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PAGE 1 OF 7

*\$350M in Pre-Market Milestones, Too*

## Ambit's Gambit Attracts Astellas; \$40M Pays Perfect 'Flit' in AML?

**By Randy Osborne**  
**Staff Writer**

Ambit Biosciences Corp.'s potential \$390 million deal with Astellas Pharma Inc. for FLT3 kinase inhibitors adds power to the push with oral small-molecule AC220, which just entered Phase II trials of the compound against acute myeloid leukemia in a patient subset that comprises about one-third of the newly diagnosed.

"We had several parties all the way to the end" of collaboration talks, said M. Scott Salka, CEO of San Diego-based Ambit, including a few that were heavy hitters in oncology with established pipelines.

"On one hand that's great, but it's a little scary for a small company that wants to play a role in the continued development of the agent," he said. "The risk is that you get

*See Ambit, Page 4*

## Eisai Buying AkaRx for \$255M; Gaining Phase II Drug for ITP

**By Trista Morrison**  
**Staff Writer**

Eisai Co. Ltd. agreed to acquire AkaRx Inc. for \$255 million, gaining control of Phase II thrombocytopenia drug AKR-501.

In a way, that means AKR-501 is returning to its Japanese roots. The small-molecule thrombopoietin receptor (c-Mpl) agonist was developed at Tokyo-based Yamanouchi Pharmaceutical Co. Ltd. But as Yamanouchi and Osaka-based Fujisawa Pharmaceutical Co. Ltd. merged to form Astellas Pharma Inc. in early 2005, AKR-501 was spun out as the lead asset of privately held AkaRx.

Bridgewater, N.J.-based AkaRx did not remain a struggling start-up for long. In mid-2007, the firm caught the eye of MGI Pharma Inc. Minneapolis-based MGI paid \$45 million up front for the option to pay another \$255 million to

*See Eisai, Page 5*

*Financings Roundup*

## Past Funding Woes, Thallion Gets Cash, E. Coli Drug Partner

**By Catherine Hollingsworth**  
**Staff Writer**

Canada's Thallion Pharmaceuticals Inc. got an early Christmas gift, an infusion of cash and a partnership that will jumpstart its pipeline drug for *E. coli* infection, a program that had languished for nearly a year for lack of funding.

The Montreal-based company last year decided to stop development on a drug for *Shiga-toxin E. coli* (STEC) bacteria until it found a partner. Thallion was dealt another blow this week when it said it would have to stop development on its brain cancer program after a study committee found that drug candidate TLN-4601 showed no meaningful response in patients with glioblastoma multiforme.

But Thallion got some much needed holiday cheer: Its wishes were granted for a partner and a windfall of cash,

*See Financings Roundup, Page 6*

*Washington Roundup*

## NCI Reports Revlimid Post-SCT Results Positive; Trial Stopped

**By Donna Young**  
**Washington Editor**

WASHINGTON – Early results from a National Cancer Institute-sponsored Phase III trial showed that multiple myeloma patients who received Celgene Corp.'s Revlimid (lenalidomide) after an autologous blood stem cell transplant had a statistically significant reduction in disease progression, the agency reported Friday.

"This study answers the important question for multiple myeloma patients regarding maintenance lenalidomide therapy," said lead investigator Philip McCarthy, associate professor of medicine at Roswell Park Cancer Institute.

Because of the superior efficacy seen in the trial, the study was stopped early, officials said.

Shares of Summit, N.J.-based Celgene (NASDAQ:CELG)

*See Washington Roundup, Page 7*

**INSIDE:** BENCH PRESS: LEPTIN PROTEIN LEVELS RELATED TO AD RATE .....INSERT  
MYRIAD SNAGS LATE-STAGE DRUG IN JAVELIN ACQUISITION.....2



## Myriad Snags Late-Stage Drug in All-Stock Javelin Acquisition

By Jennifer Boggs  
Assistant Managing Editor

Only months off its official spinout from its parent company, Salt Lake City-based Myriad Pharmaceuticals Inc. is buying Javelin Pharmaceuticals Inc. in an all-stock transaction that gives Myriad a near-term revenue stream with injectable NSAID Dyloject – now under FDA review – and provides cash-strapped Javelin with the firepower to get Dyloject to market.

Under the terms, Myriad will issue 0.282 shares of its stock for each share of Javelin. Based on 63.86 million Javelin shares outstanding, the deal values the Cambridge, Mass.-biotech at about \$1.50 per share (or about \$96 million), marking a 22 percent premium over Thursday's closing price. At the closing, Javelin shareholders would own about 41 percent of the combined company – that could increase to 45.1 percent if Dyloject approval comes before Jan. 31, 2011.

But an all-stock deal for Myriad, which has been trading below cash since its Nasdaq debut in July, left some shareholders scratching their heads. One investor on the companies' joint conference call Friday morning urged shareholders to vote against what he called "a terrible deal."

Shareholders of both companies have to approve the transaction.

