Recognizing potential in RSV

Johnson & Johnson deals out $1.75B for respiratory disease company Alios

BY KELSEY KAUSTENEN

NEW BRUNSWICK, NJ—Pharma giant Johnson & Johnson isn’t interested in closing 2014 quietly, marking the last quarter of the year instead with the $1.75 billion acquisition of privately held Alios BioPharma Inc. The South San Francisco, Calif.-based clinical-stage biopharmaceutical firm is focused on the development of antiviral therapies for respiratory diseases, so the deal nabs Johnson & Johnson a portfolio of drug candidates in a variety of indications, including influenza, rhinovirus and respiratory syncytial virus (RSV). Both companies’ boards of directors unanimously approved the transaction.

“We are so pleased to be joining the Janssen Pharmaceutical companies of Johnson & Johnson, who have an impressive track record of bringing breakthrough drugs for viral diseases to market,” Dr. Lawrence M. Blatt, president and CEO of Alios BioPharma, said in a news release. “Our portfolio of novel medications targets a diverse range of viral infections, including respiratory syncytial virus, which complements ongoing efforts by Janssen to develop innovative treatments for important and life-threatening infections.”

The transaction, which is subject to customary closing conditions including the Hart-Scott-Rodino Act, is expected to close in the fourth quarter of this year.

“We are excited that this acquisition will enable us to explore treatment options for a number of viral infections, including RSV, the last of the major pediatric diseases with no available preventive therapy,” commented Dr. William N. Hait, global head of research and development at Janssen. “AL-8176 complements our existing early-stage portfolio for RSV, which aims to prevent and treat this disease, the leading cause of acute lower respiratory infection in children under the age of five.”

AL-8176 is a nucleoside analog under development as an oral antiviral therapy against RSV. The compound inhibits RSV’s replication by acting on the viral polymerase, ALIOS CONTINUED ON PAGE 31

Expanding the pipeline

Endo to acquire Auxilium Pharmaceuticals in a cash-and-stock transaction for approximately $2.6 billion

BY JEFFREY BOULEY

DUBLIN, Ireland—Seeking in part to gain a broader offering of urology and orthopedic products that are natural complements to its current men’s health and pain products, Irish company Endo International plc announced in early October a definitive agreement with Auxilium Pharmaceuticals Inc. to acquire the Chesterbrook, Pa.-based company for $2.6 billion.

Under the terms of the deal, Endo will acquire all of the outstanding shares of common stock of Auxilium for a per-share consideration of $33.25 in a cash-and-stock transaction. The boards of directors of both companies have unanimously approved the transaction, including the repayment and assumption of debt. The ENDO CONTINUED ON PAGE 42

Mining pharma’s data

Pharmaceutical companies to share data for drug design via new UC San Diego-led resource

BY LLOYD DUNLAP

SAN DIEGO—Pharmaceutical companies will collaborate with researchers at the University of California, San Diego to provide previously unreleased proprietary data for drug discovery through a new $3.7-million effort.

The project, led by UC San Diego principal investigators Drs. Rommie Amaro, Victoria Feher and Michael K. Gilson, includes a major subcontract to Rutgers University, directed by Dr. Stephen K. Burley of the Research Collaboratory for Structural Bioinformatics Protein Data Bank.
Modeling neurodegenerative disease

Stem cells help develop cellular models for understanding Parkinson’s disease

From modeling diseases to discovering therapies, stem cells have the potential to change the way we think about medicine. Our researchers have partnered with The Parkinson’s Institute to build a path to more physiologically relevant cellular models for Parkinson’s disease using donor cells to generate induced pluripotent stem cells.

Read about the journey the researchers have started, the novel tools they have utilized, and the models they are producing to help advance Parkinson’s disease research.

Access the free white papers at lifetechnologies.com/pdmodels
WATERTOWN, Mass.—Selecta Biosciences Inc., a clinical-stage biotechnology company developing a novel class of targeted antigen-specific immune therapies, announced Oct. 15 that it has secured equity funding of more than $20 million from a combination of new and existing investors. “With strong financial support from both our current and new investors, we are now well positioned to rapidly advance our immune tolerance pipeline, including the lead program SEL-212, the first non-immunogenic treatment for refractory and tophaceous gout,” said Dr. Werner Cautreels, president and CEO at Selecta. “Severe gout is a highly debilitating disease and just one of the potential therapeutic applications of our proprietary Synthetic Vaccine Particle (SVP) platform. With a well-established development path and favorable pro-forma economics, SEL-212 is a great opportunity. SEL-212 is just the beginning for us, as we have identified many biopharmaceuticals, including existing and new classes of biologics such as gene therapy, where the effects of antidrug antibodies (ADAs) are deleterious.” Selecta reports that it has established strong research and development and manufacturing expertise to enable the company to readily adapt its proprietary SVP platform to other applications developed internally or in collaboration with partners. In addition to its lead program for severe gout (SEL-212), Selecta is advancing immune tolerance programs to prevent ADAs against Factor VIII (SEL-201), anti-TNF alpha antibodies and vectors used for gene therapy, as well as candidates for allergies and autoimmune diseases. Including the funding just secured, Selecta has obtained a total of $78.6 million in private equity funding to date from such investors as Polaris Venture Partners, Flagship Ventures, OrbiMed Advisors, NanoDimension, Rusnaco, I2BF, Eminent Venture Capital and Leukon Investments.

Rigontec raises €9.45M in first closing of Series A round

BONN, Germany—Mid-October saw Rigontec GmbH, a privately held biopharmaceutical company developing RNA-based immunotherapeutics for the treatment of cancer and viral diseases, announce the first closing of its Series A financing round, raising €9.45 million, or about $12 million. The round was co-led by Wellington Partners and Boehringer Ingelheim Venture Fund, and it included NRW Bank and High-Tech Gründerfonds. Rigontec is developing synthetic ligands of a novel receptor of the innate immune system, retinoic acid inducible gene I (RIG-I), which recognizes viral RNA. RNA motifs that activate RIG-I promote the destruction of diseased cells and the induction of a lasting immune memory, thereby treating and preventing recurrence of disease. Rigontec’s lead compound ImOl100, a proprietary first-in-class product targeting RIG-I, is currently being evaluated for development in several cancer types, including melanoma and prostate cancer. ImOl100 is a chemically synthesized mimic of the natural ligand of RIG-I with improved safety and drug-like properties. In various preclinical models, ImOl100 has demonstrated substantial tumor regression and systemic antitumor activity, including long-term protection against tumor rechallenge. Rigontec’s technology also allows the design of pipeline candidates with additional gene silencing and inhibitory activities, further broadening the applicability of this new class of drugs in the area of oncology and viral infections.
Pharmaceutical and biotech market indices

For the month of September, the Dow Jones Industrial Average fell 0.32 percent, the S&P 500 dropped 1.55 percent and the NASDAQ Composite Index sank 1.9 percent. Despite the weak month, the Burrill Select Index is up 20.03 percent for the year, strongly outpacing all of the major indices.

BY BURRILL MEDIA
SAN FRANCISCO—Seeking to discourage companies from acquiring or merging with offshore companies in so-called inversions in order to avoid U.S. taxation, the U.S. Treasury Department in September announced new rules that eliminate the ability of U.S. companies to use earnings of their foreign subsidiaries to fund acquisitions without paying U.S. taxes on that capital. The rules also make it more difficult for companies to invert by strengthening the requirement that the former owners of the U.S. entity own less than 80 percent of the new combined entity. The rules apply to deals that have not closed as of Sept. 22, 2014.

The result of these rules, not surprisingly, may be to suppress that rate of mergers and acquisitions (M&As), given that inversions have, so far, been a substantial driver of M&A activity in the life sciences in 2014. In fact, of the $286.2 billion in life-sciences M&A transactions announced so far this year, 44 percent have not closed as of Sept. 22, 2014.

Inversions announced so far this year, 44 percent have not closed as of Sept. 22, 2014.

While inversions may be cooling, at least in the short run, initial public offerings (IPOs) are still taking place at a fairly heated pace. As Burrill notes, the “brisk pace of life-sciences initial public offerings continued in September with a total of seven IPOs completed on global markets, six of which occurred on U.S. exchanges. The activity raised the total number of U.S. IPOs to 82 for the first nine months of the year for a total of $6.3 billion. That compared to 39 IPOs on U.S. exchanges during the first nine months of 2013, in which companies raised a total of $6 billion.”

The 82 IPOs so far in 2014 are already the most for a single year, indicating that companies are finding an easier time raising capital in the U.S. These included Affirmed Therapeutics (Germany), ReWalk Robotics (Israel), ProQR Therapeutics (Netherlands) and Fosun Immuno (Israel).
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Microbiome to the rescue

Vaginal bacteria reveals untapped medical potential of the human microbiome

**BY ZACK ANCHORS**

SAN FRANCISCO—One of the most common bacterial organisms found in the vagina has helped scientists at the University of California, San Francisco (USCF) reveal the extent to which the human microbiome could serve as a rich source for antibiotic compounds. The researchers found that *Lactobacillus gasseri*, a common species in the microbe community of the vagina, produces a compound, lactocillin, which closely resembles an antibiotic compound that the pharmaceutical company Novartis is currently testing in a Phase 2 clinical trial. The discovery, along with other key findings of UCSF’s study, suggests there could be many other small molecules produced by microbes in or on the human body that possess therapeutic potential.

Dr. Mohamed Donia, who drafted the new study as a postdoctoral fellow at UCSF, tells DDNews that the ability of organisms like *Lactobacillus gasseri* to produce antibiotic compounds turns the typical drug development process on its head. “We’re used to developing drugs by discovering natural products or using synthetic chemistry, and then spending years modifying these compounds to achieve the best biological activity and the least toxicity,” says Donia, who is currently an assistant professor of molecular biology at Princeton University.

Researchers at the University of California, San Francisco have discovered that the human microbiome could serve as a rich source of potential therapeutics. Pictured here is the UCSF Mission Bay campus.

Computational combat

Researchers combine molecular, quantum mechanics to screen for HIV compounds

**BY KELSEY KAUSTINEN**

ODENSE, Denmark—The HIV virus remains a difficult one to treat due to its ability to constantly mutate and to protect vulnerable binding sites. In light of this tendency, drugs that have proven effective in the past can lose their potency, leading to a constant need for new drugs targeting new facets of the virus. Given the complexity of the virus, however, identifying compounds with the potential to target it effectively is a time-consuming process—one that researchers from the University of Southern Denmark have been able to speed up through a new screening model.

The researchers in question included postdoc Vasanthanathan Poongavanam, from the Department of Physics, Chemistry and Biology at Southern Denmark, and Jacob Kongsted, an associate professor of the Department of Physics, Chemistry and Biology.

