Partners LP, with participation from existing investors Adams Capital Management, Quaker BioVentures, Birchmere Ventures, Techno Venture Management and Draper Triangle Ventures.

• **Psydon Pharmaceuticals Inc.** (formerly Ruxton Pharmaceuticals Inc.), of Germantown, Md., said New Enterprise Associates Inc. has invested \$8 million in a private financing. Psydon and **Schering-Plough Corp.**, of Kenilworth, N.J., also signed an agreement under which Psydon will acquire worldwide rights to Schering's selective dopamine D1 receptor antagonist, ecopipam. Financial terms were not disclosed. The new funds will be used for the clinical development of ecopipam for the treatment of serious central nervous system disorders. Ecopipam was discovered by the Schering-Plough Research Institute. Its clinical profile has been studied in more than 1,000 treated patients, but the optimal indication has not been found.

OTHER NEWS TO NOTE

• **Stem Cell Sciences plc**, of Cambridge, UK, entered into an agreement with CHDI Foundation Inc. to support the standardization of CHDI's mouse embryonic stem cell lines. CHDI works toward treatments for Huntington's Disease (HD). The cell lines have been produced over several years under varying conditions, and conversion to a standard methodology is expected to help their use in HD-related research. Financial terms were not disclosed.

• **Targeted Genetics Corp.**, of Seattle, said B.G. Susan Robinson has been appointed president and CEO. She previously served as vice president of business development. The company also said H. Stewart Parker, president and CEO, and Barrie J. Carter, executive vice president and chief scientific officer, have resigned. Parker remains on the board.

• **TorreyPines Therapeutics Inc.**, of La Jolla, Calif., has agreed to sell its Alzheimer's disease genetics research program to **Eisai Co. Ltd.**, of Tokoyo, for an undisclosed up-front cash payment. TorreyPines and Eisai have collaborated on the genetics program since 2002, with the most recent agreement concluding Sept. 30. The Alzheimer's disease genetics research program focused on the discovery of Alzheimer's disease targets using whole-genome family-based association screening.

• **Xechem International Inc.**, of Edison, N.J., said one of its subsidiaries, Xechem Inc., filed voluntary petitions for relief under Chapter 11 to suspend all litigation and to restructure its debt. The company's operations are expected to continue as normal throughout the bankruptcy

process. Xechem's other subsidiaries, including Nigerian subsidiary Xechem Pharmaceuticals Nigeria Ltd., which sells sickle cell drug Nicosan in Nigeria, are not included in the Chapter 11 filing.

• **XOMA Ltd.**, of Berkeley, Calif., has restructured its 2004 product development collaboration with Novartis Vaccines and Diagnostics Inc., a division of **Novartis AG**, of Basel, Switzerland, which involves six development programs including the ongoing HCDI22 program. Under the restructured agreement Novartis will make an up-front payment to XOMA of \$6.2 million; fully fund all future R&D expenses; reduce existing debt by \$7.5 million; pay potential milestones of up to \$14 million and double-digit royalty rates for two ongoing product programs including HCDI22; and provide XOMA with options to develop or receive royalties on four additional programs currently pending selection. In exchange, Novartis will have control over the HCDI22 program and the additional ongoing program, as well as the right to expand the development of those programs into additional indications outside of oncology. As part of the agreement, Novartis will pay XOMA for all project costs incurred after July 1. Novartis will pay XOMA royalties on sales of HCDI22 and one other product program candidate based on aggregate sales in all indications. If either company activates any of the four currently pending programs, the developing company will pay the other reduced royalties on sales of any resulting products. As of June 30, XOMA had \$21.3 million of outstanding principal on its secured note agreement with Novartis. Under the revised agreement, the principal has been reduced to \$13.8 million. The remaining principal of approximately \$13.8 million is due in 2015 and accrues interest at a rate of 2 percent plus LIBOR.