Piper Jaffray analyst Edward Tenthoff acknowledged that the dilution and current discount to cash might lead some shareholders to resist. "However, in the long term, if Dyloject gets approved, it could be a major positive for Myriad," he wrote in a research note.

If approved, Dyloject would be the first injectable version of diclofenac, a nonsteroidal anti-inflammatory drug widely used for postoperative pain. Javelin has estimated the nonopioid pain market potential of up to \$500 million per year.

Myriad execs defended the terms, stating that an all-stock deal preserves the company's cash, which totaled about \$159 million as of Sept. 30, to fund Dyloject's com-

mercial launch, including putting into place a 100- to 150-member hospital-targeted sales team.

The deal isn't exactly a winner from Javelin's perspective, either. But Leerink Swann analyst Gary Nachman said the deal "could lead to better offers if other potential bidders are still in the picture."

Javelin ended the third quarter with a mere \$3.3 million in cash – adding \$3.7 million in an October financing – and "had little negotiating leverage despite having just submitted the Dyloject NDA," Nachman added.

Concurrent with the definitive agreement, Myriad agreed to provide up to \$6 million of interim financing to fund Javelin's operating activities prior to the deal's close, expected in the first quarter of 2010.

Javelin had been seeking a U.S. deal for Dyloject. Early this year, the firm signed Therabel Pharma, of Brussels, Belgium, to a potential \$71.5 million European partnership, under which Javelin also is entitled to double-digit royalties on Dyloject sales. (See *BioWorld Today*, Jan. 16, 2009.)

Shares of Javelin (AMEX:JAV) gained 7 cents, to close Friday at \$1.30, while shares of Myriad (NASDAQ:MYRX) fell 30 cents, to close at \$5.03.

Myriad, which was spun out of Myriad Genetics Inc. in July in an effort to separate the biologics and diagnostics business units following Flurizan's flop in Alzheimer's disease, has several programs in earlier development, including an HIV therapy, MPC-4326, which recently began Phase IIb testing. (See *BioWorld Today*, July 2, 2009.) ■

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## AEterna Shifts to Perifosine as Sanofi Bails on Cetrorelix Deal

### From Staff Reports

AEterna Zentaris Inc. is turning its attention to perifosine, the promising multiple myeloma drug partnered with Keryx Biopharmaceuticals Inc., as its cetrorelix agreement with Sanofi-Aventis U.S. comes to an end.

Sanofi and the Quebec City-based biotech officially will end their partnership Jan. 9 for cetrorelix, a luteinizing hormone-releasing hormone antagonist, but the move has been expected since early this month when the firms reported disappointing data from a second pivotal study in benign prostatic hyperplasia.

Results from the Phase III European study showed that cetrorelix produced no clear differences in overall efficacy vs. placebo, dashing the few hopes that had remained following the failure of the North American trial in August.

(See *BioWorld Today*, Aug. 18, 2009.)

AEterna signed the deal with Bridgewater, N.J.-based Sanofi in March, picking up \$30 million in up-front cash, with the possibility for up to \$135 million in milestones plus royalties. (See *BioWorld Today*, March 9, 2009.)

The company is hoping for better luck with perifosine, which made a splash at this year's American Society of Hematology meeting in New Orleans. AEterna and New York-based Keryx and recently began Phase III testing in relapsed and refractory multiple myeloma under a special protocol assessment. (See *BioWorld Today*, Aug. 4, 2009.)

On its own, the company is working on AEZS-108, a targeted doxorubicin conjugate, which recently completed Phase II testing in ovarian and endometrial cancers, and also developing AEZS-130, a ghrelin agonist, as a diagnostic test for adult growth hormone deficiency.

Shares of AEterna (NASDAQ:AEZS) closed at 82 cents Friday, down 4 cents. ■

## OTHER NEWS TO NOTE

- **Amgen Inc.**, of Thousand Oaks, Calif., said the Committee for Medicinal Products for Human Use of the EMEA gave a positive opinion for the marketing authorization of Prolia (denosumab) for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. If approved by the European Commission, Amgen would receive marketing authorization for Prolia in all EU member states. Amgen in October received two complete response letters from the FDA, delaying approval of Prolia to treat or prevent bone loss associated with hormone ablation therapy in patients with breast and prostate cancers, and as a treatment and preventive therapy for postmenopausal osteoporosis. (See *BioWorld Today*, Oct. 20, 2009, and Oct. 23, 2009.)

- **BioNanomatrix Inc.**, of Philadelphia, elected Edward L. Erickson president and CEO. Erickson, who was executive chairman, succeeds Michael Boyce-Jacino. Tracy Warren was appointed chairman.

- **Biovator AB**, of Stockholm, Sweden, signed a collaboration with **BASF**, of Ludwigshafen, Germany, for final development of in vitro test systems capable of identifying the potential of chemical compounds to induce allergic reactions in humans. Financial terms were not disclosed, but the deal includes a five-year BASF option of final product deliveries.