**CONTINUED ON PAGE 7**
bacteria within the human body as a source for new drug molecules. But recent efforts to better understand the human microbiome has created new opportunities to explore this therapeutic potential. Scientists have made significant progress toward mapping the bacterial ecosystems found in the gut, skin, nasal passages, mouth, vagina and other parts of the human body through research funded by the NIH’s Human Microbiome Project.

However, much less is known about the small molecules that govern interactions between microbes and their human hosts. A primary purpose of the UCSF study was to identify the bioactive gene clusters (BGCs) that contain the genetic blueprints for creating such molecules. "Small molecules are the common language that almost every living cell can understand, so we wanted to interrogate what small molecules are being produced by these bacteria and find out how they interact with their host and interact with other bacteria," says Donia.

Researchers created a machine-learning algorithm that enabled a computer to identify known genes that produce small molecules with potential as drugs. When they used this algorithm to systematically analyze genes in the human microbiome, they identified 3,000 BGCs at different body sites. "We were surprised to find so many BGCs producing every small molecule type, and we were also surprised to find that so many of them were very common within a population of healthy humans," says Donia. One of the compounds that researchers identified and then studied in greater detail was the molecule produced within the vaginal microbe community, lactocillin, which belongs to a class of antibiotics called thiopeptides.

The approach taken by the UCSF researchers differed in significant ways from that of other studies carried out under the umbrella of the Human Microbiome Project. "Most studies have been focused on continuing to sequence and document just which microbes are part of the microbiome," says Donia. "We took a functional approach and tried to find out what these microbes are actually doing."

The most common method of identifying bacteria residing in humans involves genus-level analysis, but UCSF researchers found that this method is not detailed enough to predict which drug-like molecules bacteria will produce. Individual species, and different strains within each species, produce different molecules. "We need to learn what these molecules are and what they are doing," said Dr. Michael Fischbach, an assistant professor of bioengineering at UCSF and senior author of the study. "This could represent a pool of molecules with many tantalizing candidates for drug therapy."

CONTINUED FROM PAGE 6

UCSF
University. “This particular compound has bypassed that whole process, and there could be many molecules in other parts of the human microbiota with the same potential.”

The UCSF study, which was published in Cell in September, found that lactocillin serves to kill common vaginal bacterial pathogens while sparing other bacteria known to dwell harmlessly in the vagina. “This bacteria actually produced the right drug in the right place, with the exact biological activity that is needed, and probably at the time,” says Donia.

While many medicines are derived from microbes and plants, few efforts have been made to use bacterial genomes to develop new drugs. The UCSF group identified lactocillin, which belongs to a class of antibiotics called thiopeptides. The most common method of identifying bacteria residing in humans involves genus-level analysis, but UCSF researchers found that this method is not detailed enough to predict which drug-like molecules bacteria will produce. Individual species, and different strains within each species, produce different molecules. "We need to learn what these molecules are and what they are doing," said Dr. Michael Fischbach, an assistant professor of bioengineering at UCSF and senior author of the study. "This could represent a pool of molecules with many tantalizing candidates for drug therapy."

"We’re used to developing drugs by discovering natural products or using synthetic chemistry, and then spending years modifying these compounds to achieve the best biological activity and the least toxicity. " says Dr. Mohamed Donia, formerly a postdoctoral fellow at the University of California, San Francisco and now an assistant professor of molecular biology at Princeton University. "This particular gene compound has bypassed that whole process, and there could be many molecules in other parts of the human microbiota with the same potential.”

Researchers created a machine-learning algorithm that enabled a computer to identify known genes that produce small molecules with potential as drugs. When they used this algorithm to systematically analyze genes in the human microbiome, they identified 3,000 BGCs at different body sites. "We were surprised to find so many BGCs producing every small molecule type, and we were also surprised to find that so many of them were very common within a population of healthy humans," says Donia. One of the compounds that researchers identified and then studied in greater detail was the molecule produced within the vaginal microbe community, lactocillin, which belongs to a class of antibiotics called thiopeptides.

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ENDCONNECT: E111404
Platform links researchers with drug discovery expertise

BY LLOYD DUNLAP
JERSEY CITY, N.J.—The Alzheimer’s Drug Discovery Foundation (ADDF) and OnDeckBiotech have announced the launch of ADDF ACCESS, a new and improved open-access platform to connect scientists with a wide range of capabilities of academic research organizations (CROs), drug development experts and educational resources. By leveraging OnDeckBiotech’s digital technology, the enhanced ADDF ACCESS platform will streamline links between researchers and CROs specializing in diseases of the central nervous system (CNS) and the entire drug discovery and research development.

ADDF ACCESS users will see improved functionalities across the ADDF ACCESS platform, including direct communication with CROs and consultants, a suite of project management tools and educational resources focused on drug development for CNS diseases. The new ADDF ACCESS platform powered by OnDeckBiotech went live in early September right after the ADDF’s 15th International Conference on Alzheimer’s Drug Discovery, held Sept. 8-9, in Jersey City, N.J.

“This is an exciting opportunity to leverage the OnDeck technology and a dedicated development team to improve the functionality of ADDF ACCESS,” said Dr. Howard Fillit, executive director and chief science officer of ADDF, in a statement announcing the collaboration.

“The new platform will streamline the process of identifying and contracting with CROs that have pharmaceutical and computational development expertise for challenging CNS diseases. This type of expertise is critical to the success of translational CNS research programs in academia and small biotechnology companies. It’s not uncommon for a study director to spend weeks searching for and evaluating vendors experienced with a particular model. These costly delays are an unnecessary distraction for scientific teams, and any mistake can compromise an otherwise promising program,” said Cliff Culver, CEO and founder of OnDeckBiotech. “We have a unique insight into the significant percentage of time and reduced administrative cost for both sponsors and vendors on the platform, and we are confident these improvements have a positive impact on research efficiency.”

Culver notes that his company and ADDF were “working on similar things independently of each other.” ADDF realized that vendors were having trouble sourcing quality CROs, and the partnership with OnDeck was the result. OnDeck provides a cloud based platform, which has now been customized for the Alzheimer’s community, to improve functionality, with enhanced search capabilities to help researchers identify companies that provide specific, relevant services.

The service includes detailed profiles of featured CROs, including information on platform technologies, project management tools, educational resources and opportunities to rate and review CROs and directly communicate with contacts and key personnel at participating CROs. Project management tools enable users to easily distribute requests for proposals (RFPs) to multiple vendors and ensure robust, competitive bids, including an RFP template, contract templates and relationships history-tracking data. Enhanced workflows, including CRO selection and program design, including recommendations for selecting and managing CRO contracts, are expected using the ADDF’s Annual Drug Discovery for Neurodegeneration Conference are all part of the package.

By facilitating quality connections between scientists and top-tier drug discovery experts, ADDF ACCESS removes an enormous hurdle to undertaking drug discovery and development in academia and small biotechnology companies, Culver notes. In addition, it’s provided a free service to users. Vendors are able to list their expertise of being listed and profit when new business is directed their way.

“Negotiations have begun, and many parties have been in touch throughout our initial datasets. Members of the Alzheimer’s Drug Discovery Foundation database will be harvested and included into the ADDF ACCESS platform this week, showing the incredible value to researchers working with these datasets,” said Dr. Martin Karplus, a professor of chemistry and co-director of the CDDI, and a co-founder of OnDeckBiotech. “We have identified the key advancements by our new platform, and we are confident that these improvements have a positive impact on research efficiency.”

“In our initial datasets, we identified over 14 of them were capable of reproducing. The promising candidates are now being explored by Italian researchers at the University of Padova to see if they could be advanced as HIV drugs. “Our approach is not new, but we use a combination of existing approaches for this problem in a new way,” Poongavanam explains. “Methods that use molecular mechanics principles are often used to screen for chemical compounds in drug discovery because these methods are fast. But in our work, we used quantum mechanical calculation to molecular mechanics methods in order to put more effort in accuracy of the prediction.”

“This method is very different in principle, but combining these methods solve many mysteries in understanding complex molecular recognition,” he continues. “Quantum chemistry is primarily used to study in detail how a compound binds to a protein at the atomic level; therefore, this method is very accurate, but slow. On the other hand, molecular mechanics-based methods are primarily used to understand large, complex structures at the molecular scale, and they are fast. In our work, we used a ‘hybrid’ in order to achieve both speed and accuracy. This approach is very powerful, and we predict an award internationally recognized after the Nobel Prize (2015) was awarded to Prof. Martin Karplus, Prof. Michael Levitt, and Prof. Arieh Warshel, who are considered pioneers in this growing field.”

Poongavanam adds that “These approaches could be applicable to other diseases, but it needs to be tested thoroughly, as we have only validated the models for this enzyme.” He expects to see approaches such as this, utilizing computer-based predictions and screening models, become more prevalent, noting that they are areas of interest for pharmaceutical and biotech companies.

DATA

data format: page 1

The data provide atomic details of drug mechanisms and will be used to improve computer-aided drug-design methods with the aim of accelerating drug discovery.

“One of the challenges in medical research is the paucity of real-world data available to academic researchers and other interested parties to develop new and improved methods for computer-aided drug discovery,” says Amaro, associate professor of chemistry and biochemistry at UC San Diego. “Pharmaceutical companies generate lots of data in house as they conduct drug research, but often have difficulty sharing these datasets due to legal and technical barriers.”

“This project is all about helping companies release the high-quality data that they have generated, which has incredible value to researchers working to improve methods of computer-aided drug discovery,” she adds. “Companies want to help, because everything they are doing is related to the ability to develop new medications more quickly and inexpensively.”

The new Drug Design Data Resource (D3R) will span UC San Diego’s Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Chemistry and Biochemistry, Center for Research in Biological Systems, Center for Drug Discovery Innovation (CDDI) and the San Diego Supercomputer Center. The D3R is being administered through the Center for Research in Biological Systems, which is based at UC San Diego’s Qualcomm Institute. D3R researchers will act as “data brokers,” collaborating with scientists and attorneys in the pharmaceutical industry to identify, evaluate, negotiate and manage intellectual industrial datasets. The data will then be made available to the drug discovery research community in a manner designed to maximize value to such data.

A dataset will ideally be comprised of approximately 50 or more compound structures provided in smiles (simplified molecular-input line-entry system) or sdf format. D3R, along with the associated Kd, Ka, Ki or IC50 assay values, and at least five target co-crystal structures in pdb format. “There are likely to be cases where crystal structures will be further refined by Dr. Stephen Burley’s group at Rutgers,” Feher adds, “in which case, crystallographic structure factors for electron density mapping may also be provided by the company.” The UC San Diego team members are developing a webpage, drugdesignerdata.org, that will provide a portal to search and download the datasets collected from participating companies, such as PDB, PubChem, BindingDB, MOAD and ChEMBL. This webpage will also provide information, participation instructions and challenge dataset downloads.

