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PAGE 1 OF 7

## With FDA Hold Lifted, Repros Plans to Resume Dosing Study

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

Shares in Repros Therapeutics Inc. spiked Friday on news that the FDA had cleared the company to perform a new study of Proellex, lifting a long-standing clinical hold that had been placed on its drug candidate for uterine fibroids and endometriosis.

The single study will test five different doses of Proellex, one dose at a time, starting with 1 mg. The company expects to begin dosing in the new study this summer, and each dosing period is 10 weeks long.

Higher doses will not be studied, the company said, until it is confident that it is safe to proceed to the next dose and after the safety findings have been reported to the FDA, according to Repros.

Liver toxicity observed in Proellex studies led to the  
*See Repros, Page 4*

## *Financings Roundup*

## \$18M More in Hand, Inotek Sees Glaucoma Phase II Bid

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

Riding on positive results disclosed at a scientific meeting earlier this month with its lead glaucoma candidate INO-8875, Inotek Pharmaceuticals Corp., pulled down \$18 million in a preferred stock financing to push the eye-drop candidate through Phase II trials.

Data unveiled at the Association for Research in Vision and Ophthalmology annual meeting in Fort Lauderdale, Fla., showed adenosine-I agonist functions as an enhancer of outflow through the trabecular meshwork, the main pathway used by healthy eyes in elderly people.

Protein debris clogs the meshwork with age, and some patients fail to respond to approved glaucoma products, so their intraocular pressure worsens. INO-8875 could be  
*See Financings Roundup, Page 5*

## FDA Panel Unanimously Backs Novartis Oral MS Drug Gilenia

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

WASHINGTON – An FDA panel has unanimously backed approval of Novartis AG's Gilenia (fingolimod), a first-in-class sphingosine-1-phosphate (SIP) receptor modulator, to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability in patients with relapsing forms of multiple sclerosis, despite concerns about adverse cardiovascular and visual effects.

The FDA's Peripheral and Central Nervous System Drugs Advisory Committee, however, also voted 20 to 5 Thursday that Basel, Switzerland-based Novartis be required to study a lower dose of Gilenia, but agreed such examination could come postapproval.

*See Novartis, Page 6*

## NEW CO NEWS

## Membrane-Disrupting Peptides Seek and Destroy Cancer

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

With \$15 million of venture funding in its pockets and technology licensed from Louisiana State University's Pennington Biomedical Research Center, Esperance Pharmaceuticals Inc. is advancing through early clinical trials with cancer-targeted membrane disrupting peptides.

Hector Alila, president and founder of the Baton Rouge, La.-based start-up, explained that each drug candidate consists of two parts: a binding moiety and a payload of

*See Esperance, Page 7*

**Don't miss this week's *Bench Press*, inserted in this issue.**

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*Washington Roundup***Drugmakers, FDA Unify to Share Alzheimer's Data****By Donna Young  
Washington Editor**

WASHINGTON – A cadre of drugmakers, including Genentech Inc. and Forest Laboratories Inc., has agreed to share data on investigational Alzheimer's disease drugs in a first-of-its-kind database on brain disease, which will be made available to qualifying researchers.

The effort, which is being funded in part by the FDA, is aimed at speeding development of new therapies and preventions for neurodegenerative diseases by allowing researchers to more efficiently design clinical trials.

Study data for products targeting other neurodegenerative diseases, such as Parkinson's disease, are expected to soon be added to the Coalition Against Major Diseases (CAMD) database, which will be overseen by the government-funded nonprofit Critical Path Institute.

CAMD is a consortium of drug and biologic manufacturers, research foundations, patient advocacy groups and government advisers from the FDA, the European Medicines Agency, the National Institute of Neurological Disorders and Stroke and the National Institute on Aging.

Other manufacturers that are part of the coalition are AstraZeneca plc, Bristol-Myers Squibb Co., Eli Lilly and Co., Roche AG, GlaxoSmithKline plc, Johnson & Johnson, Novartis AG, Pfizer Inc. and Sanofi-Aventis Group AS.

Joshua Sharfstein, principal deputy commissioner at the FDA, said the agency is "strongly committed" to the CAMD effort.

**NIH Approves ACT Stem Cell Line**

The National Institutes of Health Friday approved Advanced Cell Technology Inc.'s MA135 human embryonic stem cell (hESC) line for federal funding.

