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*'NICE AND EASY' TERMS*

## TLC and Ablynx agree to jointly develop targeted liposome drug delivery technology

***Dave Silver, Staff Writer***

TAIPEI, Taiwan – Taiwan Liposome Co. (TLC) and Ablynx NV are planning to jointly develop a new drug delivery technology combining TLC's immunoliposome platform with Ablynx' antibody-derived nanobody technology that will enable more precisely targeted delivery of liposome-encapsulated cytotoxic compounds to disease sites in cancer patients.

Liposomes are nanoscale structures that can pass through leaks in blood vessels

See Ablynx, page 3

## Simcere charts new course for drug discovery with VC spin-off

***By Shannon Ellis, Staff Writer***

SHANGHAI – Simcere Pharmaceutical Group made headlines in December when it announced plans to go private and delist from the NYSE.

As the first Chinese biopharmaceutical company to go public in the U.S. the longtime generics maker – and growing

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NEWCO NEWS

## Telephus aims to tame biofilms in implantable devices

***By Marie Powers, Staff Writer***

In Greek mythology, Telephus was a son of Heracles who received a wound in battle that would not heal until he returned to the Greek warrior, Achilles, who had inflicted the injury. He was

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THE BIOWORLD BIOME

*IDENTICAL TWINS, MORE OR LESS*

## Down syndrome cells in disarray across all chromosomes

***By Anette Breindl, Science Editor***

Researchers have gained new insights into the cellular consequences of trisomy 21 by studying an unusual set of twins – one with the trisomy, which leads to

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NEWCO NEWS

## Scioderm seeks fast track with breakthrough drug for rare skin disorder

***By Jennifer Boggs, Managing Editor***

"The worst disease you've never heard of." That's how patient advocacy and nonprofit group Debra (Dystrophic Epidermolysis Bullosa Research Association of America)

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INSIGHT

## Will current market headwinds cause the IPO window to close?

***By Peter Winter, BioWorld Insight Editor***

It will come as no surprise that the Street's passion for biotech initial public offerings (IPO) has waned lately in the wake of the sector's overall poor market performance during the past few weeks.

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BENCH PRESS

BioWorld Science Editor Anette Breindl takes a closer look at **translational medicine**

Read this week's edition

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## IPOs

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That the three companies which have managed to complete IPOs so far in April received lukewarm welcomes to their public life may give the 20 biotech firms waiting in the wings reasons to hold off on their plans to test the uncertain current market conditions.

Vital Therapies Inc. got its IPO out of the door but had to slash its price to make it happen. The San Diego-based firm, representing, according to BioWorld Snapshots, the 31st IPO so far this year, raised $54 million, with most of the proceeds slated to fund late-stage trials of Elad, its human cell-based bio-artificial liver system. (See *BioWorld Today*, April 18, 2014.)

The offering included 4.5 million shares at $12 each, falling below an already downsized range of $13 to $15 the company set in an April 7 prospectus. Vital originally filed in October 2013, seeking to raise up to $86 million by offering 4.4 million shares in a range that subsequently was set at $16 to $18. (See *BioWorld Today*, Oct. 15, 2013.)

Also completing offerings in April were Emeryville, Calif.-based Adamas Pharmaceuticals Inc., which priced at the low end of its proposed range selling 3 million shares for $16 each; while Cerulean Pharmaceuticals Inc. priced 8.5 million shares – up from the 5 million it originally planned to sell – at $7 each, well below its proposed $11 to $13 range. (See *BioWorld Today*, April 11, 2014.)

Both companies have promising products in their pipelines. With the cash from its IPO, Adamas is planning take ADS-5102, a controlled-release version of amantadine, all the way to commercialization for levodopa-induced dyskinesia (LID) in Parkinson's patients. It also has a fixed-dose therapy for Alzheimer's disease, partnered with Forest Laboratories Inc., under FDA review.

Cambridge, Mass.-based Cerulean, plans to use the bulk of its proceeds to fund clinical development of CRLX101, a nanopharmaceutical designed to work as a dual inhibitor of topoisomerase-1 and hypoxia-inducible factor-1alpha to deliver camptothecin.

*Editor's note: This is just a portion of the article. To read the entire story, see today's edition of* BioWorld Insight, *the weekly news service that provides behind-the-scenes analysis and commentary on the biopharmaceutical marketplace. Subscribe by calling (770) 810-3144 or (800) 477-6307 if calling from the U.S. or Canada or email bioworld at salessupport@thomsonreuters.com.*

## OTHER NEWS TO NOTE

**Cubist Pharmaceuticals Inc.**, of Lexington, Mass., voluntarily recalled one lot of Cubicin (daptomycin for injection) to the user level due to the presence of particulate matter, reported via customer complaint and identified as glass particles, found in a single vial from this lot, produced by a contract manufacturer. No adverse events have been reported to date in association with a product complaint of vials containing glass particulate.