Multiple industrial partners are currently being recruited to the project. Gilson, a professor of pharmacy and co-director of the CDDI, notes that the D3R will work closely with pharmaceutical companies to publicly release data for use by researchers developing new software to speed the discovery of new medicines for a variety of diseases. “Nations have begun, and we have found several companies [which] are very enthusiastic about the project,” Feher states. “Three companies expressed their support when we initiated our grant submission, and we are looking to them for our initial datasets. Members of the computational community, whether in pharmaceutical companies or academia, recognize the value in having these datasets publicly available.”

“Unfortunately drug discovery is still to a large extent trial and error,” says Feher, who spent a decade working in the pharmaceutical industry before coming to UC San Diego. “What computational chemists globally are trying to do is to make faster, more accurate, more predictive programs to speed up the process. Part of our mission is to engage the community in these challenges to test newly developed predictive algorithms.”

Addo Gilson: “There’s a sense that, although computational drug discovery is already useful, it hasn’t reached its full potential, and that the results can be fed back into a process of continuous improvement and thus advance the field.”
The company recently announced that it has completed the first phase of development of a novel cancer drug discovery platform that replicates human tumor biology and responds to clinically relevant drug concentrations. Using its new platform, HemoShear was able to successfully replicate human therapeutic response to cisplatin, a drug approved to treat non-small cell lung cancer (NSCLC), at a therapeutically relevant concentration. Similarly, HemoShear evaluated two other drugs currently in clinical studies and confirmed a therapeutic response.

When evaluated in traditional cell culture systems and mouse studies, the same dose of cisplatin does not show a response. HemoShear’s findings reinforce the need to test cancer drug candidates under more human-relevant tumor conditions.

“Nearly 95 percent of all cancer drugs entering clinical trials fail because of toxicity or lack of efficacy,” Wamhoff says. “A major contributor to this dismal failure rate can be attributed to the inability of traditional models to uncover the underlying disease biology and predict efficacy and safety of cancer drug candidates. With our novel approach to recreating the tumor microenvironment, we have demonstrated a major step toward understanding human response to cancer drug treatments.”

Wamhoff adds, “There are a lot of 3D tumor systems available, but ours can separate cell types to see how a drug targets each one. It’s a depth of biology not available on other systems.”

HemoShear started in 2008 with the goal of validating human responses to 200 drugs in order to enter drug discovery collaborations with select pharmaceutical and biotechnology companies to identify novel therapeutic approaches. By bringing together cancer cells, stromal cells and vasculature under the right conditions, the company hopes to improve the success of drug candidates when they enter the clinic and bring them to patients faster.

Two years ago the NCI approached HemoShear to create its tumor microenvironment. The company has received more than $10 million in Small Business Innovation Research funding from the government.

HemoShear’s translational tissue systems apply physiological blood flow characteristics to human tissue to restore its in vivo biology, using material from HemoShear’s biorepository and interpreting data with cutting-edge computational analytics. In Phase 1 of the NCI-funded program, HemoShear demonstrated that NSCLC tumor structure, biology and molecular signaling pathways are restored in the HemoShear platform.

“Now the company is about a half-year away from more robustly establishing a model for NSCLC and developing one for pancreatic cancer, then one for prostate cancer and, eventually, one for any solid tumor,” says Dr. Dan Gioeli, director of tumor studies at HemoShear. “We also want to create a model to analyze the mechanism of liver cancer, the most common site for metastasis of lung and pancreatic cancer. We’re trying to understand the biology of metastasis, so we can develop drugs to target it. We want to determine how drugs affect metastasis, how metastasis affects the site and how drugs interdict those processes.”

He concludes, “HemoShear’s goal is to enter drug discovery collaborations with select pharmaceutical and biotechnology companies to identify novel therapeutic approaches. We need to have the right partners, and we’re cautiously optimistic.”
Clinical trials and tribulations

BY JEFFREY BOULEY

S OMETHING A MONTH AGO, some folks I follow online were raving about a new anime series available through a streaming video website dedicated to that genre, and I got sucked in. To get quicker, uninterrupt- ed access to the episodes, I paid for a membership. However, since I’m not into anime overall as much as when I was younger, I canceled that membership after a few mara- thon sessions to plow through the series.

I’ve done this kind of thing before. Enjoy the benefits of a free trial offer and cancel before the first payment is due. Pay for access to a site only long enough to get all the materials I need from it. Join a movie rental service and get my first dozen or so DVDs and/or CDs for a penny plus shipping and handling, and then fulfill my membership requirements as quickly and cheaply as possible to reduce identification overall still cost me less than going to a store…

…wait, that last one probably dated me a bit. Egads, I’m getting old fast (though not quite old enough yet to enjoy AARP benefits and discounts).

My point is that many of us like to enjoy these free or reduced-cost benefits, but in the vast majority of cases, eventually we need to pay. Or pay more. Or cancel. And so it is with clinical trials and the push in recent years for pharma and biotech companies to do clinical trials well outside one’s national borders. The lure has been lower costs and often easier patient recruitment.

But the bill may be coming due, and the value proposition—though it probably won’t be entirely elimi- nated—will likely drop noticeably.

By the way, I’m going to avoid the popular term “overseas trials.” Cer- tainly, Central America is not over- seas from Canadian and U.S. phar- mas. Asia is not overseas from Euro- pean phamas. And India—both a major player in pharma and a popular clinical trial locale for phamas based elsewhere—certainly isn’t overseas from itself.

Ah, India. The real impetus for this month’s editorial. Let me quote from an article in The Hindu, titled “A steel frame for clinical trials,” that caught my eye in October: “In recent months, hundreds of European and American pharma companies and clinical research organizations have been conducting clinical trials in India, the 12th most populous country in the world. Clinical trials are conducted to test new medicines and medical devices. The trials are conducted to ensure that the new medicines and devices are safe and effective. The trials are conducted under the supervision of the UK government. Clinical trials are conducted to ensure that the new medicines and devices are safe and effective. The trials are conducted under the supervision of the UK government.

For more information, visit www.DDN-News.com

[Image 206x754 to 284x854]

Jeffrey Bouley, DDNews Chief Editor

Randall C Willis

His demand is not unique, as he quickly points out, citing the Euro- pean Medicines Agency and discussions within Africa, Asia and South America to regionally harmonize drug and medical device regulations.

So, is it time for Health Canada to stick to its HHS-equivalent duties and divest drug and medical device regulations to the FDA? As I have joked with several Amer- ican friends, we Canadians look just like you. If you give us too much antacogulant, do we not bleed?

Our regulatory approvals are based on the same clinical trials data as yours, so why should Canada’s drug companies have to double-up every time they submit an NDA? And because of the dra- matically smaller potential patient populations in Canada, a drug company may find itself spending ungodly amounts of money applying for approval of a drug targeting 400 people or fewer. I have no numbers, but I wonder how many drugs do not come across the border because there is no economic model for profit.

Likewise, the practical reality is that neither country lives within a geographic bubble. What happens in one jurisdiction (with the possible exception of Las Vegas) ultimately ripples through the other one.

If FDA officials learn of unforeseen post-marketing adverse events and decide to add a black box warning to a drug’s monograph, that same black box often becomes reflected in the Canadian monograph. I leave it to The Star to determine when and why the black box is added in Canada.

A merger of the two agencies (or engulfment) would also reflect current Canadian clinical practices. Very often, in my experience, Canadi- an practice guidelines are adaptations of Ameri- can guidelines, literally referencing their counterparts and adjusting for local factors such as drug availability and treatment infrastructure. And in some cases, there is no Canadian guidance and clinicians simply work with U.S.-produced guidance.

I can hear the Canadian mob marching down the street. (Excuse me, but we are here to flag you. Hope it’s not a bad time. We can come back.)

“What about our national autono- my?” they might cry.

The science is the science; the medicine is the medicine. As in all other jurisdictions, the true autonomy comes in drug costs and formulaic coverage, which are handled region- ally, and there is nothing to suggest that this would have to change in a merged North American system.

Ultimately, the question (at least north of the border) should come down to what’s in the best interest of Canadians, and as I believe Attaran rightly points out: “The FDA is more transparent, better resource and scientifically better equipped than Health Canada will ever be.”

As for what would be in it for the FDA to accept such a merger: possibly nothing. But then, I really don’t foresee the FDA’s practices needing to change, and other than expanding its mailing lists to include Canadian addresses, I don’t foresee any increased burdens, financial or otherwise.

And who knows, perhaps the FDA can follow Health Canada’s lead on pharmaceutical mar- keting, which is dramatically more conserva- tive than the United States’ relative Wild West approach of freedom, not permission.

In any event, if you don’t hear from me after this is published, it is probably because the pitchforked, hockey-sticked mob has had its way. »

OUT OF ORDER: REGULATOR, GO TO HEAL

BY RANDALL C WILLIS

A LL ALLUED IN MY last com- mentary, life has not been good for the last few months for Health Cana- da, the governmental department that, among other things, serves the healthcare functions covered in the United States by the FDA. And much of the difficulty has been prompted by one of Canada’s national newspapers, The Toronto Star.

First, the Star did an exposé series highlighting the lack of transparency at Health Canada with regard to post-marketing adverse events, citing the lack of a centralized database that healthcare workers could access and no mecha- nism (or apparent will) to warn the population about problems as they arise. To support their position, the Star reporters cited information gleaned from an FDA site designed specifically for that purpose, information that was com- pletely hidden in Canada.

More recently, the Star published another series on the ineffectiveness of Health Canada in stopping pharmaceutical companies from importing contaminated drug compounds or excipients from other countries for use in Canadian patients. Again, as a comparator and offender identification resource, the reporters turned to the FDA web site, which highlighted several cases where the U.S. organization fined drug manufacturers for shoddy practices and banned some of the U.S. market.

The Canadian government has slowly responded to the issues raised, but by late Sep- tember, one commentator had had enough.

“We should, in part, abolish Health Canada,” proclaimed University of Ottawa professor Amir Attaran in a Toronto Star commentary.

What about our national autono- my?” they might cry.

The science is the science; the medicine is the medicine. As in all other jurisdictions, the true autonomy comes in drug costs and formulaic coverage, which are handled region- ally, and there is nothing to suggest that this would have to change in a merged North American system.

Ultimately, the question (at least north of the border) should come down to what’s in the best interest of Canadians, and as I believe Attaran rightly points out: “The FDA is more transparent, better resource and scientifically better equipped than Health Canada will ever be.”

As for what would be in it for the FDA to accept such a merger: possibly nothing. But then, I really don’t foresee the FDA’s practices needing to change, and other than expanding its mailing lists to include Canadian addresses, I don’t foresee any increased burdens, financial or otherwise.

