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PAGE 1 OF 6

ImmunoGen, Centocor Partner In Potential $43.5M TAP Deal

By Karen Pihl-Carey
Staff Writer

ImmunoGen Inc. licensed certain rights to its Tumor-Activated Prodrug (TAP) technology to Centocor Inc. in a deal worth up to $43.5 million, plus royalties.

"This is deal No. 7," said Mitchel Sayare, chairman and CEO of Cambridge, Mass.-based ImmunoGen. "It says there are a lot of companies that are interested in this, that are willing to spend millions of dollars to access our payload technology."

Malvern, Pa.-based Centocor, a Johnson & Johnson company, gains exclusive worldwide rights to develop and commercialize cancer drugs involving a Centocor antibody that binds to an undisclosed cancer target and a maytansinoid cell-killing agent developed by ImmunoGen.

Centocor will cover all research, development, manu-

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ALZA Files For Approval Of Premature Ejaculation Drug

By Jennifer Boggs
Staff Writer

ALZA Corp. submitted a new drug application for approval of dapoxetine hydrochloride, a treatment for premature ejaculation.

If approved, it will be the first prescription product designed specifically for treating PE, said Ellen Rose, spokeswoman for the Mountain View, Calif.-based company.

"It's a new oral medication specifically developed to treat PE, premature ejaculation," Rose said, adding that PE is "the most common form of male sexual dysfunction that affects about one-third of men worldwide."

The company could not comment on when it can expect a response from the FDA, she said.

A selective serotonin reuptake inhibitor, dapoxetine

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Fifty Years Of Organ Transplants

In Heart Tissue Engineering, It's Electricity, Gap, Scaffolds

By Anette Breindl
Science Editor

In December 1954, the first successful human organ transplant – a kidney – was undertaken at the Peter Bent Brigham Hospital (now Brigham & Women's Hospital) in Boston. Donor and recipient were identical twins. They had to be – it was before the advent of powerful immunosuppressants.

Transplantation medicine has come a long way in the intervening half-century, and it is no longer necessary to have an identical twin for transplants. But it still is necessary to have a donor, and that requirement is pretty much the limiting factor in the number of transplantations that can be performed. The nonprofit Organ Transplantation and Procurement Network has about

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Emisphere Accesses Cash Via Equity Deal, Revises Elan Debt

By Aaron Lorenzo
Washington Editor

Emisphere Technologies Inc., a drug delivery firm, has some added financial benefits after agreeing to a $20 million equity deal and also reworking terms of its debt with Elan Corp plc.

"The most important aspect is that these transactions strengthen our balance sheet," said Elliot Maza, Emisphere's chief financial officer, adding that the revised note terms "clean up a debt overhang that we've had on our books for a while."

To fatten its cash reserves, the Tarrytown, N.Y.-based company entered an agreement in which Kingsbridge Capital Ltd. committed to purchase up to $20 million of Emisphere's common stock over a two-year period. Terms of the commitment call for Emisphere to draw funds from Kings-

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OTHER NEWS TO NOTE

• **Affymetrix Inc.**, of Santa Clara, Calif., granted Veridex LLC, a unit of New Brunswick, N.J.-based **Johnson & Johnson**, long-term access to its GeneChip technology to create and market in vitro diagnostics for cancer. Veridex gains nonexclusive rights to Affymetrix's arrays, instrumentation systems and planned improvements to the technologies.

• **Axonyx Inc.**, of New York, completed the last six-month patient treatment period in its Phase III trial with Phenserine for Alzheimer's disease. The trial began in June 2003 and involved 375 mild to moderate AD patients who were randomly assigned Phenserine, in either 15-mg or 10-mg twice-daily doses, or a placebo, and evaluated with memory and cognition tests for required efficacy endpoints. Axonyx expects to announce results by the end of March. The company initiated two additional Phase III trials in late 2004. Phenserine is a dual-action acetylcholinesterase and beta-APP inhibitor.

• **CancerVax Corp.**, of Carlsbad, Calif., secured an $18 million loan from Silicon Valley Bank to expand the production capacity of its biologics manufacturing facility in the Los Angeles area. The company said it will use the funds to create additional warehouse and laboratory space for manufacturing Canvaxin, a therapeutic cancer vaccine undergoing evaluation in two Phase III trials involving patients with Stage III or Stage IV melanoma. CancerVax previously announced a partnership with Geneva-based **Serono SA** to develop and market Canvaxin. CancerVax received an initial $37 million payment and is eligible to receive up to $253 million through development and regulatory and commercial milestones. (See *BioWorld Today*, Dec. 17, 2004.)