ACT has seven other hESC lines awaiting the NIH's OK for use with federal funds, five of which the company noted

**Stock Movers**

06/11/10

<u>Company</u>	<u>Stock Change</u>
NASDAQ Biotechnology	+1.23%
Angiotech Pharmaceuticals Inc.	+18.3%
Repros Therapeutics Inc.	+15.9%
Sequenom Inc.	+8.4%

*(Biotechs showing significant stock changes Friday)*

were produced without embryo destruction using the Worcester, Mass.-based firm's single-blastomere "embryo-safe" technology. (See *BioWorld Today*, Feb. 23, 2010.)

The company said having federal funding available for its hESC lines could accelerate ACT's clinical activities.

"This approval is a watershed moment for the company, because it provides the company with the opportunity to pursue nondilutive federally funded research programs utilizing a stem cell line derived solely by technology that we deployed," said CEO William Caldwell, adding that he was "optimistic" ACT would secure approval for the additional lines.

ACT currently has an investigational new drug application under review at the FDA for a Phase I/II trial using its MA09 single-blastomere line to treat Stargardt disease, a genetic condition and the leading cause of juvenile blindness in the U.S.

That IND currently is on hold, and MA09 is one of ACT's lines awaiting the NIH's approval.

Since last December, the NIH has added more than 100

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## Washington Roundup

*Continued from page 2*

hESC lines to its federal funding registry. (See *BioWorld Today*, Dec. 3, 2009, Jan. 25, 2010, April 5, 2010, and April 29, 2010.)

### FDA Warns Pfizer about Tardy Reports

The FDA in a 12-page letter warned Pfizer Inc. about failing to properly submit postmarketing adverse drug reports to the agency.

The New York-based drug giant neglected to report within the required 15 days serious adverse events related to several drugs, including its cholesterol-lowering drug Lipitor (atorvastatin), regulators said in the May 26 letter obtained last week by *BioWorld Today*.

In fact, the FDA noted that certain adverse event reports had not been submitted to the agency until after they were identified last year by FDA inspectors.

Pfizer also failed to submit 15-day alert reports about serious adverse visual events related to Viagra (sildenafil), and had misclassified or downgraded reports to nonserious "without reasonable justification," the agency asserted.

The company also failed to promptly investigate and document adverse visual events reported to the firm about Viagra, the FDA stated.

From March 2006 to June 2009, Pfizer had been late submitting 5,066 15-day alert reports containing serious and unexpected adverse events involving drugs such as

Lipitor, Zithromax (azithromycin), Norvasc (amlodipine) and Prostin VR (prostadil), the agency said.

Regulators also scolded Pfizer for not having adequate written procedures for ensuring adverse drug experiences are correctly identified, assessed and reported to the FDA.

In a statement, Pfizer said it would continue to work closely with the FDA to address the issues to the agency's "full satisfaction and to assure optimal surveillance and reporting of postmarketing adverse events."

The company, which insisted patient safety was of "primary importance," said it was "committed to full compliance and timely and accurate" adverse event submissions.

### First Indian-American Poised to Lead NSF

President Obama last week formally nominated Subra Suresh, dean of the School of Engineering at the Massachusetts Institute of Technology, to be the director of the National Science Foundation.

If approved by the Senate, Suresh would be the first-ever Indian-American to lead the NSF, a federal agency created by Congress in 1950 to advance the progress of science in the U.S.

Suresh first joined MIT in 1993 as a professor of materials science and engineering. He holds a bachelor's degree from the Indian Institute of Technology in Madras, a master of science from Iowa State University and a doctorate of science from MIT. ■

## OTHER NEWS TO NOTE

- **Bionovo Inc.**, of Emeryville, Calif., reported preclinical results identifying the three classes of genes regulated by estrogen receptor beta and demonstrating that those genes are regulated by a different mechanism than ERα. Those data, which were published in the *Journal of Biological Chemistry*, could help researchers identify and select additional compounds for treating breast cancer.

- **BioTime Inc.**, of Alameda, Calif., organized a new subsidiary, OrthoCyte Corp., to develop therapeutics based on stem cell technology to treat injuries and disorders affecting the musculoskeletal system, including therapeutics aimed at regenerating bone, cartilage, tendons and ligaments. BioTime will transfer certain patents and license certain technology to OrthoCyte for use in the field of orthopedics.

- **Cubist Pharmaceuticals Inc.**, of Lexington, Mass., said it will oppose a motion filed by **Teva Pharmaceutical Industries Ltd.**, of Petach Tikva, Israel, to add a new defense in the patent litigation between the two firms. Teva is seeking to amend the answer to allege that U.S. Patent Nos. 6,468,967 and 6,852,689 are unenforceable due to

inequitable conduct. Cubist filed the suit alleging infringements on patents related to antibiotic Cubicin (daptomycin). (See *BioWorld Today*, April 13, 2010.)