**Lumiphore Inc.** said it received a National Science Foundation Small Business Innovation Research phase II grant that will permit it to continue developing its radiodiagnostic imaging and targeted radiotherapeutic technology. The Berkeley, Calif.-based company will use the funding to continue improving chelation stability of metallic radioisotopes for imaging and therapeutics, which could potentially contribute to progress in the way cancer is detected and treated. The small privately held company has several partnerships, including one with Bayer AG subsidiary Algeta ASA and another with Thermo Fisher Scientific Inc.



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## Ablynx

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such as found in cancer-site angiogenesis to target diseased cells with drugs encapsulated within. Using the next generation of this technology, ligands on the surface of the immunoliposomes – in this case Ablynx' nanobodies – will then target overexpressed cancer cell surface receptors before releasing their payload of drug molecules. In the case of the nanobody, immunoliposomes should be able to directly enter the target cells for even greater effectiveness.

It's an all-new take on the antibody-drug conjugate class of drugs, but instead of each antibody carrying a small number of linked drug molecules – and with it the risk of these links breaking and releasing toxic drugs into the bloodstream – a lot more of the drug can be delivered by liposome; around 10,000 molecules in each one.

Taipei-based TLC is building up a platform to connect with antibody companies such as Ablynx.

"Basically we can start to plug and play antibodies into the immunoliposome platform, " George Yeh, president of TLC, told *BioWorld Today*.

The Ablynx nanobody is just a part of the antibody of a particular variety discovered by the company to exist in camels and lamas, being fully functional, but lacking in light chains. This characteristic means it's also a good fit for the immunoliposome.

"For us, we don't need the whole antibody. A lot of times we just need to have the single chain. So it also fits nicely with our technology," Yeh explained.

As part of the agreement, Ablynx, of Ghent, Belgium, has identified three to five nanobodies that look to be the best fit. Going forward, the two companies will agree on a shared research budget to carry out testing of these in vitro and in vivo, with research roles shared by TLC and Ablynx at their facilities in Taiwan and Belgium, respectively.

As it's not a licensing agreement, rather a commitment to try to develop something new together. Financial terms of the deal are simple.

"It's a 50-50 type of structure. We'll split the costs, and whatever we get when we license out we also agree to equally split. It's nice and easy, and it's fair as well. We have 'A' technology. They have 'B' technology. We are merging it into a 'C' technology, a 'C' product," Yeh noted.

Yeh expects to see results from the first part of the feasibility study in as soon as six to nine months.

As well as its agreement with Ablynx, TLC is in discussions with other antibody companies to continue using its immunoliposome platform.

It's an exciting time for TLC. With a current market capitalization of $490 million and milestones including Taiwan's biggest biotech initial public offering when it went public in December 2012, to a Taiwan-record secondary offering in September 2013 raising around $100 million, the company is flying high. And it's all to plan, according to Yeh.

"Everything is on track to what we wanted to achieve. It's the realization of the third part of our strategy. The first part was in using the liposome technology to develop a product and look for partners," he said. "We have done that, with Sandoz [Sandoz AG, the generics drug affiliate of Novartis International AG of Basel, Switzerland], with Teva [Teva Pharmaceutical Industries of Petah Tikva, Israel], companies like that. The second part was to use partner market intelligence to drive the product. We have done that. With the first two parts, we own the technology and we own the product, and we just look for partners."

"But this third part is something different. It's my technology, it's your technology, together becoming a new technology. It will bring TLC to another level technology-wise," Yeh said. //



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## Simcere

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innovative drug developer – is used to taking on pioneering projects, and looks to be at it again.

In October 2013, the Nanjing-based firm kicked off Bioscikin (BSK) Pharma Pioneers, a venture arm with the goal of targeting early stage assets. With the delisting behind them, the company has begun to reveal more details about its newest enterprise.

"Since we went public in 2007, we have been doing internal R&D, and in the last seven years, Simcere has spent ¥1.2 billion in R&D," Ray Zhang, senior business development director at Simcere, told *BioWorld Today*. "We found that this has not been very efficient. We have been learning from big pharma, most do licensing and partnership to get new assets, so we developed this idea to do open innovation.