• **Gen-Probe Inc.**, of San Diego, said the FDA granted marketing clearance for the company's APTIMA Chlamydia Trachomatis assay, an amplified nucleic acid test that detects the bacterium that causes the infection. The assay can be run on Gen-Probe's semi-automated DTS instruments. The company also has filed for clearance of its stand-alone APTIMA GC assay for *Neisseria gonorrhoeae*, and it expects approval in the first quarter.

• **Halozyme Therapeutics Inc.**, of San Diego, received CE mark approval for Cumulase to treat oocytes to facilitate certain in vitro fertilization (IVF) procedures. The company anticipates launching Cumulase in the European Union in the first quarter. Cumulase is an ex vivo formulation of rHuPH20 (recombinant human PH20 hyaluronidase) to replace bovine and ovine extracts used for the preparation of oocytes prior to IVF during the process of intracytoplasmic sperm injection. Halozyme also has a pending 510(k) application for Cumulase before the FDA.

• **Myriad Genetics Inc.**, of Salt Lake City, submitted an investigational new drug application to begin a Phase I trial with MPC-2130 (previously referred to as MPI-176716), a product designed as an inducer of apoptosis in cancer cells. The study is expected to evaluate the safety and pharmacokinetic profile of MPC-2130 in patients with advanced metastatic tumors or blood cancers, as well as refractory cancer that had progressed despite chemotherapy. Myriad reported that preclinical testing showed apoptosis in ovarian cancer, prostate cancer and two lymphoma cell lines, Burkitt's lymphoma and T-cell lymphoma.

• **Pharming Group NV**, of Leiden, the Netherlands, said it will acquire **ProBio International Holdings Pte. Ltd.**, of Melbourne, Australia, to expand Pharming's commercial opportunities with recombinant human lactoferrin and to enhance its protein product technology platform. Pharming already owns about 45 percent of ProBio's shares, but it will gain control of the intellectual property portfolio through the acquisition. It also will gain rights to the non-pharmaceutical applications of recombinant human lactoferrin, and it will benefit from ProBio's relationships with pan-Asian entities. The total consideration for the acquisition will be paid in shares and accounts for about 1.5 percent of the company's capitalization. Detailed terms were not disclosed.

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Emisphere

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bridge, at Emisphere's discretion, in amounts up to 3 percent of its market capitalization at the time of the draw. In exchange for each draw, Emisphere will sell newly issued common shares to Kingsbridge. The stock will be priced 8 percent to 12 percent lower than the average trading price during the financing period, with the reduced discount applying if the stock's price is equal to or greater than $8.50.

On Tuesday, the company's shares (NASDAQ:EMIS) gained 16 cents to close at $3.56.

Emisphere, which had $24.3 million in cash, cash equivalents and investments as of Sept. 30, will control the minimum acceptable purchase price of shares issued to Kingsbridge. The right to draw funds will begin after the SEC declares effective a registration statement to be filed by the company.

"We're very bullish on our stock and believe that over the next two years, our stock will move up as we make progress on the clinical side and also clean up the balance sheet," Maza told *BioWorld Today*. "So this financing vehicle with Kingsbridge gives us two things: No. 1, it gives us a cushion so that we have a source of funds available to us, and No. 2, it allows us to access the market at our choosing, which would be as our stock price increases."

Emisphere is under no obligation to access any of the capital, and it can participate in other debt or equity financings without restriction, provided that such financings do not use any floating or other post-issuance adjustable discount to the stock's market price. Maza said that Emisphere does not have near-term plans to draw down funds from the deal.

Kingsbridge is precluded from short-selling any of the shares during the agreement. In return for the commitment, Emisphere gave Kingsbridge a warrant to purchase 250,000 shares at a premium to the current market price. Emisphere posted a $9.5 million net loss in the quarter ended Sept. 30, at which date it had about 18.4 million shares outstanding.

Regarding the Elan deal, Emisphere entered an agreement to repay its outstanding note to Elan in cash and stock. Terms of the agreement call for Emisphere to pay the Dublin, Ireland-based company a total of $26 million in cash and up to 1.2 million shares in installments through June 30. The note's current accrued value stands at about $44 million.