And who knows, perhaps the FDA can follow Health Canada’s lead on pharmaceutical mar- keting, which is dramatically more conserva- tive than the United States’ relative Wild West approach of freedom, not permission.

In any event, if you don’t hear from me after this is published, it is probably because the pitchforked, hockey-sticked mob has had its way. »
COMMENTARY: Success of new-generation metabolo-therapies in personalized medicine depends on measuring bioenergetic health

BY DAVID A. FERRICK OF SEAHORSE BIOSCIENCE & VICTOR DARLEY-USMAR OF THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

T IS NOW WIDELY ACCEPTED that com-plex diseases associated with aging involve dysfunctional metabolism. This growing healthcare problem includes obesity/diabetes, neurodegeneration, cancer and cardiovascular disease.1 3

The major driver of age-related, metabolic disease is the availability of low-cost, high-calorie foods, in combination with a contem-porary trend toward increased sedentariness in daily life. The metabolic condition of the whole body is dependent on the mitochondrial metabolism of the cells and tissues that are required for the maintenance of nor-mal health. Finally clinicians will be able to predict which patients are most likely to be successful with a particular drug by determining the maximal OCR rate of the cells and is analogous to revving a car to its maximum rpm. This measurement of the oxygen consumption rate (OCR) of the mitochondrial metabolism and its changes will serve as early sensors or predictive biomarkers of the progression of metabolic diseases such as cancer and cardiovascular disease.4 9

The major driver of age-related metabolic dysfunction is cell metabolism, which is widely known to be a common feature of these costly, debilitating and lethal diseases. This association is in large part due to its central role in the life-sustaining activities of the cell, including those required for its reproduction. For example, the cell is an example of the OCR can be used as a direct measure of mitochondrial bioenergetics, a concept that provides the foundation for the development of the Seahorse Bioscience platform. The OCR is calculated as the difference between the oxygen consumption rate (OCR) and the non-mitochondrial oxygen consumption rate (non-mitochondrial OCR). The Seahorse Bioscience platform uses OCR to measure mitochondrial bioenergetics and to identify potential therapeutic targets for the treatment of age-related diseases.

The next decade will witness the release of a new class of drugs, known as “metabolo-therapeutics,” which will target metabolic pathways and the individual metabolites that are required for the maintenance of normal health. Finally clinicians will be able to predict which patients are most likely to be successful with a particular drug by determining the maximal OCR rate of the cells and is analogous to revving a car to its maximum rpm. This measurement of the oxygen consumption rate (OCR) of the mitochondrial metabolism and its changes will serve as early sensors or predictive biomarkers of the progression of metabolic diseases such as cancer and cardiovascular disease.4 9

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The major driver of age-related, metabolic disease may take just as long to significant-ly disrupt a patient’s lifestyle and/or threaten his or her life. Until now, the ability to determine a true indication of a patient’s meta-bolic health (the key integrator of envi-ronmental factors and their interdepen-dency with specific signaling pathways has enabled researchers to reprogram them to affect drug states, and the result is a new generation of discoveries and metabolo-therapeutic approaches across the entire spectrum of age-related diseases.

Like many other classes of treatment, metabolo-therapies will probably be best utilized and result in better outcomes by employing a personalized, targeted therapeutic approach for each patient. Chronic dis-eases involve the interplay of genetic and environmental factors and can take decades to cause harm. When they do, the resulting measurements and the ability to interpret those results. This was accomplished by stan-dardizing the direct measures of metabolic flux using a proprietary technology called extracellular flux. Early translational studies suggest that this platform may be amenable for defining metabolic status and that assays may be developed to pinpoint metabolic lia-bilities in diseases that can instruct which drug is most likely to be effective.

An early finding by the group at UAB is that the mitochondrial parameters gener-ated by the Seahorse Bioscience platform are interactive. If integrated appropriately into a single value, they can serve as a sen-sitive indicator of the response of cells to environmental stress and chronic disease progression.9 This is accomplished in the BHI equation by quantifying positive aspects of bioenergetic function (reserve capacity and ATP-linked respiration) and contrasting these with potentially deleterious ones (non-mitochondrial oxygen consumption and proton leak). For example, the larger the value for reserve capacity, which raises BHI, the more effectively mitochondria can meet both the normal energy needs of the cell and the increased metabolic demand caused by stress and disease.10

Preliminary studies in several indications are in progress at the Mitochondrial Medi-cine Laboratory at UAB and other institu-tions around the world. The overall goal is to determine if BHI can be deployed as the first clinical test for assessing bioenergetic dysfunction. Can it predict early in disease progression before significant pathol-ogy and/or acutely prior to life-threatening conditions? If successful, the BHI test could become an important approach to integrat-ing personalized medicine with state-of-the-art translational bioenergetics. 9

REFERENCES

If you’d like to check out the 10 references for this commentary, just go to the online version of the commentary, which appears unabridged at:


The opinions expressed in guest commentaries do not necessarily represent those of DDNews and/or its owners, editors or other staff.
MIMETAS to pursue kidney-on-a-chip model with $1.6M

LEIDEN, the Netherlands—MIMETAS has announced receipt of $1.6 million in funding to develop a kidney-on-a-chip model for toxicological use and will collaborate in a consortium with Radboudumc and FHNW. This funding stems from the NephroTube CRACK IT Challenge, which is organized by the U.K.’s National Centre for the Replacement, Refinement and Reduction of Animals in Research and supports the development of a microfluidic renal model that can predict renal toxicity in preclinical development. The funds will allow the consortium to develop, analyze and validate a high-throughput kidney-on-a-chip model through the combination of MIMETAS’ OrganPlate 3D-culturing technology and the human renal cell line ciPTEC. This model will aid in the detection of renal tubular injury seen in drug-induced nephrotoxicity and allow for fewer animal experiments.

Ario boosts portfolio with TRPA1 acquisition

CAMBRIDGE, U.K.—Ario Pharma Ltd. has announced the acquisition of a TRPA1 antagonist research program from PharmEste, a program that includes a series of small-molecule TRPA1 antagonists, patents and related data. Ario Pharma, which has its own TRPA1 chemistry portfolio as well, plans to initiate a TRPA1 lead optimization project with a focus on orally available TRPA1 antagonist small molecules for asthma. The TRPA1 target has shown potential in inflammatory diseases and plays a key role in the pathophysiology of asthma.

“With this asset acquisition significantly strengthens Ario Pharma’s chemistry portfolio in the TRPA1 field, and we plan to select one or more development candidates within the next 18 months,” said John Ford, CEO of Ario Pharma. “We are overcoming solubility and pharmacokinetic issues associated with historical TRPA1 modulators developed by other companies and are excited by the level of target validation of TRPA1 in respiratory, pain and other inflammatory diseases.”

Scientists return human stem cells to earliest developmental state

CAMBRIDGE, U.K.—Scientists have managed to “reset” human pluripotent stem cells to their earliest developmental state, equivalent to cells found in an embryo before it implants in the womb (seven to nine days old). These “pristine” cells could be the true starting point for human development, but have until now been impossible to recreate in the lab.

The findings, published in Cell, are expected to lead to a better understanding of human development and could eventually enable the production of more reproducible starting materials for a wide range of applications, including cell therapies.

In the article, authors Dr. Yasuhiro Takashima, Prof. Austin Smith, et. al., note that, “Our findings suggest that authentic ground-state pluripotent stem cells may be attainable in human, lending support to the notion of a generic naive state of pluripotency in mammals. In human, the naive state transcription factor circuitry appears in large part to be conserved but requires greater reinforcement to be stably propagated. Disposition to collapse reflects the transient nature of naive pluripotency in the embryo (Nichols and Smith, 2009). The imperative for developmental progression may be intrinsically stronger in primates that, unlike rodents, have not evolved the facility for embryonic diapause (Nichols and Smith, 2012).”

In conclusion, the authors state that, “Human genetic variation notwithstanding, ‘resetting’ human pluripotent stem cells to an ‘embryonic’ state is a significant step toward the attainment of authentic ground-state cells.”

Researchers at the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute at the University of Cambridge (the university’s Clare College and King’s College Chapel pictured here) report that they have found a way to return stem cells to their earliest developmental state.

Centralizing research

RNAcentral launched in September to provide unified resource for non-coding RNA data

BY ILENE SCHNEIDER

CAMBRIDGE, U.K.—RNAcentral, reportedly the first unified resource for all types of non-coding RNA data, was launched in September by the RNAcentral Consortium. RNAcentral brings together information from a federation of expert databases and provides tools for easy browsing. The RNAcentral consortium currently includes 24 RNA database resources.

The initial release of RNAcentral contains about 8 million sequences. Using funding from the U.K.’s National Centre for the Replacement, Refinement and Reduction of Animals in Research and the Medical Research Council, the RNAcentral Consortium is planning to expand its database to include at least 50 RNA database resources.

The consortium also announced that RNAcentral will be the resource for non-coding RNA data for the forthcoming Gene Expression Ontology (GO) at the GO consortium meeting in June. GO is a controlled, structured vocabulary that is used to describe the functional aspects of gene expression.

Hitting the stem cell ‘reset’
Business justification for every decision is the new normal in pharma. Maximizing efficiency and minimizing costs are part of daily life these days, and that’s no different in drug discovery and development. Yet how do you balance innovation, quality, and efficiency? How do you determine the ROI for trying something different? We understand your challenges and want to start a conversation in your community to acknowledge the tradeoffs you face every day.

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A resource for cellular metabolism

Agilent teams with University of Toronto on metabolomics library

BY ZACK ANCHORS

SANTA CLARA, Calif.—Scientists at the University of Toronto’s main biomedical research laboratory will soon have a sophisticated new resource to support their studies of cellular metabolism. Agilent Technologies has announced that it is entering a collaboration with the university that will result in the creation of a comprehensive metabolomics multiple-reaction monitoring (MRM) library at the Donnelly Centre for Cellular and Biomolecular Research.

The partnership will give scientists access to technologies that will allow them to accelerate the quantification of hundreds of metabolically important compounds for cell biology and disease research. “Routine metabolite quantification plays an essential role in helping scientists understand how diseases modify metabolic pathways,” Steve Fischer, market director for Agilent’s Life Science Research Division, tells DDNews. “The development of a routine, targeted metabolite MRM method and MRM library will make available a targeted metabolomics solution that will be used by many researchers worldwide.”

Metabolomics is an field of research that aims to compare the relative differences between biological samples based on their metabolic profiles. It can provide researchers an instantaneous snapshot of the entire physiology of an organism. The system at the heart of the partnership involves Agilent’s Infinity 1290 UHPLC and 6460 triple quadrupole mass spectrometry technologies. “This high-performance, workhorse system will allow scientists at the Donnelly Centre to analyze thousands of biological samples a month to support targeted, high-throughput metabolomics studies,” says Fischer. This mass spectrometry process will be conducted after a researcher has already completed a biological hypothesis of which metabolic pathways are implicated in a disease process. The system will help confirm and quantify specific metabolites on a large, statistically valid sample set.