"BSK represents a completely new approach as we far as we know for Chinese investors," Zhang said, "I can't say there are a lot of interesting investors at the early stage in China."

This separate venture is charged with innovative drug development while its parent company, Simcere, will focus efforts on less risky late-stage assets.

"Since Simcere completed privatization," Zhang said, "the new strategy is on late-stage assets close to market. For early stage drug development, we leave that to BSK. The two companies are completely separate entities."

Simcere declined to confirm how much the fund has been seeded with, though some sources said it could be in the range of ¥1 billion. The company has said it plans to attract other investors and within five years the fund will have ¥3 billion (US$500 million).

### COMPLETELY DISRUPTIVE ASSETS

While there are more and more venture capital funds in China's biotech space, many of them aren't getting in on the early stage. (See *BioWorld Asia*, March 26, 2014.)

Zhang said being a Chinese pharma company doing investments sets it apart from typical VCs or CRO-based funds because of the unique ability to discover assets and evaluate what will work.

The company has a team of scouts in the Bay Area and Boston, as well as in Europe and China, out looking for a wide range of assets to target. In China, BSK has a dedicated management team in-house, with many returnees from multinational corporations and specialists in various stages of clinical trials and therapeutic areas to do the evaluation work.

Simcere has more than 200 drugs approved by the CFDA covering antibiotics, anti-stroke medications, anti-inflammatory drugs and anticancer medications. While BSK will start looking in these areas, Zhang said they are open-minded and are looking for "truly disruptive assets."

A bit like Goldilocks, the key will be to find them cooked to the right temperature, at a sweet spot somewhere close to the clinic, but not too far along.

"We focus on assets that in the U.S. would be phase I or almost phase Ib," Zhan noted, "and then invest until phase II."

By shepherding an asset through this crucial phase in China, BSK is expecting to reap large returns by licensing it out or partnering with others who can manage the more costly phase III trials.

"From the phase I or investigational new drug-application-ready to phase II, we know we can have five- or 10-fold return on our investment. That is how we will try to make a profit," Zhang said.

Licensing is not the only approach. BSK is also open to co-development/co-promotion deals as well as setting up joint ventures with the inventors of molecules. So far BSK has signed up three joint-venture deals.

There is apparently great interest in the services that BSK can provide, which according to Zhang is far more professional than the government sponsored incubators.

BSK has 18 companies signed up at their Nanjing site and three in Shanghai. There are plans to also open an office in Tianjin soon. BSK does not have an investment stake in most of the companies; they rent BSK's lab and office space.

According to Zhang, one of the companies decamped from its government hi-tech park location when researchers saw the top-of-the-line labs they would have access to with BSK.

While Zhang declined to get specific, she described some of the companies that have signed on as purely innovative pharma companies with a few of them biologics, one in particular working on several oncology assets. Another company is working on stem cell R&D while another from San Diego is working on antibody drug conjugation.

Another incentive to working with BSK, Zhang said, is these companies can also avail themselves to expertise in manufacturing, marketing and drug registration. //

## OTHER NEWS TO NOTE

**Navidea Biopharmaceuticals Inc.** is testing Lymphoseek injection (technetium Tc 99m tilmanocept), its FDA-approved lymphatic mapping agent, in a head-to-head study with radiolabeled sulfur colloid to see which drug causes patients less pain. The study, under way at the University of California, San Diego, is designed to determine if patients receiving Lymphoseek experience the same or less pain following injection with one or the other and will compare performance characteristics of each. The Dublin, Ohio-based company also said that the European Medicines Agency is still considering its marketing authorization application for Lymphoseek and that the company expects to discuss the drug's use in head and neck cancer with members of the Committee for Medicinal Products for Human Use's Scientific Advisory Group on Oncology soon.

## Telephus

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healed by the very spear that had pierced him.

Real life is decidedly more complicated, but the fable is an apt metaphor for Telephus Medical LLC, which is developing a first-in-class humanized monoclonal antibody to prevent *Staphylococcus* reinfection and osteomyelitis in patients following total hip or knee replacement surgery. The company's technology is designed to prevent the early events that drive the formation of antibiotic-resistant biofilm infections on implanted medical devices, which today require additional, revision surgery.

Bacterial surface attachment is divided into three phases, explained Mark Benedyk, president and CEO of San Diego-based Telephus. They include primary reversible adhesion, secondary and irreversible adhesion and biofilm formation. Each phase is controlled by the expression of proteins that mediate adhesion, replication and other functions that lead to biofilm formation and implant infection.