- **Furiex Pharmaceuticals Inc.**, of Morrisville, N.C., said **Takeda Pharmaceutical Co. Ltd.**, of Osaka, Japan, received pricing approval in Japan for DPP-4 inhibitor Nesina (alogliptin) in Type II diabetes, which triggered a \$7.5 million milestone payment to Furiex.

- **Gilead Sciences Inc.**, of Foster City, Calif., received notice that **Lupin Ltd.**, of Mumbai, India, submitted an abbreviated new drug application for a generic version of Ranexa (ranolazine extended-release tablets). Lupin has alleged that all 10 patents associated with Ranexa are invalid, unenforceable and/or will not be infringed by Lupin's product. Gilead has 45 days from receipt of the notice to commence a patent infringement lawsuit, which would restrict the FDA from approving Lupin's ANDA for up to 30 months or until a district court decision adverse to Gilead, whichever occurs first.

- **ImmunoCellular Therapeutics Inc.**, of Los Angeles, said the FDA granted orphan drug designation for ICT-107, a dendritic cell-based cancer vaccine candidate targeting glioblastoma multiforme. That status would guarantee seven years of marketing exclusivity upon approval. A Phase II study of ICT-107 is slated for the second half of this year.

## Repros

*Continued from page 1*

clinical hold that was placed on the product nearly a year ago. (See *BioWorld Today*, Aug. 4, 2009.)

Joseph Podolski, Repros president and CEO, indicated that the company has the funds to conduct the new Proellex study, which he said could take about 18 months to complete testing of all five doses. "This study isn't that expensive," he said.

Although testing will begin with the 1-mg dose, drug activity is unlikely to be seen until at least the 6-mg dose, with more robust activity likely to be seen at 12-mg strength, Podolski told *BioWorld Today*.

The goal of the new study is to see whether low-dose Proellex can reliably induce amenorrhea (the absence of a menstrual period) in female study patients, since bleeding is one of the symptoms of uterine fibroids and endometriosis.

In a Phase II U.S. trial of the 12.5-mg and 25-mg doses, a significant percentage of women with uterine fibroids stopped menstruating. Those two doses achieved highly statistically significant results when compared to placebo. In the new study, patients will be monitored for changes in menstrual bleeding patterns and ovulation as well as changes in endometrial thickness.

Each of the five doses (1 mg, 3 mg, 6 mg, 9 mg and 12 mg) will be compared to placebo with weekly assessments of liver function.

The FDA requires that an independent drug safety monitoring board be established for the new study and that patients be clearly informed about the liver toxicity previously seen with Proellex.

The Woodlands, Texas-based Repros believes the toxicity observed with the drug was dose-dependent and that the lower doses would be outside the range where toxicity was previously seen (at the 25-mg and 50-mg doses).

If a safe and effective dose is identified in the new study, and the FDA is in agreement, Repros anticipates that it will be able to proceed with large efficacy trials for both uterine fibroids and endometriosis. But the larger trials would be contingent on the company having the available fund or being able to out-license Proellex to a major pharmaceutical company, Repros said.

Repros already was running low on cash when it stopped dosing patients in its Proellex trials after finding significant increases in liver enzymes with 25-mg and 50-mg doses. Then it faced a lawsuit on behalf of shareholders, alleging that the company issued false and misleading press releases regarding the results of Proellex clinical trials.

Late last year, the company reached a settlement with its major creditors for the large majority of the debt incurred associated with the previously suspended Proellex clinical program, which allowed the company to continue its other drug program, Androxal, for the immediate term. Androxal is in Phase II for hypogonadism and Type II diabetes.

Results from a small exploratory study reported last year showed that Androxal restored sperm counts in men receiving testosterone treatments for hypogonadism, in which the body does not produce enough of the hormone testosterone. (See *BioWorld Today*, Oct. 8, 2009.)

At the end of March, Repros had cash and cash equivalents of about \$974,000. In its annual report for the year ended 2009, an independent accounting firm stated that there was substantial doubt about Repros' ability to continue.

Repros has since generated additional funds from the direct sales of shares of common stock into the capital market from its shelf registration statement, with Ladenburg Thalmann as placement agent. To date, the company has raised more than \$5.5 million since it has begun the trading program. No warrants or discounted shares have been offered or issued as part of the "at the market" financing.

Matthew Kaplan, an analyst for Ladenburg Thalmann who has a neutral rating on the company, told *BioWorld Today* that while Repros has the cash to conduct the low-dose study, based on his read of public documents, the company does not have the funds to take Proellex to market, if all goes well in testing.