Agilent will work with Drs. Amy Caudy and Adam Rosebrock at the Donnelly Centre to create the MRM library and methodology. The MRM library will be a database that contains compound information and fragmentation spectra of MRM transitions and their optimal collision energy and other method information, such as retention time. This database will allow users the flexibility to select which metabolites they wish to analyze using Agilent’s mass spectrometry system.

The collaboration originated when Caudy and Rosebrock purchased instruments from Agilent in 2010 for metabolomics shortly after arriving at the University of Toronto. Agilent remained in touch with the researchers, and after several years the researchers saw an opportunity for a collaborative relationship. “We are impressed with Agilent’s mass spectrometry instruments and software solutions, and we look forward to working together to enable use of LC-MS metabolomics by a larger scientific audience,” according to Rosebrock, a principal investigator whose lab focuses on biofuel development and nutrition. Metabolomics results can also be used to supplement gene expression or proteomics studies.

Fischer tells DDNews he expects the new metabolomics MRM library to be completed...

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RNA

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the UK’s Biotechnology and Biological Sciences Research Council (BBSRC), partner institutes throughout the world were able to come together and build what they see as a practical solution to a shared problem.

Since the 1950s, scientists have thought of RNA as an intermediate molecule that provides a link between stable DNA and proteins. However, in recent decades it has become clear that RNA plays a much wider range of roles in living organisms. Researchers have discovered a lot about different types of RNA, but until now these data have not been put in one place.

“During the last decade, there has been a great increase in the number of noncoding RNA genes identified, including new classes such as microRNAs and piRNAs,” explains Alex Bateman, head of Protein Sequence Resources at EMBL-EBI (the European Bioinformatics Institute). “There is also a large amount of experimental characterization of these RNA components. Despite this growth in information, it is still difficult for researchers to access RNA data, because key data resources for noncoding RNAs have not yet been created. The most pressing omission is the lack of a comprehensive RNA sequence database, much like UniProt, which provides a comprehensive set of protein knowledge.”

Before RNAcentral, finding the RNAs encoded by a specific genome required gathering information from several independent resources, for example miRBase for microRNAs and HAVANA for IncRNAs. “There is plenty of published data on noncoding RNAs, but each subtype is maintained separately,” according to Bateman. “This is the first time we have a central place where you can find it all: piRNAs, ribosomal RNAs, everything. A lot of that information has typically been locked up in supplementary materials, or referred to only by a non-standard gene name. RNAcentral is a big step towards making RNA sequence as easy to access for research as protein sequence.”

RNAcentral 1.0 gives researchers access to data from 10 different expert databases and provides stable accession numbers that can be used consistently in the literature, other molecular databases and search engines. The RNAcentral website features a faceted search that enables users to explore different RNA sequences according to source, species and molecular function. Further expert databases will be included in future releases.

The RNAcentral consortium has its roots in a workshop held on the Wellcome Genome Campus in 2010. At that time members of the RNA community came together to discuss the lack of centralized access to RNA data.

“It is really satisfying to see this project come to fruition,” said Sam Griffiths-Jones of the University of Manchester. “The growth in non-coding RNA sequence and functional information is phenomenal and shows no signs of slowing. There has never been a greater demand for a universal resource for these data. The collaboration of RNAcentral consortium members to produce this resource represents an enormous step forward for the RNA field.”

According to BBSRC Chief Executive Prof. Jackie Hunter, “Fundamental research into noncoding RNAs has many potential applications, including disease diagnostics, new therapies and biotechnology. With the abundance of data now available due to next-generation DNA sequencing, there is an urgent need for informatics tools to decipher it. RNAcentral is a vital resource that will aggregate and inte-
“About a year ago, I published an article (at genomebiology.com) that describes a novel biomarker of aging that allows one to measure the age of the vast majority of human tissues, organs and cell types,” he adds. “Recent data have convinced me that the epigenetic clock measures at least some aspects of biological age. Many people have asked me whether caloric restriction or certain diets keep us young. We do not yet know whether the epigenetic age of liver tissue relates to all causes of mortality or even to the onset of various age-related diseases. It is, of course, a plausible hypothesis that the age of the liver should have prognostic and diagnostic utility, but we will need prospective cohort studies to rigorously test these hypotheses.”

Also, it is well known that obese people are more susceptible to certain types of cancer, Horvath notes. “But we don’t quite understand why that is the case,” he adds. “Our study points to an intriguing explanation. Since age is a major risk factor of many cancers, it would make sense that livers that are older than expected are also at an increased risk of malignant transformation.”

Horvath’s team also studied whether weight loss reverses the epigenetic age of liver tissue. “Unfortunately, we could not observe a beneficial effect within nine months of bariatric surgery,” says Horvath. “But it is unclear whether a rejuvenating effect due to weight loss can be observed after a longer follow-up. I don’t think our study points to new drugs and therapies for controlling obesity, per se. But it might lead to drugs that control the adverse effects of obesity.”

“What is new in our study is the very strong effect observed in liver tissue: There, we find a strong correlation of 0.42 between BMI and epigenetic age acceleration,” he says. “At this point, only the epigenetic clock can be used to measure the ages of most human tissues and cell types, but there are several alternative epigenetic biomarkers of aging that can be applied to blood tissue.”

According to the Proceedings of the National Academy of Sciences article, Horvath’s theory includes an aging clock which uses a previously unknown time-keeping mechanism in the body to accurately gauge the age of diverse human organs, tissues and cell types.

Horvath used this epigenetic clock to measure the biological age of several tissues in mouse model subjects. The aging clock proved accurate in matching biological to chronological age in lean subjects. But liver tissues from obese subjects tended to have a higher biological age than expected.

In this latest study, Horvath looked at almost 1,200 human tissue samples, including 140 liver samples, to study the relationship between epigenetic age acceleration and body weight. While obesity doesn’t affect the epigenetic age of fat, muscle or blood tissue, he and his collaborators found that on average, the epigenetic age of the liver increased by 3.3 years for every excess 10 body mass index units.

Horvath will continue pursuing the research with Hampe, “a leading expert on the epigenomic underpinnings of non-alcoholic fatty liver disease and related complications,” he says. “At this point, it is too early to consider a potential marketing partner. I am looking for collaborators who would be interested in testing whether the epigenetic age of liver tissue is prognostic of adverse health outcomes for liver cancer. I am also looking for collaborators who are interested in developing drugs that prevent accelerated aging effects.”

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STEM

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epigeneome status may influence consistency of both undifferentiated phenotype and differentiation behavior. Low genomic H3K9me3 and genome-wide DNA hypomethylation point to epigenome erasure in reset cells, as in early embryos. It will be of great interest to determine the precise functional impact of such epigenetic cleaning.

Human pluripotent stem cells, which have the potential to become any of the cells and tissues in the body, can be made in the lab either from cells extracted from a very early-stage embryo or from adult cells that have been induced into a pluripotent state.

However, scientists have struggled to generate human pluripotent stem cells that are truly pristine (or naïve). Instead, researchers have only been able to derive cells which have advanced slightly further down the developmental pathway. These bear some of the early hallmarks of differentiation into distinct cell types—they’re not a truly “blank slate.” This may explain why existing human pluripotent stem cell lines often exhibit a bias toward producing certain tissue types in the laboratory. In this latest work, the team led by the Wellcome Trust-Medical Research Council (MRC) Cambridge Stem Cell Institute at the University of Cambridge has managed to induce a ground state by rewiring the genetic circuitry in human embryonic and induced pluripotent stem cells. Their “reset cells” share many of the characteristics of authentic embryonic stem cells isolated from mice, suggesting that they represent the earliest stage of development.

“Capturing embryonic stem cells is like stopping the developmental clock at the precise moment before they begin to turn into distinct cells and tissues,” explains MRC Prof. Austin Smith, co-author of the paper. “Scientists have perfected a reliable way of doing this with mouse cells, but human cells have proved more difficult to arrest and show subtle differences between the individual cells. It’s as if the developmental clock has not stopped at the same time and some cells are a few minutes ahead of others.”

The researchers overcame this problem by introducing two genes—NANOG and KLF2—causing the network of genes that control the cell to reboot and induce the naïve pluripotent state. Importantly, the introduced genes only need to be present for a short time. Then, like other stem cells, reset cells can self-renew indefinitely to produce large numbers, are stable and can differentiate into other cell types, including nerve and heart cells.

By studying the reset cells, scientists will be able to learn more about how normal embryo development progresses and also how it can go wrong, leading to miscarriage and developmental disorders. The naïve state of the reset stem cells may also make it easier and more reliable to grow and manipulate them in the laboratory and may allow them to serve as a blank canvas for creating specialized cells and tissues for use in regenerative medicine. “Our findings suggest that it is possible to rewire the clock to achieve true ground state pluripotency in human cells,” Smith adds. “These cells may represent the real starting point for formation of tissues in the human embryo. We hope that in time they will allow us to unlock the fundamental biology of early development, which is impossible to study directly in people.”

Dr. Rob Buckle, head of regenerative medicine at the MRC, added: “Achieving a true ground state in human pluripotent stem cells is seen as a significant milestone in regenerative medicine. With further refinement, this method for creating ‘blank’ pluripotent cells could provide more reliable and renewable raw material for a range of cellular therapies, diagnostics and drug safety screening tools. This is likely to be a highly attractive prospect to industry and regulators.”

The paper published in Cell is entitled “Resetting transcription factor control circuitry towards ground state pluripotency in human.”

EDITCONNECT: E111408

AGILENT

CONTINUED FROM PAGE 14

in the fall of 2015. It will be added to Agilent’s existing collection of MRM libraries, which address a variety of applications, including pesticides, veterinary drugs, forensics and toxicology.

Agilent uses collaborations as a key component of its strategy to maintain strong ties with current and prospective customers. “Through customer collaborations, Agilent learns about the customer problem in great detail so that we can satisfy that customer’s challenge and offer the solution to the many customers that have similar problems,” says Fischer. “This relationship is one of many that Agilent has with customers.

“Agilent is already a leader in untargeted, discovery mass spectrometry based metabolomics, and the development of a routine, targeted metabolite MRM method and MRM library will establish Agilent as a leader in targeted MS-based metabolomics.”

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Preclinical trials show experimental drug from seeds of Australian Blushwood tree fruit destroys cancer tumors

BY LORI LESKO

YOUNGBURRA, Australia—Scientists at QIMR Berghofer Medical Research Institute have developed an experimental drug produced from the seeds of the fruit of the Blushwood tree—found in a far north Queensland rainforest—that has cured solid cancer tumors in preclinical trials. The drug, called EBC-46, has been found to be effective in treating pets with cancer, according to Dr. Greg Glenn, lead author of the study published Oct. 1 in the journal PLOS One.