- **ISTA Pharmaceuticals Inc.**, of Irvine, Calif., said it submitted a supplemental new drug application to the FDA for once-daily XiDay (bromfenac ophthalmic solution), a topical nonsteroidal anti-inflammatory compound, as a treatment for ocular inflammation and pain following cataract surgery. The firm currently markets a twice-daily form of bromfenac ophthalmic solution 0.09 percent under

the brand-name Xibrom.

- **Ligand Pharmaceuticals Inc.**, of San Diego, said partner **GlaxoSmithKline plc**, of London, received a positive opinion for Revolte (eltrombopag/Promacta) from the European Medicines Agency's Committee for Medicinal Products for Human Use for the oral treatment of thrombocytopenia in adults with chronic immune thrombocytopenic purpura.

- **MediciNova Inc.**, of San Diego, and **Avigen Inc.**, of Alameda, Calif., said their respective stockholders have approved their merger agreement, in which Avigen will be paid \$1.24 per share in cash or convertible notes, which can be exchanged for MediciNova shares worth \$6.80 each, with MediciNova shelling out \$1.19 per share at the closing of the deal, and the other 5 cents per share will be paid on June 30 of next year. (See *BioWorld Today*, Aug. 24, 2009.)

- **Mesoblast Ltd.**, of Melbourne, Australia, reported preclinical data from its adult stem cell platform, showing that a single dose of the human mesenchymal precursor cells injected into mice with diabetes resulted in a significant increase in blood insulin levels and sustained reduction in blood glucose levels for the entire three-week period of follow-up. The stem cell treatment also induced a twofold increase in total numbers of pancreatic islets.

- **Millennium Pharmaceuticals Inc.**, of Cambridge, Mass., the oncology unit of Japanese drugmaker Takeda Pharmaceutical Co. Ltd., said that the FDA has approved a supplemental new drug application for Velcade, which expands the label to include long-term (median follow-up 36.7 months) overall survival data from the landmark trial known as VISTA (VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone). In addition, the label includes specific dosing recommendations for patients with hepatic impairment. The VISTA trial examined the use of Velcade-based therapy in patients with previously untreated multiple myeloma.

## Ambit

*Continued from page 1*

squeezed out of the picture.”

Astellas, of Tokyo, is still building its presence in cancer, under a five-year plan. “Ambit is one more piece of the picture,” Salka said. “We get to be part of that story.” Among Astellas’ recent deals in the space is the October alliance that gave San Francisco-based Medivation Inc. \$110 million up front for a Phase III prostate cancer drug. (See *BioWorld Today*, Oct. 28, 2009.)

Ambit’s second-generation FMS-like tyrosine kinase-3 inhibitor was developed by way of KINOMEScan profiling technology, and moved from initial chemistry to clinical candidate selection for IND-enabling studies in 18 months, the company said.

With Astellas, Ambit will develop AC220 for AML in patients who have the internal tandem duplication mutation in the FLT3 kinase, as well as other indications. Behind the compound are other candidates in the class, known among scientists as “flit threes,” for cancer and more, including autoimmune and inflammatory disorders, Salka said.

Responsibility for developing AC220 and others will be split along with costs between the firms in the U.S. and Europe, with Astellas taking full duties in other territories.

“This was very much part of the conversations with all of the companies – we were not interested in licensing the compound out,” Salka told *BioWorld Today*, and Ambit knew we “had to be willing to put up half” of the development costs in order to retain a share of the value later.

AC220’s Phase II trial is enrolling adult and elderly patients with relapsed/refractory AML that have the internal tandem duplication mutation in the FLT3 kinase, an indicator of a poor prognosis and decreased response to existing treatments, including chemotherapy and hematopoietic stem cell transplant.

“We will continue running the trials,” with help from a joint steering committee, he said. Enrollment at 100 sites in the U.S. and Europe is ahead of schedule so far, with three up and running and two more to be added this week. All sites are expected to be enrolled early next year.

The \$350 million in milestone payments from Astellas are all pre-commercial, rising as approval nears, but rewards if sales goals are met also come with the deal, as well as tiered, double-digit royalties. In the U.S., Ambit holds an option to co-promote under a 50/50 profit-and-loss-sharing arrangement.

AML has proven tricky for drug developers lately, especially given the FDA’s dim view of single-arm trials, deployed by some firms in an attempt to win accelerated approval for compounds against the disease in the elderly, with an eye to broadening the label later. (See *BioWorld Insight*, Dec. 21, 2009.)

FLT3s themselves have run into trouble. Frazer, Pa.-based Cephalon Inc.’s multikinase inhibitor lestaurtinib

(CEP-701), which hits FLT3 among other targets, fizzled this summer in a Phase III trial when combined with chemotherapy. Novartis AG, of Basel, Switzerland, had PKC412, a multi-kinase inhibitor with FLT3 activity that also failed in a Phase III combo trial. Cambridge, Mass.-based Millennium Pharmaceuticals Inc. (now part of Japanese drug maker Takeda Pharmaceutical Co. Ltd.) didn’t make it with MLN518, either.