But if the company is able to define a safe and effective dose in the study without a liver toxicity signal, then that could make the company attractive to a potential partner.

PregLem SA's uterine fibroid candidate Esmya (ulipristal acetate) recently hit its endpoints in the first of two Phase III trials and, if the second study is equally successful, the small Swiss firm aims to file for European approval by the end of this year. That product is partnered with France's HRA Pharma. (See *BioWorld Today*, May 19, 2010.)

Neurocrine Biosciences reported another positive Phase II study of elagolix in women with endometriosis, this time clearing a major hurdle by confirming that new study endpoints, developed with input from the FDA, were sensitive enough to detect symptom improvements. (See *BioWorld Today*, May 26, 2010.)

Repros shares (NASDAQ:RPRX) were up 8 cents, or 15.9 percent Friday, closing at 56 cents. ■

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## OTHER NEWS TO NOTE

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• **RXi Pharmaceuticals Corp.**, of Worcester, Mass., said its RNAi therapeutic strategy will focus on two core areas: dermatology, in which the firm is developing an anti-scarring indication, and ophthalmology, in which it has a program in retinal disorders. The company will explore additional indications through preclinical development in the areas of neurology and oncology that are of strategic interest and might provide partnership opportunities. Other indications could go forward in instances where programs are funded by potential partners.

## Financings Roundup

*Continued from page 1*

used along with such agents as New York-based Pfizer Inc.'s top-selling glaucoma compound, the prostaglandin analogue Xalatan (latanoprost).

Paul G. Howes, president and CEO of Inotek, noted that Xalatan goes off patent next year and as many as 50 percent of glaucoma patients need more than one medicine, so there's been particular interest in INO-8875 as a combination therapy, but Lexington, Mass.-based Inotek will be trying its candidate as a stand-alone, too.

"The best outcome is superiority to a prostaglandin as a monotherapy," he said. INO-8875 targets the primary pathway, which accounts for about 70 percent of the trouble in glaucoma, whereas prostaglandin analogues work in the uveoscleral pathway (managing the outflow of aqueous humor), which accounts for the rest.

Beta blockers, designed to reduce the inflow of aqueous humor, started the modern age of glaucoma treatment in the early 1980s with Timoptic (timolol), from Merck & Co. Inc., of Whitehouse Station, N.J., where Howes worked for many years. Then came the carbonic anhydrase inhibitors such as Trusopt (dorzolamide), also from Merck, launched in 1995.

The latter class is not as effective as prostaglandin analogues, and must be dosed three times per day, often in combination with other therapies.

Inotek's Phase II experiments will first establish the best dose, and then test INO-8875 when added to what's available commercially. Trials will be done in single eyes for 14 days.

The latest financing "will certainly get us as far as we need to get, and at that point we can make a decision on whether we want to do the ultimate Phase II trial – two eyes and 28 days," Howes told *BioWorld Today*.

Decisions will be made near the end of the year. Venture capital backers could decide to "load up the tank again" so that Inotek could continue without a partner, possibly even going into Phase III trials that could last a year to 18 months.

"You'd probably have an active comparator instead of placebo" in Phase III, Howes said, adding that beta blockers historically were the FDA's gold standard in such experiments but the field has changed. "We would probably use a prostaglandin," he said.

Going it alone is "at least manageable for a VC-funded company" in glaucoma, "one of the few [eye diseases] that has a surrogate marker that is the basis for approval – the ability to lower intraocular pressure," Howes said. Other areas of ophthalmology, such as retinal disease, have regulatory pathways that are less simple and certain, he said.

Devon Park Bioventures, a new investor, led the latest round of financing with participation from existing investors Rho Ventures, Care Capital, Pitango Venture Cap-

ital, MedImmune Ventures and Bio\*One Capital. John Leaman, principal with Devon, has joined Inotek's board.

In other financing news:

- **Ensycse Biosciences Inc.**, of Houston, is receiving up to \$1.5 million in funding from the State of Texas Emerging Technology Fund for the development of single walled carbon nanotube therapeutics for the delivery of siRNA. The funds are expected to support preclinical development, hire additional staff and move the technology into the clinic.