A foreign body implanted in a patient is particularly susceptible to bacterial colonization because the surface of the device is rapidly coated with a mixture of water, proteins and lipids derived from patient cells and extracellular materials. That colonization can lead to devastating implant infections.

Eighty percent of the biofilm infections in orthopedic implants are caused by *Staphylococcus spp.* bacteria, according to Benedyk, who said Telephus identified staphylococcal proteins expressed early in the process of biofilm development as potential drug targets to suppress implant infection. In animal models, administering antibodies against one of the proteins inhibited biofilm formation, lowered the incidence of implant infection and suppressed the bone damage that often accompanies implant sepsis.

The company's lead compound, TPH 101, is designed to inhibit a key biofilm enzyme used by clinically significant strains of *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), and to assist a patient's own immune system in protecting against infection during postsurgical recovery. The company has a second antibody in development to reduce or eliminate replication and colonization of staph bacteria on surfaces and to prevent the bacteria from invading and hiding in bone cells, where they can later break free and recolonize elsewhere in the body.

"Bacteria have a pretty sophisticated defense system, so you want to hit it with as much as you can at different stages of this biofilm formation," Benedyk told *BioWorld Today*.

Biofilm infections are different from hematogenous infections of free-floating bacteria. The shaft of an implanted device is a porous metal, which is integrated with bone to provide structural definition and prevent slippage, Benedyk explained. Once bacteria penetrate the metal and move into the sponge-line cancellous bone, they're difficult to eradicate.

Other companies have candidates that specifically target MRSA, including tedizolid phosphate, an oxazolidinone developed by Trius Therapeutics Inc., which was snagged last year by Cubist Pharmaceuticals Inc. in a cash deal valued at approximately $704 million. (See *BioWorld Today*, July 31, 2013, and Aug. 1, 2013.)

At the end of March, the FDA's Anti-infective Drugs Advisory Committee (AIDAC) unanimously supported approval of tedizolid, branded by Lexington, Mass.-based Cubist as Sivextro. The drug, which was compared with a regimen of linezolid (Zyvox, Pfizer Inc.), has a PDUFA date of June 20. (See *BioWorld Today*, April 1, 2014.)

The AIDAC also gave unanimous backing to Durata Therapeutics Inc.'s Dalvance (dalbavancin), a second-generation, semisynthetic lipoglycopeptide with a long half-life. That candidate, which has a PDUFA date of May 26, was compared with a regimen of vancomycin and linezolid.

However, Benedyk is unswayed about the prospect that these candidates will perform better against biofilms than the armful of marketed products for which MRSA is an approved indication.

"From what I've seen in the literature, unless you remove the implant for a long period of time you still have a pretty low success rate," he said. "Our goal is to prevent establishment of this infection in the first place."

### 'WE'LL BE OPEN TO ANY KIND OF TRANSACTION'

Benedyk, former senior director and head of the Pfizer Incubator in San Diego, was running consulting firm Rila Partners LLC when he began working with Edward Schwarz, professor of orthopedics at the University of Rochester (N.Y.) School of Medicine and Dentistry. Schwarz had discovered the underlying technology and was interested in forming a company to explore commercial applications. Benedyk, who was intrigued by the preventive nature of the platform, had a previous connection with officials in the university's technology transfer office, facilitating a speedy spin-off.

Telephus was launched in 2012, with Schwarz as founder and chief scientific advisor. The university was sufficiently enthused about the technology to invest in the company even before the licensing deal was signed. In addition to advancing TPH 101, the initial capital infusion funded production of the second antibody against the additional enzyme in the biofilm formation process.

"That was a great situation for us because we could move the technology to a de-risked stage of development and continue to bring in new investment," Benedyk said.

In March, the company's humanization partner, Bioatla LLC, also of San Diego, completed a key protein engineering phase of TPH 101, moving the mouse antibody into a humanized state. Once a particular cell line is selected, the company can begin

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## Down syndrome

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Down syndrome, and one without.

Perhaps the first surprising thing is that such a set of twins exists at all – an extra chromosome being a rather large genetic difference for two supposedly genetically identical individuals.

"This is a very rare event," Stylianos Antonarakis told *BioWorld Today*. "The zygote probably starts as a trisomy 21, and in one of the first cell divisions the extra chromosome 21 is lost in one of the daughter cells."

That rare event gave Antonarakis, who is at the Swiss University of Geneva, and his colleagues a way to specifically look at the effects of the extra chromosome 21, without needing to find a way to separate them from individual differences in gene expression. They published their findings in the April 17, 2014, issue of *Nature*.