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CLINIC ROUNDUP

• **Aradigm Corp.**, of Hayward, Calif., reported the results of a study comparing aerosol delivery and distribution, as well as pharmacokinetics and safety of inhaled aqueous solution of treprostinil delivered via the Aradigm's AERx Essence inhaler, vs. the Nebu-Tec Optineb air nebulizer, which was used by **Lung Rx Inc.**, of Silver Spring, Md., in a Phase III study of inhaled treprostinil for pulmonary arterial hypertension patients. Data showed that the AERx Essence inhaler efficiently delivered aerosolized treprostinil deeper into the lung than delivery by the Optineb nebulizer. Lung Rx will be responsible for funding the remainder of the development of treprostinil in the AERx inhaler through registration and commercial launch. Aradigm will receive full reimbursement of its expenses for activities on this program conducted for Lung Rx.

• **AVI BioPharma Inc.**, of Portland, Ore., said its partner **Global Therapeutics**, of Bloomfield, Colo., said it has initiated the first trial of a drug-eluting stent that uses a peptide-conjugated morpholino phosphorodiamidate oligomer-based RNA therapeutic agent aimed at silencing C-MYC, one of the genes responsible for causing arteries to reclose after stenting (restenosis). The feasibility study is a prospective, open label, multicenter trial being performed in Germany. As many as 90 patients will be enrolled and all subjects will undergo clinical follow-up at 30 days and six months.

• **Celgene Cellular Therapeutics**, a wholly owned subsidiary of Celgene Corp., of Summit, N.J., said the FDA accepted the its investigational new drug application to initiate a clinical trial using PDA001, an immunomodulatory therapy utilizing human placenta-derived stem cells obtained via CCT's proprietary processes. The Phase I multicenter trial will begin by the end of the year for patients with moderate-to-severe Crohn's disease, who are refractory to oral corticosteroids, such as prednisone and immune suppressants.

• **Cell Therapeutics Inc.**, of Seattle, said results of a study investigating the use of short-course CHOP-R followed by Zevalin ([90Y]-ibritumomab tiuxetan) and extended rituximab as first-line treatment in follicular non-Hodgkin's lymphoma patients was published in the Nov. 1, 2008, issue of *Clinical Cancer Research*. Addition of the Zevalin therapeutic regimen increased the complete responses from 40 percent for patients evaluated after three cycles of CHOP-R alone to 82 percent after the Zevalin regimen.

• **DOR BioPharma Inc.**, of Ewing, N.J., said it has reached agreement with the FDA on the key clinical study design components of a confirmatory Phase III study evaluating OrBec for the treatment of acute gastrointestinal graft-versus-host disease. The agreement includes all key study design components including maintenance of the proposed primary endpoint, "treatment failure rate at day 80." That endpoint was successfully measured as a secondary end-

point ($p = 0.005$) in the prior Phase III study as a key measure of durability following a 50-day course of treatment with OrBec (i.e., 30 days following cessation of treatment).

• **EntreMed Inc.**, of Rockville, Md., said MKC-1, in combination with pemetrexed (Alimta, Eli Lilly and Co.), met the primary endpoint of tumor response for the efficacy portion in the open label Phase I/II study in non-small-cell lung cancer patients. MKC-1 is a novel, orally active cell cycle inhibitor with efficacy against a broad range of human solid tumor cell lines, including multidrug-resistant cell lines. EntreMed is considering options for further studies in NSCLC patients. Options include the continuation of the current single-arm study or a randomized Phase II study in the same patient population.

• **EyeGate Pharma**, of Waltham, Mass., enrolled the first dry eye patient in a Phase II safety and efficacy study of EGP-437. The trial is a single-center, randomized, double-masked, placebo-controlled study of two doses of a corticosteroid solution (EGP-437) over three weeks in dry eye patients.

• **Fibrogen Inc.**, of South San Francisco, reported clinical data demonstrating that treatment with hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) increased blood hemoglobin concentration with induction of low circulating levels of endogenous erythropoietin tenfold to fortyfold lower than EPO levels associated with erythropoiesis-stimulating agent therapy. Data were presented at the American Society of Nephrology Renal Week meeting in Philadelphia. In preclinical studies, the company's FG-2216 showed that it was able to alleviate anemia associated with chronic kidney disease in a rat remnant kidney model and increase hemoglobin levels without increasing systolic blood pressure. Other data from preclinical and clinical studies demonstrated that HIF-PHI compounds are orally active, which also sets them apart from ESAs, which must be administered by injection.