- **Harbor BioSciences Inc.**, of San Diego, closed its previously announced sale of approximately \$2.06 million of its common stock and warrants in a registered direct offering, issuance and sale to select investors, pursuant to a shelf registration. The shares of common stock and warrants were sold in units, with each unit consisting of one share of common stock and a warrant to purchase 0.6 shares of common stock. The purchase price per unit was 35 cents. ■

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## OTHER NEWS TO NOTE

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- **Trojan Technologies USA**, a company recently formed by Verdant Ventures Advisors LLC, completed a licensing agreement with **Trojantec Ltd.**, of London, under which Trojan was granted exclusive right to commercialize its Antennapedia protein transduction technology within the field of prevention, diagnosis and/or treatment of infectious diseases. Financial terms were not disclosed.

- **ViroStatics srl**, of Sassari, Italy, formed a partnership with **Vichem Chemie Ltd.**, of Budapest, Hungary, to identify, synthesize, screen and develop next-generation Antiviral HyperActivation Limiting Therapeutics in HIV/AIDS and other chronic diseases. Financial terms were not disclosed.

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## CLINIC ROUNDUP

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- **Aastrom Biosciences Inc.**, of Ann Arbor, Mich., said full results from the Phase IIb RESTORE-CLI trial testing the firm's autologous tissue repair cells (TRCs) showed that the study reached statistical significance on amputation-free survival in patients with critical limb ischemia. The company previously reported top-line data from an interim analysis showing that the TRCs were more effective than placebo in a composite efficacy endpoint assessing time to first occurrence of treatment failure, defined as major amputation, all-cause mortality, doubling in wound size and de novo gangrene. Data were presented at the Society for Vascular Surgery meeting in Boston.

## Novartis

*Continued from page 1*

If it wins the FDA's OK, with a decision expected in September, Gilenia potentially could be the first oral drug on the U.S. market to treat multiple sclerosis.

"Neurologists clearly want an oral option" for patients with multiple sclerosis, noted Leerink Swann analyst Joshua Schimmer.

Given the dissatisfaction with the so-called injectable ABCR drugs – Biogen Idec Inc.'s Avonex (interferon beta-1a), Bayer AG's Betaseron (interferon beta-1b), Teva Pharmaceutical Industries Ltd.'s Copaxone (glatiramer acetate) and EMD Serono Inc.'s Rebif (interferon beta-1a) – and fears over progressive multifocal leukoencephalopathy (PML) with Biogen's Tysabri (natalizumab), "we are starting to see Gilenia as a very competitive player and probably a greater threat in the MS space than most appreciate," Schimmer said.

Gilenia acts as a functional antagonist of the SIPI receptor on lymphocytes, inducing its uncoupling and internalization. Under normal circumstances, T-cells selectively require SIPI activation for emigration from the thymus, and both T- and B-cells require this receptor to egress from peripheral lymphoid organs.

The internalization of SIPI renders those cells unresponsive to SIP, depriving them of the obligatory signal to egress from lymphoid organs and recirculate to peripheral inflammatory tissues. That effect results in a dose-dependent reduction of the peripheral lymphocyte count.

Gilenia was first developed for the prevention of acute rejection after renal transplantation in combination with cyclosporine A and corticosteroids.

But due to Gilenia's inability to show advantages over the standard of care, the renal transplantation program in nearly 2,300 patients, which included two Phase III studies, was discontinued and subsequently shut down in February 2008.

The clinical program for Gilenia in multiple sclerosis was initiated in 2003 based on preclinical data showing efficacy in animal models, with an investigational new drug application submitted in May 2005.

In Phase III studies, which involved more than 2,800 patients, Gilenia demonstrated a reduction in the frequency of relapses and a reduction in the risk of disability progression relative to placebo.

The drug also reduced relapse and MRI activity measures compared with Avonex.

But the FDA raised concerns about adverse cardiovascular effects with Gilenia, especially given the known effect of SIP modulation on heart rate.

The most common cardiac events were dose-related bradycardia and atrioventricular block, which had an onset within the first six hours after the initial dose of Gilenia. Regulators also noted that there was an excess of cardiovascular deaths in renal transplant studies at the 5-mg/day dose.

There also was a dose-related increase in the incidence

of macular edema, with four cases reported with Gilenia 1.25-mg/day and one case at the 0.5-mg/day dosage. Four additional cases of macular edema-related events were reported in Novartis' ongoing study 2309, with two of those patients receiving Gilenia 1.25-mg/day and one on the 0.5-mg/day dosage.

One case was serious enough to warrant ocular surgery to repair a macular hole, but regulators noted that the patient had a reasonably good outcome, with visual acuity at 20/40 in the affected eye six months after surgery.