Such differences are difficult enough to separate out when scientists look at a single gene. But with an extra chromosome, the expression levels of several thousand genes are changed.

When those changes are superimposed on natural variation, separating signal from noise becomes extremely difficult. And so while on one level, the problem in Down syndrome is beyond obvious – an extra chromosome – on the level of pathways or individual genes, the basis of trisomy 21 caused health issues are largely unknown.

Last year, scientists from the University of Massachusetts and Sangamo Biosciences reported that they were able to silence the third chromosome in cell lines derived from Down syndrome patients via gene editing, providing another avenue to looking at gene dosage effects. (See *BioWorld Today*, July 18, 2013.)

One of the big questions has been to what extent trisomy 21 influences the gene expression on other chromosomes. Clearly many of Down syndromes' symptoms, which include a high risk for heart disease and certain cancers as well as all but universal early onset Alzheimer's disease, are due to high levels of proteins that are produced by the extra chromosome 21 itself, a so-called gene dosage effect.

But the excess proteins produced off of the extra chromosome 21 include regulatory proteins, which act on all chromosomes. Antonarakis said the biggest surprise to come out of his team's work was how much the extra chromosome 21 changes expression on the rest of the genome. Down syndrome, he said, is "a general pan-genomic disorder," because the extra copy of chromosome 21 changes gene expression patterns on all chromosomes.

The expression level of each gene in the genome is likely to be similar to that of its neighbors. Chromosomes are organized in stretches of multiple genes whose expression is either high or low.

In cells with three copies of chromosome 21, lightly transcribed regions of the genome produced more protein than usual, while heavily transcribed regions produced less. When the authors produced induced pluripotent stem cells (iPSCs) from both twins, those differences in gene regulation lasted through the reset.

Antonarakis said his team plans to understand which proteins are responsible for regulating the gene expression level. In an editorial that accompanied the paper, Benjamin Pope of Florida State University, said there are two possible mechanisms.

Proteins translated off of chromosome 21 could affect the overall chromatin structure, affecting how accessible the genome is to the DNA transcription machinery.

Another possibility is that the presence of extra DNA itself binds proteins that are then not available to interact with other chromosomes. //



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## Scioderm

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refer to epidermolysis bullosa (EB), a rare genetic disorder characterized by fragile skin that it often leaves its sufferers with chronic open wounds and blisters.

Currently, there are no approved therapies for EB. Patients – typically children, since the disorder is diagnosed in infancy – face continual wound cleaning and bandaging, with families spending upward of $10,000 or more on bandages per month. In addition to pain and itching, the wounds also leave these children – called "butterfly children" due to the fragility of their skin – susceptible to infection, thus raising their risk for developing antibiotic resistance.

"There's nothing out there for them," said Robert Ryan, president and CEO of Scioderm Inc., a 2012 start-up looking to change that, possibly as early as next year if data from the ongoing phase IIb drug testing topical candidate SD-101 prove compelling.

Ryan and Scioderm's chief operating officer, Robert Coull, acquired the asset from another firm, which had demonstrated a wound healing effect at a lower concentration of the active ingredient before the topical cream product's advancement was stalled by lack of funding. A subsequent open-label study in children with one of three subtypes of EB – simplex, recessive dystrophic or junctional – demonstrated complete closure of 88 percent of target chronic lesions within one month, plus a 57 percent reduction in body surface area coverage of lesions and erosions after three months of daily treatment.

Those data won SD-101, the FDA's coveted breakthrough therapy designation, which allows for a possibly expedited development and review process for drugs designed to treat serious or life-threatening conditions. And Scioderm is hoping that data from the ongoing phase IIb study will convince the FDA to great accelerated approval.

The company recently enrolled 48 patients and anticipates data by late summer, Ryan said. The three-month study, which will be followed by an active rollover period, is designed to measure complete wound closure at the primary endpoint, "the gold standard at the FDA," he added.

Additional endpoints include improvement in the body surface area. And SD-101 could have benefits beyond wound healing, most notably in reducing itching, a complication of EB that can be the most difficult for the youngest patients.

"We saw signals in earlier testing, so we'll be looking for that [in the phase IIb study], too," Ryan said.

Assuming data are positive, Scioderm will approach the FDA about the possibility of approval and, if the agency agrees, SD-101 could be on the market in the second quarter of 2015.