None of that troubles Salka or, apparently, Astellas. AC220, he said, is the first FLT3 inhibitor that has shown single-agent efficacy “beyond the stray anecdote,” and achieved “complete shutdown of signaling of the receptor over the entire dosing period, as long as the patient stays on the once-a-day pill.”

Other compounds “got some modest to significant inhibition,” but their effect pulsed – function would return for 12 hours, leading up to the next dose, he said, crediting the Ambit technology with yielding potency that is tenfold higher. ■

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## OTHER NEWS TO NOTE

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• **Neurogen Corp.**, of Branford, Conn., was notified by Nasdaq that it has not regained compliance with the \$1 minimum bid price. The company has filed for a hearing, during which time its stock will continue to trade on Nasdaq. Neurogen expects its stock to continue trading through the expected close of its merger with San Diego-based **Ligand Pharmaceuticals Inc.** by the end of this year. (See *BioWorld Today*, Aug. 25, 2009.)

• **Somaxon Pharmaceuticals Inc.**, of San Diego, said it has scheduled a meeting with the FDA for Jan. 20 to discuss the complete response letter the firm received earlier this month for its new drug application for Silenor (doxepin) for the treatment of insomnia. Somaxon said it was seeking a pathway for potential approval of the NDA, focusing on alternatives that use the clinical data that have been submitted to the FDA to date. The firm said it would provide an update about its discussions with the FDA relating to the Silenor NDA promptly after the company has analyzed the feedback it receives at the meeting. (See *BioWorld Today*, Dec. 8, 2009.)

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## Eisai

*Continued from page 1*

acquire AkaRx any time before Jan. 8, 2010. (See *BioWorld Today*, Aug. 30, 2007.)

At the time, MGI saw AKR-501 as a good strategic fit for its pipeline.

The big biotech was marketing Aloxi (palonosetron hydrochloride) for chemotherapy-induced nausea and vomiting and Dacogen (decitabine) for myelodysplastic syndromes (MDS), so it had sales teams targeting hematology and supportive care. It was also planning to move into the acute care market with injectable anesthetic Aquavan, now known as Lusedra (fospropofol disodium).

All of those sales reps could one day come in handy when pushing AKR-501 for idiopathic thrombocytopenic purpura (ITP), an autoimmune disease involving reduced platelet count. But since AKR-501 was only in Phase II trials, MGI and AkaRx agreed on a deal structure that would allow the bigger firm to test the drug for a few years before committing to the acquisition.

Testing could not have advanced far when MGI was acquired by Tokyo-based Eisai for \$3.9 billion. (See *BioWorld Today*, Dec. 11, 2007.)

Yet Eisai kept working on AKR-501. Spokespersons from the Japanese firm were not immediately available for comment, but a press release said AKR-501 is now in Phase II for both ITP and thrombocytopenia associated with liver diseases. Additional trials in cancer chemotherapy-induced thrombocytopenia are planned, and Eisai has achieved clinical proof of concept in the ITP setting.

And so, with three weeks left before its option to acquire AkaRx was due to expire, Eisai announced its plans to exercise that option. The acquisition is expected to close by Jan. 8.

AKR-501 is advancing into a space that is far more crowded than it was when the molecule's development began. A few years ago, ITP was usually treated with surgery, glucocorticoids or intravenous immunoglobulin (IVIG) – treatments that were not always effective.

But in August 2008, Amgen Inc. gained FDA approval of Nplate (romiplostim), a weekly subcutaneous injection for treatment-failure ITP patients. The engineered therapeutic fusion protein stimulates a patient's bone marrow to produce platelets. (See *BioWorld Today*, Aug. 25, 2008.)

A few months later, Ligand Pharmaceuticals Inc. and GlaxoSmithKline plc gained FDA approval of Promacta (eltrombopag), a daily pill for ITP. (See *BioWorld Today*, Nov. 24, 2008.)

AKR-501's oral administration might give it an edge over Nplate, and the drug is a full agonist of c-Mpl rather than a partial agonist like Promacta, which may provide further differentiation. But by the time AKR-501 comes to market, its competition will be firmly entrenched.

Other biotechs developing ITP drugs include Rigel Pharmaceuticals Inc., which explored its oral syk kinase

inhibitor R788 in a Phase II ITP trial; Symphogen A/S, which has the anti-Rheuss D recombinant polyclonal antibody Sym001 in Phase II for ITP; and Immunomedics Inc., which is exploring its humanized anti-CD20 antibody veltuzumab for ITP. ■

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## CLINIC ROUNDUP

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• **Cardiome Pharma Corp.**, of Vancouver, British Columbia, said its Phase III European comparator study of vernakalant (I.V.) vs. amiodarone in acute conversion of atrial fibrillation met its primary endpoint. The study achieved statistical significance in demonstrating the superiority of vernakalant over amiodarone in the conversion of atrial fibrillation to sinus rhythm within 90 minutes of the start of drug administration. Overall data suggested that the drug was well tolerated in the study population, with no vernakalant-related deaths or cases of Torsades de Pointes. Cardiome partnered European rights to I.V. vernakalant to Whitehouse Station, N.J.-based **Merck & Co. Inc.** in April.