Novartis, which licensed the rights of Gilenia from Mitsubishi Tanabe Pharma Corp., has been in a race with Geneva, Switzerland-based Merck Serono AG, of a division of Merck KGaA, to be the first on the market with an oral multiple sclerosis medication. Just last week, Merck Serono had resubmitted a new drug application for cladribine tablets in reducing relapses in patients with relapsing forms of multiple sclerosis after receiving a refuse-to-file letter in November from the FDA.

Cambridge, Mass.-based Biogen also is developing an oral multiple sclerosis drug, BG-12, which began Phase III testing in 2007.

Even if Gilenia gains approval this fall as expected, and Avonex fails to provide any further market growth, Biogen can preserve its leadership role in multiple sclerosis by identifying a patient population at low risk for PML with Tysabri and by bringing BG-12 to the market, Leerink's Schimmer argued. ■

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## CLINIC ROUNDUP

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• **Allos Therapeutics Inc.**, of Westminster, Colo., said updated data from an ongoing Phase I trial of Folutyn (pralatrexate) in relapsed or refractory cutaneous T-cell lymphoma showed that 10 of 22 evaluable patients (45 percent) showed a response to treatment. Of the patients who received Folutyn at the optimal dose or higher, 18 of 34 patients (53 percent) achieved a response, including one complete response and 17 partial responses. In a subgroup analysis, responses to the drug were observed in patients who had failed prior systemic therapies, including 10 of 24 patients (42 percent) who had failed oral bexarotene, four of 10 (40 percent) methotrexate failures, seven of 20 (35 percent) of HDAC inhibitor failures and four of 17 (24 percent) of interferon failures. Data were presented at the Congress of the European Hematology Association meeting in Barcelona, Spain.

• **Bristol-Myers Squibb Co.** and **Pfizer Inc.**, both of New York, said they agreed to stop the Phase III AVERROES trial of anticoagulant apixaban in patients with atrial fibrillation because a predefined interim analysis revealed clear evidence of a clinically important reduction in stroke and systemic embolism compared to aspirin in AF patients considered intolerant of or unsuitable for vitamin K antagonist therapy.

## Esperance

*Continued from page 1*

membrane disrupting peptides.

Cancer cells are more negatively charged than normal cells, and Esperance's peptides are positively charged, providing a natural attraction. But Alila said a higher concentration of drug is needed to trigger lysis, which is where the targeting moiety comes into play.

For now, Esperance is focused on targets on the surface of the cancer cell membrane, which means the drug does not have to be internalized by the cell to exert its membrane-disrupting mechanism of action.

"We can target anything on the surface," Alila said, although he added that the technology also potentially could be used to target an intracellular membrane such as that of the mitochondria.

Additionally, unlike chemotherapy, Esperance's peptides are not toxic. Alila explained that targeted chemotherapy drugs enter into a cell and release their toxins, but once the cell is destroyed, the toxins circulate through the body, causing side effects. Esperance's peptides destroy the cancer cell, but the lysis process releases enzymes that then destroy the peptides, preventing off-target activity.

And while chemotherapy targets only dividing cells, Esperance's compounds have been shown to kill both dividing and nondividing cells, including those that are resistant to chemotherapy.

Lead product EP-100 targets luteinizing hormone-releasing hormone (LHRH) receptors, which are overexpressed in cancers of the breast, prostate, ovary, endometrium, testicles, pancreas, colon, lung, liver and cervix. In preclinical studies, the drug destroyed LHRH receptor overexpressing OVCAR-3 cells within an hour.

An open-label, multicenter, dose-escalation Phase I trial in LHRH-overexpressing solid tumors started last August, and Esperance expects to determine an optimal dose by the end of this year. The Phase Ia portion of the study will then roll into a larger Phase Ib portion, with final data expected by the end of 2011.

Behind EP-100, Esperance is working on EP-302, which targets the cancer-associated protein nucleolin. Preclinical data were presented at the American Association for Cancer Research annual meeting this spring, demonstrating that EP-302 destroyed nucleolin-expressing cancer cells within one hour when tested in vitro in 20 human cancer cell lines.

In vivo studies showed that the drug resulted in significant tumor regression and improved survival in mice with PC-3 xenografts. Esperance expects to start investigational new drug application-enabling studies next year.

Alila said Esperance has other candidates in earlier stages of development.

And for each drug candidate, the company is developing a companion diagnostic to ensure that the patients

enrolled in its trials actually overexpress the target.

Esperance was founded in 2005 when membrane-disruption research at Pennington caught the eye of investors Louisiana Fund I LP, Themelios Ventures Partners LP and Research Corp. Technologies Inc. They contributed \$9 million to a Series A round in 2006, but Alila said the company didn't really become operational until 2007, when he came on board.