Accelerated approval is no guarantee, Ryan said, "but we have a lot of optimism. The agency is clearly engaged with us on this product. [The FDA] knows about this disorder, knows that there really isn't anything out there and that this is also a very painful disease." SD-101 also has been granted orphan status. EB affects roughly one of every 20,000 live births. And rare diseases, particularly those affecting pediatric patients, gained additional measures under 2012's Food and Drug Administration Safety and Innovation Act. "So we've got avenues that weren't there before," Ryan noted.

If data from the phase IIb are allowed to serve as the basis for a regulatory filing at the end of this year, Scioderm should be able to get through registration on its first venture funding round, a $16 million series A financing raised in 2012 from lead investor Morgenthaler Ventures and participating investor Technology Partners.

Prior to that round, Scioderm had been self-financed.

Regardless of the FDA's decision on accelerated approval, the company is moving ahead with plans for a phase III study for European approval. That trial, which will include sites predominately in Europe, though a few might be added in the U.S., is expected to launch at the end of this year and to have a similar design to the phase IIb.

"We do believe the endpoints and the duration likely will be the same," Ryan told *BioWorld Today*.

Durham, N.C.-based Scioderm operates with six full-time employees, including a recently hired chief scientific officer along with four to five "almost full-time" consultants, and has come a long way on just a modest amount of venture financing.

Moving forward, the company is pursuing a "parallel-track strategy at the moment," COO Coull explained. One of those tracks is to possibly go public via an initial public offering, though the "market has been pretty fragile in the last few weeks," to raise money necessary for Scioderm to bring the product to market on its own, at least in the U.S., where physicians treating EB patients could be reached with only a small sales force.

At the same time, the company also will look at potential corporate partners.

It's already working closely with patients. Ryan serves on the board at Debra, and "we participate as much as we can at events," Coull said.

SD-101 might also have use in other skin disorders, though pursuit of additional indications will be farther down the road. As will the possibility of in-licensing additional orphan candidates, Coull said. The focus now for Scioderm is "100 percent on EB." //

## Telephus

Continued from page 5

ramping up to produce clinical trial material. The tentative timetable calls for submission of an investigational new drug application next year followed by phase I studies in the first half of 2016.

If the technology proves its mettle in the clinic, Benedyk envisions bright commercial prospects for the platform, given the colliding forces of an aging population with a high prevalence of obesity and diabetes, the growing frequency of staph infections and what he called the looming imposition of "the managed health care regime" in the wake of the Affordable Care Act.

He estimated a potential $400 million market for a product that would reduce current revision re-infection rates of 40 percent to 50 percent following joint prosthesis infection.

A total hip replacement, on average, costs $25,000 per procedure in the U.S., Benedyk said, while septic revisions cost four to six times more.

Telephus is screening 15 additional antibodies, with the goal of building a franchise in the indication.

The university's investment in Telephus initiated a rolling series A, which Benedyk hopes to close by the end of the summer with a total raise of $5 million.

The company also is applying for grants from the National Institutes of Health and Department of Defense.

Once TPH 101 moves into the clinic, and provided human studies confirm in vitro and in vivo findings, Telephus will seek a strategic partner.

"Our goal is to stay capital efficient, focus on our lead product and develop intellectual property around the second candidate," said Benedyk, who is the company's only employee. "We'll get to the clinic, we'll see if we get a signal and then we'll be open to any kind of transaction at that point." //

## PHARMA: OTHER NEWS TO NOTE

**Actavis plc**, of Dublin, and **Forest Laboratories Inc.**, of New York, said each has received a request for additional information from the Federal Trade Commission (FTC) in connection with Actavis' pending acquisition of Forest. The information request was issued under notification requirements of the Hart-Scott-Rodino (HSR) Antitrust Improvements Act, and the effect of the second request is to extend the waiting period imposed by the HSR act until 30 days after Actavis and Forest have substantially complied with the request, unless that period is extended voluntarily by the parties or terminated sooner by the FTC. Actavis and Forest said they intend to cooperate fully with the FTC and they continue to expect the transaction to close in mid-year 2014. Separately, Actavis said it has entered into agreements with **Akorn Inc.**, of Buffalo Grove, Ill., and **Hi-Tech Pharmacal Co. Inc.**, of Amityville, N.Y., to purchase four currently marketed products and one product under development for cash consideration. The closing of the purchase agreements are contingent upon the consummation of Akorn's acquisition of Hi-Tech. Financial terms of the agreements were not disclosed. Included are three products marketed under abbreviated new drug applications — ciprofloxacin hydrochloride ophthalmic solution, levofloxacin ophthalmic solution and lidocaine hydrochloride jelly — and one product marketed under a new drug application: lidocaine/prilocaine topical cream. The agreements also include one product under development.