• **Clinuvel Pharmaceuticals Ltd.**, of Melbourne, Australia, said preliminary results from 36 patients with PLE, a recurrent seasonal UV-related skin disorder, showed that afamelanotide 20-mg implants revealed a trend toward reduction of characteristic dermal symptoms. Analysis of the physician's Global Severity Index during the 120 days and 150 days of seasonal treatment demonstrated a reduction in severity of symptoms over placebo.

• **Flamel Technologies SA**, of Lyon, France, started a Phase IIa trial of its Interferon alpha-2b XL, which is based on the company's Medusa platform for controlled-release biologics. The 84-patient trial will evaluate INF-alpha-2b XL in combination with ribavirin in genotype-1 chronic hepatitis C patients who are either naïve to treatment or are previously nonresponders to standard interferon therapy. The study will assess viral response, with a primary endpoint of viral load reduction at week four and at week 12. Investigators also will be looking at the percentage of patients achieving rapid virological response, defined as an undetectable viral load at week four, and early virological response, defined as a viral load reduction greater than 2 log at week 12.

• **PolyMedix Inc.**, of Radnor, Pa., completed the first two segments of a Phase Ib trial of PMX-30063, a small-molecule mimetic of host defense proteins, with data showing that administration of multiple doses of the drug at varying levels are safe and well tolerated. The first two segments included 56 healthy volunteers, who received up to five doses of either PMX-30063 or placebo. Further clinical development is planned for the initial indication of the drug as a broad treatment for *Staphylococcus* infections.

## Financings Roundup

*Continued from page 1*

critical for reviving the languishing *E. coli* program.

The company sold its Caprion Proteomics Inc. subordinated promissory note back to Caprion for an immediate cash payment of \$1.85 million. The promissory note was originally issued in July 2007 as part of the proceeds under the sale of its wholly owned proteomics business. Thallion will continue to retain its roughly 16 percent equity interest in Caprion.

Separately, Thallion and French firm LFB Biotechnologies have entered a deal worth a potential \$142.5 million to develop Shigamabs, monoclonal antibodies designed to bind specifically and exclusively to the Shiga toxin 1 and Shiga toxin 2 toxins secreted by STEC bacteria. The dual antibody approach enables Shigamabs to address any cases where one and/or the other Shiga toxin is present and also overcomes the inability of existing diagnostic technology to distinguish between cases caused by only one of the two toxins.

The companies have signed a letter outlining the terms of the agreement, but the actual definitive agreement to seal the deal is expected to be completed in the next four to six weeks.

Under the terms, Thallion would receive an up-front payment of about C\$2.3 million (US\$2.5 million) and about C\$150 million (US\$140 million) in additional payments plus tiered, double-digit royalties based on product sales.

LFB Biotechnologies will receive commercial rights to Shigamabs for Europe and South America, while Thallion retains the rights for North America and the rest of world. Thallion will retain primary responsibility for the conduct of the clinical program, whereas LFB Biotechnologies will be responsible for the manufacture and supply of Shigamabs for both clinical study and commercial sale.

"With a partner, now we can afford to move that program forward and not be at risk of running out of cash," Michael Singer, chief financial officer at Thallion, told *BioWorld Today*. "We are very excited to end 2009 on this foot," he said. The recent cash injections will extend the company's cash runway well into the future, said Singer, adding that he did not foresee any additional fundraising in the near term.

The company reported having just over \$12 million in cash in the third quarter. Year-end financial results are due in February.

Thallion has completed multiple preclinical studies and four Phase I trials evaluating the efficacy and safety of Shigamabs. The trials demonstrated that Shigamabs are

safe and well tolerated when administered both individually and in combination at various dose levels. No serious adverse events were experienced in any of the 50 healthy volunteers that have received the drug.

Thallion and LFB plan to move toward the start of a Phase II study of Shigamabs in South America.

STEC infections are primarily foodborne bacterial infections that affect about 314,000 people annually in the industrialized world. Shigamabs have been granted orphan drug status both in the U.S. and in Europe. There are no approved products available for the treatment of STEC infections.

Shares in Thallion (TO:TLN) were up C2 cents, or 22 percent, closing at C11 cents.

In other financing news,

- **Arrowhead Research Corp.**, of Pasadena, Calif., has raised about \$3.2 million in gross proceeds from a private placement of about 5 million units. Units were sold for 63.4 cents each, 12.5 cents higher than the 50.9 cents closing bid price of the company's common stock on Nasdaq Dec. 11, the date of the sale. Each unit consisted of one share of newly issued common stock and one warrant to purchase an additional share of common stock at an exercise price of 50.9 cents per share.