Alila set about building up Esperance, which now has nine employees and works out of the Louisiana Emerging Technology Center incubator. He also raised \$6 million in a Series A-I round in 2008 from the firm's existing investors as well as some individual investors.

That money will allow Esperance to complete its ongoing Phase Ib trial with EP-100. "Then we will decide whether to exit or raise additional funds," Alila said. For now though, the company remains focused on "advancing through pre-clinical and clinical studies," he said. ■

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## CLINIC ROUNDUP

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• **Cell Therapeutics Inc.**, of Seattle, said exploratory analyses of the pivotal PIX301 trial of Pixuvri (pixantrone dimeleate) in relapsed or refractory, aggressive non-Hodgkin's lymphoma showed that patients who achieved a complete response to Pixuvri had up to a 63 percent probability of being alive at 24 months compared to a 20 percent probability for patients treated with comparator agents. The study showed a 21 percent improvement in overall survival for all patients who received Pixuvri that was independent of factors known to influence survival such as prior Rituxan (rituximab, Genentech Inc./Roche AG and Biogen Idec Inc.) use, international prognostic index score, prior stem cell transplant, baseline level of LDH or refractory status based on univariate Cox regression analyses of survival. Data were presented at the Congress of the European Hematology Association meeting in Barcelona, Spain.

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BIO WORLD LOOKS AT TRANSLATIONAL MEDICINE

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## Avastin Risk of Protein Loss Greater Than Expected: Study

Cancer patients treated with the chemotherapy agent bevacizumab (Avastin, Genentech Inc.) may be at an increased risk of severe loss of protein from the kidney into the urine that can lead to significant kidney damage and can compromise the efficacy of cancer treatment.

That's the conclusion from a study of more than 12,000 patients by Shenhong Wu and colleagues at **Stony Brook University Medical Center**. Their findings were reported online June 10, 2010, in the *Journal of the American Society Nephrology*.

Previous research has indicated that treatment with bevacizumab can lead to urinary protein leakage (proteinuria) and kidney damage, but the overall risk associated with the drug and patient risk factors was unknown. Bevacizumab blocks a protein called vascular endothelial growth factor, thus inhibiting the production of new blood vessels around tumors.

Wu said the new research that bevacizumab "significantly increases the risk of proteinuria fourfold, and additional risk factors may include tumor type and higher drug doses. Patients with the renal cell carcinoma . . . had the highest risk, with a cumulative incidence of more than 10 percent," he added, "and the incidence among patients who received higher doses was more than twice that of those receiving lower doses."

Wu and colleagues analyzed published data from 16 studies nationwide comprising 12,268 patients with a variety of tumors, including breast, pancreatic and kidney cancers.

Severe proteinuria occurred in 2.2 percent of patients taking bevacizumab.

Compared with patients taking chemotherapy alone, patients taking bevacizumab combined with chemotherapy had a 4.79-fold increased risk of developing severe proteinuria and a 7.78-fold increased risk of developing nephrotic syndrome, a group of symptoms including protein in the urine, low blood protein levels, high cholesterol levels, high triglyceride levels and swelling.

## New Modes of Alzheimer's Treatment

Researchers have discovered how mutations in the presenilin 1 gene cause early-onset Alzheimer's disease. The finding, reported online in the journal *Cell*, opens the door to developing treatments for AD and for the more common, late-onset form that develops later in life.

The presenilin gene is most commonly associated with

the early onset familial form of Alzheimer's, which runs in families and can strike people in their 30s.

The gene was discovered 15 years ago, but until now no one understood how mutations in the gene caused the disease.

The researchers in the departments of psychiatry and cell biology at **NYU Langone Medical Center** discovered that the presenilin 1 gene performs a crucial biological function that enables cells to digest unwanted proteins and is essential for brain cell survival. The mutations, they reported, disrupt this cellular protein-recycling process, killing nerve cells.

In mouse models of Alzheimer's disease and in skin cells of patients with Alzheimer's disease caused by presenilin mutations, the researcher said they observed that the ability to break down and reuse normal proteins and to remove potentially toxic damaged proteins and organelles is severely impaired. The impairment can kill nerve cells, and the loss of neurons does not appear to be dependent on amyloid beta, the plaque-forming protein found in the brains of patients.

While most of the drug development for Alzheimer's has focused on removing amyloid, the new findings suggested that there are alternative pathways that can be targeted as well. For example, therapies could be aimed at repairing the cellular mechanism that eliminates toxic proteins before they damage the brain, the scientists said.