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# BENCH PRESS

## BioWorld looks at translational medicine

*By Anette Breindl, Science Editor*

### Heat shock to the system

Researchers from Children's National Medical Center and Yale University have shown that the transcription factor heat shock factor 1 was activated by multiple environmental stressors that can cause fetal brain damage. The developing brain is vulnerable to many environmental toxins. Exposure can show up not only at birth, in the form of syndromes such as fetal alcohol disorder, but also decades later, when those exposed to neurotoxins in the womb have a higher risk of diseases such as schizophrenia. In their work, the authors showed that exposure to several different fetal neurotoxins led to increased levels of heat shock factor 1. They also looked at the responses of iPS-cell derived neurons to those neurotoxins, and found that neurons from schizophrenics produced higher levels of heat shock factor 1 in response to environmental stressors than those from controls. Heat shock factor 1, the authors concluded, "plays a crucial role in the response of brain cells to prenatal environmental insults and may be a key component in the pathogenesis of late-onset neuropsychiatric disorders." They published their findings in the April 10, 2014, online edition of *Neuron*.

### Conscious uncoupling fights flu

Scientists from St. Jude Children's Research Hospital and the British University of St. Andrews have shown that they could protect mice from flu virus infection by treating them with proteins that target the sialic acid receptor. Flu virus initially infects cells in the respiratory tract by binding to sialic acid receptors, which have different subtypes in the upper and lower respiratory tract. In their experiments, the authors showed that by treating mice with recombinant proteins that prevented this binding, they were able to protect mice from otherwise lethal doses of the 2009 pandemic H1N1 virus. The mice did, however, develop an immune response to the virus, which might add to protection against future exposure to the same virus. "This host-targeted approach could provide a front-line prophylactic that has the potential to protect against any current and future influenza virus and possibly against other respiratory pathogens that use sialic acid as a receptor," the authors concluded. They published their work in the April 14, 2014, issue of the *Proceedings of the National Academy of Sciences*.

### Goldilocks and the reactive oxygen species

Reactive oxygen species (ROS) or free radicals can be a bane or boon to an organism, depending on their levels. They are important for fighting bacterial infections, but can also damage host cells by the same mechanisms by which they attack those bacteria. Now, researchers from Genentech Inc. have identified a protein that helps fine-tune ROS levels produced by macrophages. Mice lacking this protein, which the authors called negative regulator of ROS or NRROS, were better at fighting off bacteria such as *Listeria monocytogenes* and *E. coli*, but that ability came at a price. The animals were also prone to developing central nervous system damage due to oxidative damage to their tissues. The authors suggested that "further understanding of this pathway may provide novel therapeutic approaches to target ROS production in various diseases." Their work appeared in the April 13, 2014, online issue of *Nature*.

### Prostaglandins work both sides of immunity

Scientists from the British University College London have linked prostaglandins, which stimulate both the innate and adaptive immune systems via pro-inflammatory effects, to immunosuppression in advanced liver cirrhosis. The authors looked at the plasma levels of prostaglandin E2 in patients with acute decompensated cirrhosis and end-stage liver disease, and found that they were several times as high in patients with cirrhosis as in healthy controls. Administering albumin, which decreases the availability of prostaglandin E2, improved the ability of macrophages to activate the immune system. In mice, experimentally induced liver injury also led to increased levels of prostaglandin E2 and subsequent immunosuppression. Inhibiting the prostaglandin E2 restored immune function in the animals. The authors concluded that reducing circulating prostaglandin E2 levels could attenuate immune suppression and reduce the risk of infection in patients with acutely decompensated cirrhosis or end-stage liver disease. The findings appeared in the April 13, 2014, online issue of *Nature Medicine*.

### Parkinson's: Too much protein synthesis?

Mutations in leucine-rich repeat kinase 2 (LRRK2) are frequent in Parkinson's disease, but which protein the kinase is phosphorylating to produce its untoward effects has not, to date, been worked out. Now, a team from Johns Hopkins University School of Medicine has presented evidence that the problem lies in LRRK2's phosphorylation of the protein-producing ribosomal machinery. LRRK phosphorylates the ribosomal subunit s15. When the scientists changed one amino acid of this protein so that it could no longer be phosphorylated, it prevented the degeneration of dopamine neurons and the motor deficits that are the hallmarks of Parkinson's in both cellular models of Parkinson's

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and transgenic fruit flies. They also showed that s15 phosphorylation by LRRK2 produced an across-the-board increase in protein synthesis, linking aberrant protein synthesis to Parkinson's disease. The findings appeared in the April 10, 2014, issue of *Cell*.