- **OctoPlus NV**, of Leiden, the Netherlands, has completed an equity raising of €4 million (US\$5.7 million) through a private placement of ordinary shares with new and existing investors. In addition, the company obtained a new credit facility of up to €2 million. The financings give the firm a financially secure future, the company said. In connection with the offering, OctoPlus said that it has obtained a new credit facility at more favorable conditions from Fortis Bank Nederland of up to €2 million, which replaces the company's existing credit facility.

- **Spectral Diagnostics Inc.**, of Toronto, and **BioMS Medical Corp.**, of Edmonton, Alberta, said that BioMS Medical and a syndicate of investors have invested \$14 million in Spectral to advance toraymyxin, a treatment for severe sepsis, toward regulatory approval and commercialization in the U.S. A pivotal U.S. trial is expected to start in the first half of 2010. In connection with the financing, BioMS and Spectral also agreed to enter a three-year \$3 million services agreement at closing, whereby BioMS will provide clinical, regulatory and capital market consulting services to Spectral. The transaction is expected to close in early February 2010. Spectral's board unanimously supports the proposed transactions and recommends that shareholders vote in favor of them. ■

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## Washington Roundup

*Continued from page 1*

shot up \$5.33 Friday, or 10.5 percent, to close at \$55.95.

Revlimid currently is approved in the U.S. in combination with dexamethasone as a treatment for multiple myeloma in patients who received at least one prior therapy.

Oppenheimer analyst Brian Abrahams predicted that maintenance use of Revlimid could add \$400 million in sales to Celgene's bottom line by 2013.

But Baird & Co. analyst Christopher Raymond was even more optimistic, surmising that with 5,000 U.S. patients receiving autologous stem cell transplants each year, with two years of treatment potential, additional revenues in the out years could reach up to \$900 million.

The NCI-funded trial, known as CALGB 100104/ECOG 100104, was conducted by a network of researchers led by the Cancer and Leukemia Group B, in collaboration with the Eastern Cooperative Oncology Group and the Blood and Marrow Transplant Clinical Trials Network, a network co-sponsored by the NCI and the National Heart, Lung and Blood Institute.

The study enrolled 568 multiple myeloma patients ages 18 to 70 who had received no more than 12 months of prior therapy and no prior transplant. All patients received autologous transplantation following a high dose of melphalan, a drug commonly used to treat multiple myeloma.

Of those, 460 patients with adequate organ function and no evidence of progressive disease were randomized about three months after transplant to receive Revlimid or placebo. Results showed that there was a 58 percent reduction of disease progression in patients receiving Revlimid as a maintenance therapy after transplant, which the NCI said was "highly statistically significant," compared with half of those on placebo whose disease worsened within 778 days, or nearly 26 months.

The NCI said that the study was the first Phase III trial to demonstrate a clinical benefit of Revlimid following transplant for multiple myeloma. Officials noted, however, that the trial has yet to show evidence of an overall survival benefit with Revlimid.

An FDA advisory panel last week gave the thumbs down to OSI Pharmaceuticals Inc.'s Tarceva (erlotinib) as a maintenance therapy in lung cancer, insisting that perhaps treating at progression might be better for that drug. (See *BioWorld Today*, Dec. 15, 2009, and Dec. 17, 2009.)

"To answer that question, survival becomes a critical endpoint," said Credit Suisse analyst Michael Aberman. Nonetheless, he insisted, the NCI study coupled with an earlier Revlimid trial "would lead to meaningful adoption in the maintenance setting."

### Import Blockers Got Big Drug Bucks

Senators who voted last week to block prescription drug importation legislation, which failed 51-48, received an average of \$85,812 in contributions over the past six

years from the drug industry – a 69 percent increase over the \$50,767 received by those who voted in favor of the measure, the bipartisan watchdog MAPLight.org reported.

The provision, offered by Sen. Byron Dorgan (D-N.D.) as an amendment to the Senate's health reform package, would have relaxed restrictions on imports from Canada and other highly developed countries. But 30 Democrats sided with 17 Republicans and one Independent to take down the measure.

MAPLight.org found that the Senate Democrats who voted against the legislation received an average of \$73,729 each from drugmakers over the past six years – 76 percent more than the \$41,894 received by Democrats who voted in favor of imports.

MAPLight.org's research previously has shown alignment of pharma campaign money and votes in Congress.

For instance, Democrats on the Senate Finance Committee who voted down a measure in September that would have required drugmakers to pay \$106 billion over 10 years in rebates aimed at closing the Medicare drug gap received 4.2 times more in campaign money from the industry than those who voted in favor of the measure. (See *BioWorld Today*, Sept. 28, 2009.)

### H1N1 Flu Vaccine Now Abundant in U.S.

Health officials last week said 100 million doses of the H1N1 flu vaccine have been shipped, with restrictions now lifted in most states.

"Many people have been patiently waiting their turn to get vaccinated, so our message is take advantage of the increased supply and get vaccinated as soon as you can," said Health and Human Services Secretary Kathleen Sebelius, who said she got her shot last Wednesday.