## Sialidase Promotes Nerve Growth

Researchers at the **Johns Hopkins University School of Medicine** showed that treating injured rat spinal cords with an enzyme, sialidase, improves nerve regrowth, motor recovery and nervous system function.

The team built upon earlier research where they discovered that sialidase treatment improved the growth of nerves into a graft.

Mimicking injuries that often result from automobile accidents where vertebra shift and pinch the spinal cord, severing the long spinal nerve axons, they treated rats after a spinal cord impact injury by injecting sialidase directly to the injury site.

Rats with lower-back impact injury – severe enough

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to lose hind-limb function – were injected with sialidase directly over the spinal cord immediately following injury.

The researchers then implanted into each rat a small pump that delivered a steady stream of sialidase directly to the injury over the course of two weeks. They then let the rats recover for another three weeks before assessing the degree of recovery.

Using a well-established, 21-point scale where zero represents paralysis and 21 is normal function, the team of researchers assessed treated and untreated rats for a range of functions. The initial injury rendered all rats to score below four, and all rats, treated or not, recovered somewhat by the end of two weeks.

By the end of five weeks after injury most untreated rats scored 12 or less, while most treated rats scored better than 15.

They also found that treated animals had improved blood pressure control.

Looking at the nerve ends under a microscope they found that treated nerves showed an increased number of “sprouted” nerve ends.

The research was published in the early edition of the *Proceedings of the National Academy of Sciences*.

## HIV Protein in 3D

Researchers at the **University of Iowa Carver College of Medicine** and **University of Nebraska Medical Center** have created a three-dimensional picture of an important protein that is involved in how HIV is produced inside human cells.

The picture may help researchers design drugs that can prevent HIV from reproducing.

The research team combined expertise in protein chemistry and X-ray crystallography – a technique for observing protein structures – to produce the first crystal structure of the HIV protein called Tat. The structure showed Tat attached to the human protein that the virus hijacks during infection.

The structure showed how Tat latches on to that particular human protein and how the interaction alters the shape of the human protein. The study was published in the June 10, 2010, issue of the journal *Nature*.

## Mechanism of Membrane Transport

Scientists from **Columbia University Medical Center** and **Weill Cornell Medical College** have outlined the molecular mechanism of membrane transport. The research showed how a protein transforms its shape to transport substances across the cell membrane to regulate transmission of the brain's messages across the synaptic gap from one neuron to another.

Because widely used medications for depression modulate this transport process by binding to the transporters,

the new findings help explain how the medications work, and the way in which stimulants like cocaine and amphetamine produce their effects, the scientists said.

This new understanding should also prove useful in the development of more targeted medication therapies for anxiety, depression, schizophrenia and substance abuse.

The researchers looked at transporter proteins in the family of Na<sup>+</sup> symporters, which remove neurotransmitters from the synapse in a process called reuptake that is essential to the proper function of neural transmission. Antidepressants such as Prozac and Zoloft, which are selective serotonin reuptake inhibitors (SSRIs), and cocaine interfere with the reuptake mechanism and alter the normal exchange process between cells.

The paper describing the new findings was published in the May 13, 2010, issue of *Nature*. In the journal's News & Views section, reviewers noted that until now biologists have been unable to view transporters on a single-molecule detail, but the new research “lifts the curtain and shines a spotlight onto some of the choreography” of membrane transport.

In this spotlight, the new research illuminates the pathway of transported molecules revealing how transporter proteins escort ions and molecules through membranes by forming passageways in a manner the researchers liken to gates opening and closing.

## Year of the Rat?

Researchers at **UT Southwestern Medical Center** have added another experimental research animal to the scientific stable: the rat.

In a new study appearing in the June 2010 issue of *Nature Methods*, researchers detailed how they created 35 new rat lines, with each type of animal harboring mutations in specific genes.

More than half of those mutated genes are associated with biological processes linked to human diseases, including cancer, diabetes, Alzheimer's disease, aberrant circadian rhythms and mental illness.

The rat is important compared to the mouse, researcher said, because the rat is larger and more intelligent, is often better for biochemistry, pharmacology and physiology studies, and its behavior often is more in tune with that of humans.

The UT Southwestern studies are focused on sperm-cell biology and fertility genes, but ultimately other scientists will be able to utilize the relatively simple, cost-effective techniques to generate genetically altered rats for use in experiments related to human disease, researchers said.

One of the keys to producing the mutated rats was to prevent rat sperm stem cells – sperm precursor cells – from differentiating, permanently into sperm. The animal produces genetically altered sperm, resulting in mutant offspring that can be used for biomedical research.