• **Gene Signal International SA**, of Lausanne, Switzerland, said results from a Phase II study showed that its GS-101 eye drops demonstrated significant regression of corneal neovascularization, while the placebo group showed an increase in new vessels. The optimal treatment group achieved 86 percent regression. Data were presented at the American Academy of Ophthalmology meeting in Atlanta. Gene Signal is starting a Phase III study of GS-101, an oligonucleotide approach aimed at blocking blood vessel formation, in the prevention of corneal graft rejection.

• **Genentech Inc.**, of South San Francisco, and **Novartis AG**, of Basel, Switzerland, reported data from a Phase III study showed Xolair (omalizumab) for subcutaneous use significantly reduced asthma attacks in children 6 to 11 with moderate or severe persistent allergic asthma inadequately controlled with inhaled corticosteroids. Xolair currently is approved for adults and adolescents 12 and older, and is the only approved therapy that blocks immunoglobulin E, a major component of allergic asthma. Genentech plans to submit those data to the FDA seeking to expand the current labeled indication for Xolair. Results from the trial were first presented at the European Respiratory Society Annual Congress in October.

CLINIC ROUNDUP

• **Genomic Health Inc.**, of Redwood City, Calif., said data from a study indicated that results from Oncotype DX assay, a multi-gene expression test, impact the way physicians treat early-stage breast cancer: 37 patients (44 percent) with node-negative estrogen receptor-positive breast cancer received treatment change, and 33 patients, who would have received a recommendation for chemotherapy based on the 2007 National Comprehensive Cancer Network guidelines, received a recommendation for hormone therapy alone based on their Oncotype DX Recurrence Score of less than 18. Four patients who would have received a recommendation against chemotherapy based on the 2007 NCCN guidelines were placed in the high-risk group based on their Recurrence Score of greater than 31 and received a recommendation for chemotherapy. Those data were published in the October 2008 issue of the *American Journal of Surgery*.

• **InterMune Inc.**, of Brisbane, Calif., **F. Hoffmann-La Roche Ltd.**, of Basel, Switzerland, and **Pharmasset Inc.**, of Princeton, N.J., said the first patients have been dosed in a trial in patients chronically infected with the hepatitis C virus. The trial is the first to investigate the combination of two oral antiviral molecules in the absence of interferon. The initial study will evaluate the safety and combined antiviral activity of R7227 (ITMN-191), a protease inhibitor,

and R7128, a polymerase inhibitor, in 14 days of combination therapy in treatment-naïve patients infected with HCV genotype 1. The direct antiviral combination study will evaluate the therapeutic potential of an all-oral, interferon-free combination treatment for HCV.

• **Ophthotech Corp.**, of Princeton, N.J., said it has treated the first patient with Volociximab, a monoclonal antibody targeting alpha5beta1 integrin, in a Phase I trial for the treatment of wet age-related macular degeneration. The trial will assess the safety, tolerability and pharmacokinetic profile of Volociximab.

• **Sepracor Inc.**, of Marlborough, Mass., said data from Phase III studies of Alvesco HFA (hydrofluoroalkane) Inhalation Aerosol in patients not previously treated with inhaled corticosteroid, indicated that the product improved total daily asthma symptom scores compared to placebo. Alvesco was also well tolerated in patients switched from a different inhaled corticosteroid or a combination of inhaled corticosteroid products. In addition, Sepracor presented Phase I data for a ciclesonide HFA MDI (metered-dose inhaler) nasal aerosol formulation for the treatment of allergic rhinitis. The study evaluated the pharmacokinetics, pharmacodynamics, safety and tolerability of two dosages (150 mcg and 300 mcg) of an HFA MDI formulation of the intranasal corticosteroid, and showed that both doses were well tolerated. Those results were presented at the annual meeting of the American College of Allergy, Asthma & Immunology in Seattle.

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