The Australian research team reported that just one injection of EBC-46 led to rapid breakdown of tumors in a range of human tumor models, suggesting the drug could be effective in treating human patients as well. “We were able to achieve very strong results injecting EBC-46 directly into melanoma models, as well as cancers of the head, neck and colon,” Boyle said. “In most cases the single injection treatment caused the loss of viability of cancer cells within four hours, and ultimately destroyed the tumors.”

EBC-46 works in part by triggering a cellular response which effectively cuts off the blood supply to the tumor and kills it. “In preclinical trials we injected it into our models and within five minutes, you see a purpling of the area that looks like a bruise,” Boyle said.

OnCore marks milestones in hep B mission

BY ZACH ANCHORS

DOYLESTOWN, Pa.—OnCore Bio- pharma has made a series of important steps toward its goal of developing a cure that destroys hepatitis B. During the last couple months, the biopharma firm has gained an exclusive world- wide license to a series of second-generation cyclophilin inhibitors for the treatment of hepatitis B and acquired a pharmaceutical company with two novel drug discovery programs that could prove crucial in the development of a cure.

OnCore was founded in 2012 by a team of former executives from Pharmasset (acquired by Gilead Sciences in 2011) who were involved in developing the drug Sovaldi, a hepatitis C therapy that was approved by the FDA last December. The new company’s mission is to discover and develop an all-oral cure for hepatitis B.

Hepatitis B is a serious infection of the liver that is transmitted by exposure to infectious body fluids. It can lead to chronic liver disease, which increases a patient’s risk of death from liver cirrhosis and liver cancer. The World Health Organization estimates that more than 780,000 people die every year due to infection. The therapies that are currently available to treat the disease work by suppressing the hepatitis B virus (HBV), but do not lead to a cure in the vast majority of patients. Identifying a functional or complete cure remains a significant area of unmet medical need.

OnCore’s strategy to develop a treatment for hepatitis B involves developing an all-oral treatment that targets covalently closed circular DNA (cccDNA) in HBV-infected hepatocytes. cccDNA is a unique DNA structure that can propagate the virus as it propagates. The company believes this strategy of targeting cccDNA has the potential to result in a functional cure that lowers the risk of death from liver disease to the same level experienced by a person with a naturally resolved infection.

OnCore is working to develop a treatment that combines agents against cccDNA with other novel direct-acting antiviral mechanisms that engage immune response.

Cutting off the avenues of ESKAPE

Novel antibiotics from Melinta show in-vitro potential against resistant bacteria

BY KELSEY KAUSTINEN

NEW HAVEN, Conn.—Melinta Therapeutics has released an update on its ESKAPE Patho- gen Program, presenting two posters at the Interscience Conference on Antimicrobial Agents and Chemotherapy on its RX-P873 molecule that demonstrated its activity against a range of Gram-negative bacteria, including multidrug resistant strains and those designated on the U.S. Center for Disease Control and Prevention’s (CDC) list of urgent threats.

The ESKAPE pathogens consist of Enterococcus faecium, Staphylococcus aureus, Klebi- siella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species and Escherichia coli. These resistant bacteria are the most difficult to treat, and 66 percent of all hospital infections are the result of these pathogens. Drug-resistant bacteria have, in recent years, been named one of the leading health concerns in the United States. According to the CDC, approximately 2 million people in the United States develop infections caused by resistant bacteria, and more than 23,000 people die each year from infections caused by these bacteria.

From Melinta’s three novel classes of antibiotics, more than 2,500 molecules have been produced, and Melinta is completing preclinical work to advance the most promising leads into Phase 1 clinical studies.
“About 24 hours later, the tumor area goes black, a couple of days later you see a scab and at around the 1.5 week mark, the scabs fall off, leaving clean skin with no tumor,” he said. “The speed certainly surprised me.”

In more than 70 percent of pre-clinical cases, the response and cure was long-term and enduring, with very little relapse over a period of 12 months, he said.

EBC-46 was actually discovered by the Queensland biotechnology company EcoBiotics. It is EcoBiotics’ subsidiary, QBiotics, that is developing the drug as a human and veterinary pharmaceutical. The experimental drug has been used by veterinarians to successfully destroy or shrink tumors in companion animals, including dogs, cats and horses. QBiotics is currently undertaking formal veterinary clinical trials with EBC-46 in Australia and the United States, Boyle said. A final regulatory approval is still required for a human Phase 1 clinical trial.

“At this point, EBC-46 will only be trialed in the short-term for tumors which can be accessed by direct injection or topical application,” Boyle said. “There is no evidence to suggest EBC-46 would be effective against metastatic cancers.”

Ethical approval was recently granted for Phase 1 human clinical trials, but even if those proved successful, it is unlikely the drug would replace conventional chemotherapy treatment for cancer, he said.

“Chemotherapy is still used because it is very effective for a lot of people,” Boyle said. “But EBC-46 could perhaps be used in people who, for some reason, chemotherapy doesn’t work, or for elderly patients whose body can’t sustain another round of chemotherapy treatment.”

The preclinical trials at QIMR Berghofer have been largely funded by QBiotics with additional support from Australia’s National Health and Medical Research Council. Dr. Victoria Gordon, CEO and managing director of EcoBiotics, and her husband, fellow scientist Dr. Paul Reddell, discovered the drug and spent years developing EBC-46 and demonstrating its effectiveness in animals, including treating hundreds of horses, dogs and cats. “Paul and I discovered EBC-46 via our biodiscovery technology EcoLogic about eight years ago,” according to Gordon. Prof. Peter Parsons and Boyle have been working on the early-stage preclinical development of the drug as directed and paid for by QBiotics, which has spent about AU$30 million so far and owns the patents on EBC-46 (which have now been granted in all major regions), she said, adding that Boyle’s particular focus in the development efforts thus far has been on the mechanism of action of the drug.

The company team (including directly employed as well as contracted participants) has worked on formal preclinical development of the drug (including toxicology studies, pharmacokinetic and pharmacodynamic studies), domestica- tion and grow-out of the source plant (Blushwood), R&D as well as GMP manufacture of the active pharmaceutical ingredient and the drug product, veterinary clinical development and now human clinical development, Gordon says. EcoBiotics was founded by Gordon and Reddell in 2000, based on the biodiscovery technology they developed and call EcoLogic.

“We have built the company up over the years and now have laboratories and offices in Far North Queensland and offices in Brisbane,” Gordon says. “We placed EBC-46 into a subsidiary company for development (QBiotics) so that we could focus the capital-raising strategy on drug development rather than drug discovery, which are two quite disparate areas.”

PD-L1 (B7-H1, CD274) inhibits activated T cells by binding to its receptor, PD-1, on the surface of activated T cells. Studies demonstrate that PD-L1 is expressed by tumor cells and suggest that the PD-L1/PD-1 interaction contributes to the malignancy of various tumors by helping them avoid immune detection. As a result, PD-L1 has gained much attention as an immune-based therapeutic target.
Shionogi & Co., Ltd. announced that it has entered into an agreement with AstraZeneca PLC for the potential treatment of acute coronary syndrome (ACS). Shionogi will have an option to license AstraZeneca’s biologic research and development arm of AstraZeneca, recently in-licensed from Shionogi for the treatment of acute coronary syndrome (ACS). Through AstraZeneca has had an ongoing relationship with Shionogi, licensing the cholesterol drug Crestor—which AstraZeneca and Shionogi co-market—from Shionogi in 1998, this is some of the first work between MedImmune and Shionogi.

"Cardiovascular and metabolic disease (CVMD) is a core therapeutic area for MedImmune, and Shionogi’s biologic program will be a valuable and strategic complement to our existing cardiovascular program," Cristina Rondinone, vice president and head of the MedImmune CVMD Innovative Medicines Unit, said in a news release. "We are committed to sourcing the best scientific research across the globe. We were pleased to identify this early-stage program and will work to advance its research and development as quickly as possible to hopefully bring an important new medicine to ACS patients."

The American Heart Association describes ACS as "an umbrella term for situations where the blood supplied to the heart muscle is suddenly blocked." Heart attacks and unstable angina are both examples of ACS. HDL levels have the potential to decrease independently of lipoprotein levels. In the body, HDL works to move cholesterol from the tissues and eliminate it out of blood vessels and plaques, and higher HDL levels have the potential to decrease individuals’ residual risk of cardiovascular disease.

"Maybe action against LDL is not enough for some patients," Rondinone explains. “You will need to raise HDL for those patients who have really low HDL and actually cannot take cholesterol from the tissues and eliminate that bad cholesterol. So this approach, and some of the approaches that we are having at MedImmune, is mainly to strive to modify the metabolism of the good HDL and try to make the HDL functional.”

MedImmune, the global biologics research and development arm of AstraZeneca, recently in-licensed a biologic program from Shionogi for the potential treatment of acute coronary syndrome.

Shionogi has high hopes that S-649266 will be effective in treating Gram-negative bacterial infections unable to be treated by available antibiotics.

ONCORE
CONTINUED FROM PAGE 18

OnCore anticipates that combination therapy will be required to completely eradicate HBV from patients’ livers.

OnCore gained rights to cyclophilin inhibitors that are central to this strategy through a licensing agreement with NeuroVive Pharmaceutical AB, a Swedish mitochondrial medicine company. The license agreement has a total value of up to $150 million, excluding royalty payments. OnCore will pay NeuroVive upfront payment, development and sales milestones and royalties based on future sales.

NeuroVive’s cyclophilin inhibitors, known as sangamides, are based on a new and unique polyketide chemistry platform. The lead drug candidate in the company’s cyclophilin program, NVP018, has undergone extensive preclinical development. OnCore anticipates that NVP020 will be evaluated in clinical trials in 2015.

"NVP018 is a promising antiviral drug candidate that has tremendous clinical potential for oral use as a novel treatment for patients with chronic hepatitis B infection," said Michael Sofa, OnCore’s chief scientific officer. "We believe that a curative therapy for HBV will likely contain an immunomodulatory agent, such as NVP018, combined with multiple antiviral agents with different mechanisms of action.”

Jan Nilsson, NeuroVive CEO, said the OnCore management team’s experience developing a treatment for hepatitis C made the company an appealing partner. "OnCore stood out in negotiations, which included several leading pharmaceutical companies, because of its exclusive focus on hepatitis B and its plan to bring the drug candidate to market as quickly and efficiently as possible,” he said.

OnCore’s acquisition of Enantigen Therapeutics, a privately held pharmaceutical company, is also intended to support its goal of developing a hepatitis B cure. The acquisition will allow OnCore to assume development of Enantigen’s two novel discovery programs, one targeting inhibition of surface antigen secretion and one targeting capsid assembly inhibition.