## Alzheimer's protein in normal learning

Researchers from the Massachusetts Institute of Technology have gained new insights into the function of the regulatory protein p25 in both normal synaptic activity and in Alzheimer's disease. P25, which has been implicated in several neurodegenerative disorders, can activate cyclin-dependent kinase 5. Its levels may be elevated in Alzheimer's disease and transgenic mice that overproduce p25 develop a heavy burden of amyloid plaques as they age, but the molecular link between the two has not been clarified, nor was it known whether p25 played a role under normal conditions. In their work, the authors demonstrated that p25 could be activated by normal physiological activity, and that mice that did not produce p25 formed stronger memories in response to equivalent stimuli. Lack of p25 also led to less amyloid-beta formation in transgenic Alzheimer's mice. The authors concluded that "these results reveal a physiological role of p25 production in synaptic plasticity and memory and provide new insights into the function of p25 in [amyloid beta]-associated neurotoxicity and [Alzheimer's disease]-like pathology." The study appeared in the April 10, 2014, issue of *Cell*.

## Screening classifies response signatures

By testing the reaction of roughly 6,000 strains of yeast to roughly 3,000 different drugs, a team from the Canadian University of British Columbia has identified 45 basic chemogenomic signatures that account for the strains' variations in drug response. The authors first screened a library of 50,000 druglike compounds for effects on the growth of wild-type yeast. Molecules that affected growth were further screened against strains with only one copy of each of the 1,100 essential yeast genes, and against nearly 5,000 strains lacking both copies. The authors said that "our results provide a resource for the discovery of functional interactions among genes, chemicals, and biological processes." The results were published in the April 11, 2014, issue of *Science*.

## The curious case of the missing myelin

Researchers from Harvard University have shown that the thickness of the myelin sheath can vary considerably on different parts of a single axon. Myelin forms the electrical insulation that makes high-speed neuronal communication possible, and when it is damaged, multiple sclerosis as well as other neurological and psychiatric disorders can result. The thickness of the myelin sheath varies between different types of neurons, which influences their communication, but has been assumed to be uniform along the axon. In their experiments, the researchers used high-resolution imaging to look at individual axons along their length, and found that myelination thickness could vary considerably, including segments that were not myelinated at all, and that such nonmyelinated segments differed between different layers of the neocortex, which have specialized functions in information processing. An editorial published with the paper said that "the findings are likely to spark new concepts about how information is transmitted and integrated in the brain." Paper and editorial appeared in the April 18, 2014, issue of *Science*.

## FMRP MOA ID'd

Researchers from the Wadsworth Center and the University of California at San Diego have identified how Fragile X Mental Retardation Protein (FMRP) inhibits protein synthesis. Loss of FMRP causes Fragile X syndrome, which is a major cause of inherited mental retardation and includes symptoms of autism spectrum disorders. Scientists had known that FMRP inhibits protein synthesis, and its loss led to widely deregulated protein synthesis, but the molecular details of its effects were unknown. In their studies, the authors found that normal FMRP binds to the ribosome, which is the cell's protein translation hub, and inhibits protein translation by preventing transfer RNAs from docking. The findings appeared in the April 17, 2014, advance online issue of *Molecular Cell*.

## New dendritic cell vaccine

Scientists from Yale University and Celldex Therapeutics Inc. have reported results from a phase I trial of CDX-101, an off-the-shelf vaccine targeting dendritic cells. Most of the success in cancer immunotherapy to date has come from T-cell-based approaches, but dendritic cells, which present antigens to other immune system cells, could in principle target a much broader range of antigens. In their trial, the authors used a monoclonal antibody that combined a dendritic cell receptor with the cancer marker NY-ESO-1, which is expressed on many different tumor types, to treat 45 patients. They observed no dose-limiting toxicities, and a third of patients had stable disease or tumor shrinkage. CDX-101 also appeared to improve the effects of subsequent checkpoint inhibitor therapy. The authors concluded that their "first-in-human study of a protein vaccine targeting DCs demonstrates its feasibility, safety, and biological activity and provides rationale for combination immunotherapy strategies including immune checkpoint blockade." They published their results in the April 17, 2014, issue of *Science Translational Medicine*.

## LET US KNOW WHAT YOU THINK

**We welcome your feedback. Contact Anette Breindl at anette.breindl@thomsonreuters.com, or call (770) 810-3134.**