"We have a chance to lessen the impact or even prevent a big third wave when flu season really hits, and we need to seize that opportunity right now," she told reporters.

### NCI SBIR Grants \$11.5M in Bridge Awards

The National Cancer Institute Small Business Innovation Research Program (SBIR) last week announced \$11.5 million in Phase II Bridge awards to four small businesses, including Altor BioScience Corp.

Each of the awardees has raised substantial matching funds from investors. Bridge funding is aimed at helping small businesses overcome the funding gap known as the "valley of death" between the end of the SBIR Phase II award and the subsequent round of financing needed to advance a product or service toward commercialization, which officials said was "especially critical during these economic times."

Altor BioScience's award is intended to help advance the Miramar, Fla.-based biotech's bifunctional T-cell receptor-based immunotherapeutic directed against multiple types of cancer. The other three awardees in the round were device makers. ■

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BIO WORLD LOOKS AT TRANSLATIONAL MEDICINE

MONDAY, DECEMBER 21, 2009

PAGE 1 OF 2

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## Higher Levels of Leptin Protein Related to Higher Rates of AD

Persons with higher levels of leptin, a protein hormone produced by fat cells and involved in the regulation of appetite, may have an associated reduced incidence of Alzheimer's disease and dementia, according to a study in the Dec. 16, 2009, issue of the *Journal of the American Medical Association*.

Previous studies have shown that overweight and obesity in mid-life are associated with poorer cognitive function and an increased risk of dementia. And there has been evidence that leptin exerts additional functions on the brain outside the hypothalamus.

Researchers with the **Framingham Heart Study** and colleagues examined the relationship between measurements of plasma leptin concentrations and incidence of dementia and Alzheimer's disease. Plasma leptin concentrations were measured in 785 persons without dementia (average age, 79 years; 62 percent female), who were in the original Framingham study group (1990-1994). A subsample of 198 dementia-free survivors underwent volumetric brain magnetic resonance imaging between 1999 and 2005, approximately 7.7 years after leptin was measured. Two measures of brain aging were assessed: total cerebral brain volume and temporal horn volume, both of which are markers of early AD pathology and subsequent dementia risk. During a median follow-up of 8.3 years, 111 participants developed dementia; 89 of them were diagnosed with AD.

The researchers found that higher leptin levels were associated with a lower incidence of all-cause dementia and AD. The incidence of dementia decreased gradually across increasing levels of leptin: A person with a baseline leptin level in the lowest quartile group had a 25 percent risk of developing AD after 12 years of follow-up, whereas the corresponding risk for a person in the top quartile group was only 6 percent. Higher leptin levels also were associated with higher total cerebral brain volume. Lower temporal horn volume was not significantly related to leptin levels.

The findings are consistent with recent experimental data indicating leptin improved memory function in animals through direct effects on the hippocampus and strengthens the evidence that leptin is a hormone with a broad set of actions in the central nervous system, researchers said.

## Nanoprobes Hit Tumor Targets

Tiny nanoprobes have shown to be effective in delivering cancer drugs more directly to tumor cells – mitigating the damage to nearby healthy cells – and **Purdue Uni-**

**versity** research has shown that the nanoprobes are getting the drugs to the right cellular compartments. Researchers found that the nanoprobes, or nanorods, when coated with the breast cancer drug Herceptin, are reaching the endosomes of cells, mimicking the delivery of the drug on its own. Endosomes perform a sorting function to deliver drugs and other substances to the appropriate locations. The nanoprobes were inserted into live human tumor cells during laboratory testing. Using fluorescent markers to differentiate organelles, or subunits of cells, researchers were able to determine the number of nanoprobes accumulating in the endosomes, lysosomes and membranes of those cells. Researchers will next try to attach multiple drugs to a nanoparticle and track their distribution within cells. They also want to determine the timing of a drug's release from the nanoprobes after attaching to the tumor cells.

## Liver-Friendly Protein Found

A team of scientists from the **UC San Diego School of Medicine** and **Osaka University** in Japan have identified a protein switch that helps prevent liver damage, including inflammation, fibrosis and cancer. The findings suggested that a better understanding of how the protein, TAK1, works could lead to new insights into the development of liver disease and cancer. TAK1 is a kinase, a type of signaling protein involved in regulating various cell activities, including cell growth. Researchers have known that TAK1 activates two specific proteins, NF-kappaB and JNK, which are both involved in immunity, inflammation, programmed cell death and cancer. But NF-kappaB helps protect liver cells from dying and protects against cancer development. In contrast, JNK promotes cell death and cancer. However, it has been unclear whether TAK1 promotes or prevents the development of liver cancer. To find out, researchers created a mouse model in which liver cells lacked the gene *Tak1*, which makes the TAK1 protein. In a series of experiments, they found a high rate of liver cell death in young animals lacking TAK1. The animals' livers then went into overdrive, producing too many liver cells to make up for the loss and causing liver damage, including inflammation and fibrosis – liver scarring – and eventually, cancer.