"We are very proud of the discovery work that we have done in hepatitis B," said Entenagen President and CEO Xiaodong Xu. "We believe that OnCore is in the best position to rapidly advance our programs into human clinical trials, and we look forward to joining the OnCore research team to help realize their vision."

“Our plan is to combine Entenagen’s drug candidates with our existing oral portfolio of HBV compounds and advance multiple combination regimens into human clinical trials,” said OnCore CEO Patrick Higgins. “Erena
tigen programs, together with our lead cyclophilin inhibitor, NVP018, and our cccDNA formation and cap-
sid assembly inhibitors programs, give OnCore the most comprehensive platform of assets consolidated to target a cure for hepatitis B.”

EDITCONNECT: E111415
RX-P873 CONTINUED FROM PAGE 18

antibiotic-resistant infections.

Melinta’s ESKAPE Pathogen Program combines the company’s crystallography and computational chemistry experience to generate new classes of antibiotics and new molecules to treat extensively drug resistant and multidrug resistant bacteria. As noted on the company’s website, “Melinta researchers generated three unique molecular scaffolds with high binding affinity, low off-target effect and broad-spectrum antibiotic properties. Compounds based on these molecular scaffolds—the pyrrolocytosines—have shown in-vitro activity and preclinical efficacy against multidrug resistant Gram-negative and Gram-positive strains of bacteria known to cause complicated urinary tract infections, skin and lung infections, as well as sepsis.” From Melinta’s three novel classes of antibiotics, more than 2,500 molecules have been produced, and Melinta is completing preclinical work to advance the most promising leads into Phase I clinical studies.

RX-P873 falls within the pyrrolocytosine class of compounds. It was specifically tested against Gram-negative species of bacteria, including 10 from the Enterobacteriaceae family, as well as Pseudomonas aeruginosa and Acinetobacter baumannii. The compound demonstrated potent activity against the Enterobacteriaceae family, as it inhibited more than 97 percent of isolates. RX-P873 was also shown to be highly active against P. aeruginosa, including strains that are resistant to cefazidime or meropenem, and was the most active agent tested against A. baumannii; in that area, it displayed greater activity than colistin.

“Melinta’s discovery team employs a highly disciplined structure-based design approach that we believe can deliver both next-generation antibiotics and completely new classes, which can be fine-tuned to address current and emerging threats.”

Dr. Erin Duff y, chief scientific officer of Melinta

On Sept. 6, Melinta announced, along with Hartford Hospital, that in-vitro results from a recent study highlighted delafl oxicin’s activity in low-pH environments, which are indicative of infection sites. When tested in samples from patients suspected to have urinary tract infections (UTI), delafl oxicin demonstrated activity against E. coli and K. pneumoniae, both of which are associated with complicated UTIs. Two days later, the company shared results from in-vitro studies supporting delafl oxicin’s potential in targeting Neisseria gonorrhoeae, the organism that causes gonorrhea. This pathogen has developed resistance to all classes of antimicrobials that have previously been recommended to treat gonorrhea, Melinta noted in a press release. In comparison, delafl oxicin demonstrated activity against all 50 of the ciprofl oxacin-resistant isolates tested in a study with University of Washington collaborators. In a separate in-vitro study, the compound proved to be more rapidly bactericidal against ciprofl oxacin-susceptible and -resistant N. gonorrhoeae strains than ceftriaxone, the recommended first-line treatment for gonorrhea.

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SPECIAL REPORT

So life-like

DISEASE MODELING

After decades of questionable results, are disease models turning a corner?

BY RANDALL C WILLIS

“IT’S YOUR SON’S BIG DAY,” his birthday, and he is surrounded by friends, cake, balloons and a ton of wrapping paper. But he’s been bouncing off the wall waiting for his gift from you. With a big smile, you give him a beautifully wrapped box.

“I know how much you love airplanes,” you wink as he rips into the package like a hyena on carrion.

Desperately, he claws at the top of the box and reaches inside to withdraw...a single sheet of blank printer paper.

You beam with pride. He stares confused. His friends stare at their shoes.

“But if you fold this just thus and so, it’s a pretty good approximation.”

A decade later, the same boy struggles at his lab bench to develop a new drug compound, when suddenly another scientist runs into the lab, all excited and carrying a small case.

“You have it?” the boy smiles, his friend nodding like a hypercaffeinated bobblehead.

The boy rips off the cover and reaches inside to withdraw...a culture flask of pinkish cells.

“It couldn’t get you an actual plane,” you explain. “But if you shake this just thus and so, it’s a pretty good approximation.”

“Are you human or a mouse?”

It is undoubtedly true that the biggest expense in developing a new drug and getting it to market is accommodating the failure of a molecule to translate preclinical success to the clinical setting. For any number of reasons, something is often lost between the efficacy and safety of a compound in an animal or cell culture model of a disease and in patients who actually have the disease.

“We have found more ways to cure heart disease in mice than you can imagine,” says Brian Wamhoff, co-founder and vice president of research and development for HemoShear, a company working on more physiologically relevant in-vitro models of human disease.

Wamhoff’s comment echoes the sentiment expressed years ago by oncology specialist Judah Folkman, who suggested that medical research has become very good at curing cancer in mice.

“You can create models of fatty liver disease in a mouse. It looks like it; it smells like it. But how that mouse develops fatty liver disease is completely different than how a human does it.”

So you develop a drug to treat fatty liver disease in a mouse with a target that may or may not exist in a human, and then you go into a human and wonder why didn’t this work or worse, why is it causing liver injury now?” he adds, giving voice to the frustration felt across the pharma industry.

As Wamhoff suggests, part of the problem may be that in many animal models, a disease is just that: a model. It gives all the outward appearance of being, say, rheumatoid arthritis (RA). The joint inflammation may show the same pathophysiology as human RA, but the question becomes if it is really the same condition at the molecular level, be that gene expression or metabolic pathway perturbation.

And even if the disease is the same, does the compound react with the rest of the model animal’s physiology as it does in a human? Is the animal more or less tolerant of the test compound? Or are there unforeseen off-target effects to which the animal is less prone or completely immune?

Highlighting the ubiquity of the frustration of insufficient animal models, Wamhoff points to comments made by Elias Zerhouni, former director of the U.S. National Institutes of Health (NIH) and current president of global research and development at Sanofi, in June 2013.

“We have moved away from studying human disease in humans,” Zerhouni lamented to the NIH’s Scientific Review Management Board meeting. “We all drank the Kool-Aid on that one, me included.”

“The problem is that it hasn’t worked, and it’s time we stopped dancing around the prob-
And that shift away from relying on human disease in humans has potentially been expensive. “It takes about seven years to get into the clinic and anywhere between $30 million and $150 million depending on what you’re developing,” Wamhoff suggests. “If the target and the disease biology you’re starting with from day one are wrong, you lose seven years.” Thus the interest in moving back to more human-based studies, and the opportunity for companies like HemoShear.

“What our partners are telling us now is that we want to start with more meaningful targets and more meaningful human disease biology,” Wamhoff continues. “It may still take seven years, but after those seven years, we’re going into the patient for the first time with more understanding of the human disease than we’ve ever had before.”

The recent research of Robert W. Davis and colleagues in the Inflammation and Host Response Laboratory’s Large Animal Collaborative Research Program may point to molecular reasons why the translation of results from mouse to human may be so difficult.

Publishing their results in PNAS in early 2013, the researchers examined gene expression profiles in both humans and mouse models of trauma, burn and endothelial assault. They found that the genomic responses across the different inflammatory insults were highly similar within the human populations but that these patterns were not reproducible in the mouse models of the same stresses, suggesting a disconnect that could easily translate to different responses to potential treatments.

To some extent, they suggested, the differences could be explained in evolutionary terms, with different immune systems maturing from different environmental stressors.

“Relative to the human response, mice are highly resilient to inflammatory challenge,” the authors wrote. “For example, the lethal dose of endotoxin is 70 to 25 mg/kg for most strains of mice, whereas a dose that is 1,000,000-fold less (30 ng/kg) has been reported to cause shock in humans.”

By no means, however, are the researchers advocating for the elimination of mouse models, but rather for the application of more stringent model parameters.

“Because virtually every drug and drug candidate functions at the molecular level, one practical approach forward is to raise the bar by requiring molecular detail in the animal model studies indicating whether the model mimics or fails to mimic the molecular behavior of key genes, key pathways or the genome-wide level thought to be important for the relevant human disease,” they suggested.

“The quality of the animal model could then be determined by how well it reproduces the human disease on a molecular basis rather than simply phenotype.”

One of the complaints about this study, however, was that the researchers only examined one strain of mice, and several commentators suggested that the findings might be less clear if a broader range of test animals had been studied.

“To some extent, this belief was borne out in a similar study by Michigan State University’s Daniel Hollern and Eran Andrechek, published earlier this year in Breast Cancer Research.

Using extensive databases of mouse mammary tumor samples used to model human breast cancers, the researchers compared gene expression and pathway activation patterns both within and across mouse models (e.g., Mys, Neu, p53, BRCA). Even within models, they observed significant heterogeneity at both the gene expression level and the pathway activation level, with some genes or pathways elevated in sample subgroups within each model.

They then compared their mouse analysis with similar analyses in human breast cancer tissues and found a large number of mouse mammary tumor models had similar gene expression profiles to human breast cancers. Interestingly, however, they found that no single group of human breast cancer was modeled by a single mouse model at the pathway level.

Thus, the researchers concluded that mouse mammary tumors could be effective models of human breast cancer, but cautioned that “great care should be taken to appropriately choose the mouse model to use and that a genomic and histological characterization of tumors should be completed following experimentation.”

So what about cell culture models using human cells?

Closer with stem cells?

Cell culture models bring researchers closer to the organism of interest — in this case, humans — but even here problems can arise, because primary human cell cultures can be difficult to grow and maintain. Immortalized cells, meanwhile, are easier to grow but may be so significantly modified at the molecular level from their normal progenitors that the results of compound screening efforts may be suspect.

The advent of stem cell technologies, however, has opened a door to not only studying normal cells — healthy or diseased — but also studying the cells of individuals with the disease in question.

“What you can do today is get or make a stem cell from that person, turn it into a liver and now technically in that dish you have a liver cell that has the same genetic mutations as the liver cell in that child,” Wamhoff says. Furthermore, as highlighted time and again at the International Society for Stem Cell Research (ISSCR) conference back in June, gene editing tools such as CRISPR and TALENS mean that researchers can go into their gene-affected cell lines and “fix” the errant genes to create healthy controls that have essentially the same genetic makeup as the donating patient. This allows scientists the opportunity to then test for the impact on the compound on these cultures and clearly distinguish between disease-specific effects and potential off-target effects.

Such efforts may be particularly useful when examining conditions where cell biopsy can be difficult and/or dangerous, such as in neurological conditions.