The debt stems from a 1996 joint venture with Elan to develop oral heparin. In connection with the repurchase of Elan's joint venture interest in 1999, Emisphere issued a zero coupon, $20 million note maturing in July 2006, for $55 million.

"They are getting shares, and Elan decided that they liked the idea of an immediate cash payment plus the upside of shares," Maza said. "That was very attractive to them."

Emisphere's eligen technology has been developed to allow for oral delivery of otherwise injectable drugs. To date, it has been used to enable the oral delivery of proteins, peptides, macromolecules and charged organics. Emisphere and its partners have advanced oral formulations or prototypes of salmon calcitonin, heparin, insulin, parathyroid hormone, human growth hormone and cromolyn sodium into clinical trials.

In advance of the two financial transactions, the company entered eligen licensing deals with Novartis AG, of Geneva, and F. Hoffmann-La Roche Ltd., of Basel, Switzerland. (See *BioWorld Today*, Nov. 19, 2004, and Dec. 3, 2004.)

"This is the culmination of a year of significant progress," Maza said, "on the clinical development side, partnering side and now also on the financial side." ■

APPOINTMENTS AND ADVANCEMENTS

PharmaFrontiers Corp., of Houston, appointed Tony Kamin to its board.

Phyton Biotech Inc., of Ithaca, N.Y., appointed Charles Swindell vice president of research and development.

Saegis Pharmaceuticals Inc., of Half Moon Bay, Calif., appointed Ann Neale vice president of clinical operations.

Spectranetics Corp., of Colorado Springs, Colo., appointed Craig Walker to its board.

Spectrum Pharmaceuticals Inc., of Irvine, Calif., appointed Stuart Krassner to its board.

Tapestry Pharmaceuticals Inc., of Boulder, Colo., appointed Elliot Maza to its board.

Tm Bioscience Corp., of Toronto, appointed Daynna Wolff to its scientific advisory board.

Ventaira Pharmaceuticals Inc., of Columbus, Ohio, promoted Leslie Williams to president and CEO.

Viropro Pharma, of Montreal, appointed Max Bergoin to its scientific advisory committee.

ImmunoGen

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facturing and marketing expenses of any product that results. ImmunoGen will receive a $1 million up-front payment for the license, and it is entitled to a total of $42.5 million in milestone payments related to clinical progress. The company also would receive royalties.

In addition, ImmunoGen will receive compensation for product development research and for the production of preclinical and early clinical materials for Centocor. Sayare declined to give further financial details.

As Sayare mentioned, Centocor is the seventh major company that has licensed ImmunoGen's TAP technology.

"It's yet another deal out-licensing our technology platform that is focused on the use of monoclonal antibodies to treat cancer," Sayare told *BioWorld Today*. "So I think we've hit the big three: Biogen Idec, Centocor, and of course, Genentech."

The agreement with Biogen Idec Inc., of Cambridge, Mass., was signed in October and also is worth about $43 million. The collaboration with South San Francisco-based Genentech Inc. was formed in 2000. (See *BioWorld Today*, May 5, 2000; May 9, 2000; and Oct. 7, 2004.)

The other agreements are with Aventis SA, of Lyon, France, which now is part of the Sanofi-Aventis Group; Boehringer Ingelheim GmbH, of Ingelheim, Germany; Millennium Pharmaceuticals Inc., of Cambridge, Mass.; and Abgenix Inc., of Fremont, Calif.

The deals, Sayare said, fulfill ImmunoGen's business model of out-licensing its platform in order to pay for the company's own products in development. Those products include huN901-DM1, which is in a Phase I/II trial for small-cell lung cancer. Initial data from that trial will be reported in the spring at the American Society of Clinical Oncology meeting. A second internal product in development is huC242-DM4 for colorectal and pancreatic cancers. ImmunoGen expects to move that product back into the clinic in the middle of 2005. It was in the clinic at one time, but the company pulled it back to tweak it, Sayare said.

With about $95 million in cash as of Sept. 30 and a burn rate of between $10 million and $13 million a year, ImmunoGen has plenty of money going forward. It might even hold onto its internal products through clinical trials and regulatory filings, as opposed to forming partnerships early in development.

"We know that we'll go at least through the establishment of proof-of-concept data," Sayare said.