### Let Us Know What You Think

Have comments? Questions? Complaints? We'd like to hear it all. Contact Managing Editor Glen Harris at [glen.harris@bioworld.com](mailto:glen.harris@bioworld.com), or (404) 262-5408.

Researchers said the study is the first to demonstrate the role of TAK1 in cancer development, and strongly suggested that the protein also contributes to cancer development in other organs. In addition, the liver cancer mouse model that the team developed is associated with sustained liver inflammation and fibrosis – key features of human liver cancer – and should be useful in investigating whether fibrosis influences liver cancer development.

## Cystic Fibrosis Screening

An increase in the number of screened carriers for cystic fibrosis (CF) was associated with a decrease in the number of children born with CF in northeast Italy, according to a study in the Dec. 16, 2009, issue of *JAMA*. Some studies have suggested that there has been a progressive decrease in the incidence of newborns with CF in some areas. Researchers with the **Cystic Fibrosis Center**, Verona Hospital in Verona, Italy, and colleagues evaluated the association between CF carrier screening and CF birth incidence in northeastern Italy. Since the early 1990s, a significant progressive decrease of CF birth rates has been recorded for this area. In this region, two different carrier detection approaches were identified: the western region, in which CF carrier tests are offered only to relatives of patients or to couples planning in vitro fertilization; and the eastern region, in which carrier testing is offered to relatives and carrier screening to infertile couples and to couples of reproductive age. A total of 779,631 newborns underwent CF neonatal screening between January 1993 and December 2007, of whom 195 had CF detected. During the study period, a time-related decrease in CF birth incidence was found, with an average annual percentage decrease of 0.16 per 10,000 neonates. The rate of decrease was greater in the eastern region (0.24 per 10,000) than the western region (0.04 per 10,000). In the western region, 2,559 carrier tests were performed; 314 carriers and nine carrier couples were detected. In the eastern region, 87,025 carrier tests were performed; 3,650 carriers and 82 carrier couples were detected. Carrier rate (number of carriers/number of tests) was 1/8.1 in the western region and 1/23.8 in the eastern region. The reduction appeared to be connected with the extensive use of mutation analysis in the general population, as the number of individuals screened with the CF carrier test progressively increased, CF birth incidence gradually and constantly decreased, the researchers wrote.

## Filling in the ALS Gap

Researchers at **UT Southwestern Medical Center** have found that a molecule produced naturally by muscles in response to nerve damage can reduce symptoms and prolong life in a mouse model of amyotrophic lateral sclerosis (ALS). As ALS kills nerves, the muscles they control begin to wither. The damaged muscles, however, can re-

innervate themselves by prompting healthy nerves to send new branches their way, like limbs in a damaged hedge filling in a gap. Researchers said skeletal muscles produce a molecule called microRNA-206 (miR-206) to serve as a chemical signal to steer the new nerve endings and maintain their interactions with muscles. But the research suggested that miR-206 can only work for so long. As nerves continue to die, there comes a point where the surviving nerves can no longer carry the load, and symptoms like muscle weakness appear. Because miR-206 only exists in skeletal muscle, a drug based on it might not affect other tissues, which would limit its risk of side effects, researchers said. They are working in collaboration with MiRagen Therapeutics to develop such a drug.

## Nitric Oxide and Septic Shock

Scientists at the research institute **VIB** and **Ghent University** in Flanders, Belgium, have found an unexpectedly for the treatment of septic shock, the major cause of death in intensive care units. By inducing the release of nitric oxide gas in mice with septic shock, researchers discovered that the animal's organs showed much less damage, while their chances of survival increased significantly. That's contrary to all expectations, since it is generally assumed that nitric oxide is responsible for the potentially lethal drop in blood pressure in septic shock. The research appeared in the *Journal of Experimental Medicine*.

## Benefits of Fyn

Scientists at the **University of Pennsylvania School of Medicine** have developed a new model of skin cancer based on the knowledge that a common cancer-related molecule called Src kinase is activated in human skin cancer samples. Previous work demonstrated that Src kinases are activated in human squamous cell carcinomas of the skin. In the proof-of-principle study, published in the December 2009 issue of *Cancer Research*, the authors found that genetically engineered mice expressing a K14-Fyn transgene develop precancerous lesions and invasive squamous cell carcinomas (SCCs) spontaneously in five to eight weeks. The study demonstrated that Fyn is a potent oncogene in skin. When Srcasm levels are raised in the mouse skin cancer model, tumor formation is dramatically inhibited showing that Srcasm functions as an anti-oncogene. The findings highlighted an important relationship between Fyn and Srcasm: Fyn encourages growth, while Srcasm inhibits it. Adding Srcasm back to the system lowers Fyn levels and restores order, researchers said. Analysis of human skin tumor samples confirmed that Srcasm levels are decreased and Src kinase activity is increased. The authors concluded that one potential means of combating skin cancer would be to inhibit Src kinases and/or increase Srcasm.

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