ImmunoGen has two partnered products in the clinic. Millennium developed MLN2704, a TAP compound that is in Phase I/II testing for prostate cancer. And Boehringer Ingelheim developed the TAP compound bivatuzumab mertansine, which moved into clinical testing in October 2002.

The TAP technology is designed to provide cancer-targeting engineered antibodies with clinical activity. ImmunoGen attaches a cell-killing agent, called a "payload," to the antibody, which carries it to cancer cells.

As more companies have focused on monoclonal antibodies in treating cancer, they have turned to ImmunoGen's technology for help when the antibodies don't seem to do anything, Sayare said.

"Those companies have come to us" to access that payload technology, he said, and ImmonoGen is able to improve the performance of the antibodies.

ImmunoGen's stock (NASDAQ:IMGN) rose 82 cents Tuesday, or 11.5 percent, to close at $7.93. ■

Transplants

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87,400 people on its national waiting list.

A variety of approaches are being pursued in hopes of alleviating that imbalance between donors and recipients. Xenotransplantation (the transplantation of animal organs) is under development. Another approach is the engineering of artificial organs. Similarly, artificial tissue could be used to repair damaged organs so that a transplant might be avoided altogether.

In the Dec. 28, 2004, issue of the *Proceedings of the National Academy of Sciences*, researchers from Harvard Medical School and the Massachusetts Institute of Technology reported on tissue engineering to create functional heart tissue. Their paper is titled "Functional assembly of engineered myocardium by electrical stimulation of cardiac myocytes cultured on scaffolds."

At the risk of belaboring the obvious, the core feature of heart muscle is its ability to beat synchronously in response to electrical stimulation. Heart tissue is thus characterized by cells connected to enable the free flow of electrical impulses from cell to cell (the so-called "gap junctions") and a contractile apparatus. To date, there has been limited success in inducing cultured heart cells to differentiate into mature, functional tissue that shows that ability. Physical therapy for cells, in the form of mechanical stretching, has been shown to improve matters to some degree. But the resulting tissue, while it shows improved ability to contract, still lacks several structural hallmarks of mature heart tissue.

Given that electrical activity is a critical feature of heart muscle function, the authors of the current *PNAS* study decided to apply electrical stimulation to cells isolated from neonatal rat hearts during the culturing process.

"We expected some improvement," said Gordana Vunjak-Novakovic, principal research scientist at MIT and senior author of the study. "What was unexpected was the extent of the improvement, and how critical electrical signaling really is." Functionally, she described the tissue as "a patch for a broken heart."

The scientists isolated neonatal rat heart cells, transferred them onto scaffolds, allowed them varying amounts of time to recover from the harvesting procedure and attach, and then stimulated them electrically for five days.

Electrical stimulation led to improvements in the molecular, structural and functional properties of the stimulated cells. On the molecular level, there was an increase in proteins necessary for development of gap junctions and a contractile apparatus. Structurally, the cells resembled mature heart cells in several respects, including their alignment with the electrical field, elongated shape and the presence of structural features of muscle cells that enable their contraction. Functionally, the cells showed evidence of electrical coupling (i.e. working gap junctions), and after eight days of stimulation, their ability to contract was about seven times that of non-stimulated controls.

The researchers also treated cultures with drugs designed to interfere with spreading of the electrical stimulation, contraction of the cells in response to the stimulation or the coupling between the two.

When contraction was blocked, the cells developed gap junctions, but the development of the contractile apparatus was impaired, reducing but not eliminating contractions even after removal of the drug. Blocking either the spread of electrical stimulation through gap junctions or the downstream effects of electrical stimulation and contraction had more serious effects. Cells remained morphologically immature, and electrical stimulation did not lead to organized contractions, even after removal of the drugs.

To Avoid Confusion, Timing Is Everything

Vunjak-Novakovic and her colleagues also found that electrical stimulation needs to be timed carefully to coincide with the right level of cellular maturation. During the harvesting of neonatal heart cells, the cells are separated from each other. Before they can benefit from electrical stimulation, cells need to reconnect by laying down new gap junctions, as well as a contractile apparatus, in a period of protein synthesis.

"If you stimulate during protein synthesis, you just confuse the cells," Vunjak-Novakovic said. The "confused" cells neither differentiate properly nor develop the ability to contract as much as cells that are first allowed a few days in preculture to assemble the necessary proteins. Conversely, waiting too long leads to declining amounts of those proteins, also reducing the effectiveness of electrical stimulation. Vunjak-Novakovic added that her group also is working with other cell types, and while the exact timing is different, the basic existence of a critical period is the same in the cell types they have looked at so far.

When asked where her work fits into the spectrum of research applicability, Vunjak-Novakovic cautioned that it was only "the beginning" of the road to the clinic. For any clinical benefit to be realized, at least two things need to happen. First, benefits of the approach need to be demonstrated in vivo: "We need to patch hearts [with the tissue], and show that it integrates and leads to recovery of function," she said.

The researchers also need to show that their approach works with human cells. Experiments with a variety of cell types, including human embryonic stem cells, are ongoing.

Vunjak-Novakovic described a constant interplay of basic scientific and clinical findings and advances. In the biomimetic approach, "we try to mimic normal conditions, but really, very little is known about those conditions. So we build tissue and try to mimic conditions that will allow it to grow. And along the road, we learn things that will allow us to build a little bit better tissue next time." ■

ALZA

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hydrochloride is a "unique pharmacological product that inhibits the serotonin transmitter," the neurotransmitter that causes ejaculation, Rose said.

Details of ALZA's Phase III trials have not yet been released.

"We'll be presenting clinical data in scientific forums in the first half of 2005," Rose said.

The product will be marketed in the U.S. by Ortho-McNeil Pharmaceutical Inc. Both ALZA and Ortho-McNeil are subsidiaries of New Brunswick, N.J.-based Johnson & Johnson.

The company has long-term plans to sell the product outside the U.S., she said.

Rose said she could not provide marketing or sales estimates of dapoxetine hydrochloride and said neither ALZA nor Ortho-McNeil has announced the name under which dapoxetine hydrochloride might be sold.

ALZA has worked to develop the product since licensing dapoxetine from PPD Inc., of Wilmington, N.C., in January 2001. Under terms of that agreement, ALZA received worldwide rights to develop and commercialize the product and bears the responsibility for manufacturing, clinical, regulatory and marketing costs, while PPD received an undisclosed up-front payment and would receive royalties.

PPD, in turn, had in-licensed dapoxetine from Indianapolis-based Eli Lilly and Co. in 1998 before out-licensing it to ALZA. In December 2003, PPD purchased the dapoxetine patents from Lilly for $65 million, thereby terminating their license agreement. At the time, dapoxetine was in Phase III trials under ALZA, and PPD officials estimated dapoxetine could sell $750 million at its peak. (See *BioWorld Today*, Dec. 22, 2003.)

In January, ALZA amended the dapoxetine license agreement with PPD so that certain sales-based payments would be abated for a period following NDA approval. ALZA would make a cash payment to PPD and agreed to a fixed milestone payment upon FDA approval.

PPD completed some Phase II work on dapoxetine before licensing it to ALZA, which conducted its own trials, Rose said.

ALZA, which focuses on drug delivery platforms, in July received an FDA approvable letter regarding its on-demand acute pain product, Ionsys.

The application for Ionsys, an iontophoretic, fentanyl-containing transdermal analgesic, was submitted in September 2003. The product is a credit card-sized patch. ■

OTHER NEWS TO NOTE

• **Sonus Pharmaceuticals Inc.**, of Bothell, Wash., and **Synt:em SA**, of Nimes, France, revised the terms for a proposed acquisition of Synt:em originally announced in November. Under the new agreement, Sonus will issue a maximum of 5.4 million shares, instead of 7.6 million to 8.9 million shares, to acquire all of the outstanding shares of Synt:em. The new terms state that Sonus' shares at closing will have a value of about $12 million, and additional shares will be issued at certain milestones met by Synt:em's product candidates entering Phase II trials, instead of Phase I trials. Synt:em shareholders will own 20 percent, as opposed to 25 percent to 29 percent, of the combined entity if the milestone payments are earned. The new agreement also includes a mechanism to reallocate a portion of the Sonus shares issued at the closing to the contingent milestone pool if Sonus reaches an agreement with the FDA on Phase III testing or if it enters a partnership for Tocosol Paclitaxel, a cancer product. The transaction is expected to close in the first quarter. The terms were amended following an end-of-Phase II meeting with the FDA regarding Tocosol Paclitaxel. (See *BioWorld Today*, Nov. 5, 2004.)