“The Salk Institute’s Fred Gage and colleagues presented some of their efforts to model autism spectrum disorder (ASD) by generating neural progenitor cells and mature neurons from affected and age/gender-matched control cell lines. While the results are quite preliminary, the researchers noted altered cell cycle and levels of excitatory and inhibitory markers of neural cells during early stages of cell differentiation, providing a possible window into autism pathology.”

Also working in ASD, researchers at CHOC Children’s Research Institute described their efforts to build a repository of more than 200 cell lines from ASD patients and unaffected volunteers that can be differentiated into neurons and glia. The goal is to provide a resource to evaluate and compare data from different cell lines to better understand the causes and then develop new therapeutics or better diagnostics.

But even here there may be a problem, for it seems that newly minted stem cells may possess all of the tools of their newfound trade, but that doesn’t make them identical to the cells they’re mimicking.

“It turns out that they are very naive,” Wamhoff explains. “They’re immature at best, cannot do all the things that the actual cell in the disease state has.”

In a review published in Acta Pharmacologica Sinica, Harbin Medical University’s Xiao-long Xu and GSU China’s Zhong Zhong concurred, placing their focus on neurological diseases.

“Many neurodegenerative diseases are late-onset diseases, and their key phenotypes may not manifest easily within a short period of time in culture,” they wrote, further suggesting that many of these conditions also involve interactions between cell types and/or responses to environmental stressors.

“Therefore, it may be necessary to expose cells to the relevant biological, chemical or environmental stressors to reveal the underlying disease phenotypes when modeling late-onset, non-cell-autonomous and complex multimodal diseases using iPSCs,” they concluded.

At ISSCR, Daniela Cornacchia and colleagues from Sloan-Kettering Institute for Cancer Research and Weill Cornell Medical College described their efforts to do just that, by looking for factors that could induce aging in iPSCs. Earlier efforts by the same group had shown that they could reinduce age markers erased during cellular reprogramming through ectopic expression of progerin, the mutant protein involved in the premature aging disease progeria. In the current studies, they set about to identify age-related transcriptional and epigenetic markers by comparing primary cells from young and old donors, as well as the iPSCs arising from those cells.

“Differential factors identified by our studies are employed to yield an improved ‘aging cocktail’, aimed at testing our primary hypothesis that induced in vitro aging allows the development of more faithful models of late-onset degenerative disorders including [Parkinson’s disease],” they wrote.

A potential challenge to this approach, however, is that you are introducing artificial factors to the cellular mix, albeit factors based on biological reasoning.

Wamhoff, in contrast, takes a more reductionist view, advocating the idea of going back to the original physiology.

“You need to take those cells and put them back in their physiological context,” he continues. “You need to find their neighbors and bring them back in. You need to restore blood...
**LIFE-LIKE**

CONTINUED FROM PAGE 23

flow, restore contraction. And when you do that, the really naïve, naive, naive liver you created from a stem cell can now become like an adult rare disease liver cell, and now you can go after a therapy."

Spheroids and organoids

As noted in the feature Life moves on (July 2014 issue of DDNews), there has been significant movement toward the development of 3D cell cultures as a mechanism to gain some of the biologically critical information lost when cells are plated 2D.

In a review published in Stem Cells in 2013, Robert Hynds and Adam Giangreco of University College London set that complex intercellular communication and organization networks normally found in tissues can be difficult to identify or may be lost when using 2D cultures. "This is because in vivo, cells exist within a complex network that provides important signalling and biomechanical components," they wrote, echoing Wamhoff’s thoughts. "Overall, 3D cultures recapitulate in vivo cell-cell and cell-matrix interactions more successfully than 2D plastic substrate cultures. Thus, 3D culture models allow for the emergence of more physiologically relevant cell phenotypes."

Increasing awareness of this phenomenon has led to rapid growth in the market for cell culture and media to support research on organoid types of tissues such as the liver. "The goal, according to Hynds and Giangreco, is to then use these more complex models so much as we currently use 2D cell culture models of human disease."

"Multitwell plate-based organoid assays would then be channelled into compound toxicity and efficacy screening systems such as gene expression microarray, protein mass-spectrometry and multiplex ELISA platforms," they suggested. "High-throughput and high-content analysis would be achieved using automated cell manipulation and readout systems."

But even organoids have their limitations. Beyond a certain size, diffusion becomes a limiting factor for any test because a lack of circulation, whether of nutrients or test compounds. To some extent, this issue can be moderated through improvements in bioreactor technology, but as Wamhoff indicated earlier, there is more to life than simply having the right cell combinations and being able to feed them.

**Organ recitals**

"It was not just a matter of bringing two cells together in a laboratory, because people had done that before and that wasn’t working," he says. "There is something else missing. That something else was physiology and the physical forces that act on those cells within the human body."

"In a blood vessel, the cell that lines the blood vessel wall senses the idea of flow and pressure, as the heart begins to beat in development," he continues. "The cells respond to blood flow and that blood flow dictates the function of that cell. And that cell talks to its neighbor and dictates the function of it."

Thus, to create a more accurate model of human health or human disease, it is critical to reproduce the dynamics of physiology back into the cell culture system, and while technically challenging, this has been done in a number of ways. At the Wyss Institute at Harvard, for example, Founding Director Don Ingber and colleagues have taken a microfluidics approach to essentially create organs-on-chips. Organ-appropriate cells line the channels where they can be exposed to each other and to fluids or gases. But just as importantly, the chips—about the size of a memory stick—have been designed to allow physical processes such as flexing to be incorporated.

In a video, Ingber introduces the lung-on-a-chip model. "It has human airway cells from the air sac on a membrane that’s porous. On the other side of the membrane are human capillary blood vessel cells. There’s air on one side. There’s flowing medium with human blood cells in it like blood on the capillary side. And the whole thing stretches and relaxes, just like our lung does when we breathe."

The breathing action is the result of changes in air pressure in two channels that line the main physiological channel. As the vacuum increases in these passages, it stretches the tissue, which then relaxes as the vacuum is diminished. "We mimic various types of physiological responses to drugs, toxins or various types of materials that we encounter on a daily basis," adds Technology Development Fellow Dan Huh.

In proof-of-concept experiments, the researchers were able to introduce bacteria to the airway and watch as white cells in the blood stream responded by moving through the membrane and ingesting the bacteria. They monitored cell migration using high-content imaging.

The group was also able to mimic IL-1β-induced edema that can occur in cancer patients receiving the cytostic. At IL-2 levels commonly given to cancer patients, small amounts of fluid translated from the blood stream side to the airway when the system was static. When the system mimicked lung expansion and contraction, however, the fluid completely filled the airway chamber and blood clots were noted in the airway.

Since their first publication in 2010, the organization has developed more than 10 organ models, including chips for liver, gut, kidney and bone marrow, and in late July, they announced the launch of the company Organs-on-Chips to commercialize the technology.

Aside from the chips themselves, however, the group has also developed an instrument to automate the various chips and fluidically link the organs-on-chips together to better mimic whole-body physiology, human-body-on-chips. HemoShear took a somewhat different approach (see the sidebar in this section titled “How’d they do that?”).

"We set out to create, first, a healthy human blood vessel in a laboratory," Wamhoff explains. "And we did that by superimposing on the vascular system human physiological parameters that were deduced from a human high-resolution MRI."

To do this, they co-cultured endothelial cells and smooth muscle cells in a 75-mm Transwell plate and then added a cone and plate drive to simulation hemodynamics, as well as in-flow and out-flow tubing to move culture fluids across both cellular surfaces. As he goes on to explain, this work couldn’t have been done 15 to 20 years ago, as the technology went.
to understand how the mechanical forces were somehow sensed and then recreate them on the bench really didn’t exist until the early 2000s, when molecular physiologist Wamhoff and company co-founder and biomechanical engineer Brett Blackman first met at the University of Virginia.

The combination of technologies was a total game-changer to Wamhoff.

“When you take a cell and you put it in a dish, you can squirt a drug on it and get the response that you think you’re looking for,” he explains. “It turns out that the concentration of that drug is usually so high that you can never achieve that concentration in a human. So how do you make a decision off of that?”

“Once we let the cells talk to each other and gave them the physiological forces back, they now started responding to drugs at in-vivo concentrations.”

But as with drug discovery, success on the bench does not always translate into broader commercial success. Thus, it was critical for HemoShear to validate both their vascular and liver models.

As Wamhoff explains, potential pharma partners weren’t about to sign on to collaborate with HemoShear if they couldn’t validate their system, because any IND filings arising from the research would slam up against FDA questions.

“It took us well over five years and a lot of drugs and burning a lot of cash to validate it,” he says.

The company has screened more than 200 drug compounds, most of them FDA-approved therapeutics, to validate that they can reproduce the known in-vivo effect at clinical concentrations.

“We can show efficacy, safety or harm, and we’ve had a pretty good track record,” he adds.

The company has screened more than 200 drug compounds, most of them FDA-approved therapeutics, to validate that they can reproduce the known in-vivo effect at clinical concentrations.

As a more recent show of success, the company announced in October the successful completion of the first phase of a project with the National Cancer Institute to recreate the cancer tumor microenvironment.

“We had tumor vasculature, the tumor cells and the stromal support cells, and the hypothesis would be that if you bring all of that together in the right physiological context, you’d see drug responses at clinical therapeutic concentrations,” explains Wamhoff.

As proof-of-concept, the company created a non-small cell lung cancer tumor platform and then probed their construct with cisplatin, a drug commonly used to treat various cancers. Unlike what had been seen in mouse or other in-vitro models, HemoShear was able to demonstrate that they could effectively reduce tumor growth at clinically relevant IC50 levels.

The next step in the agreement is to generate models for other tumor types and then validate those models against other FDA-approved drugs and combination therapies.

Aside from filling in for traditional preclinical mouse models and tissue culture, Wamhoff also sees opportunities for the HemoShear system in areas such as drug repurposing (scanning other disease models), identification of off-target effects and potentially testing drugs in broader patient populations.

The last opportunity may become significant, as many drugs are approved based on data from focused patient populations, e.g., Caucasian adults aged 25 to 55.

But what about the impact of those drugs in the aged, children or people of different ethnic backgrounds or environmental exposures?

The company has already performed experiments where they examined differences in the gastrointestinal bleeding profiles of Caucasian women 70 years or older vs. Caucasian women less than 70 years old to understand the underlying cause of the bleeding.

But for all of their technical achievements, these new disease models run second to animal and traditional cell culture models in one significant way: throughput.

Wamhoff is the first to admit that the HemoShear platform is low-to-medium-throughput, although he balances that against the type of information arising from his system and the company’s arsenal of 120 simultaneous experiments being more than enough for a company HemoShear’s size.

That being said, he acknowledges that the pharma industry has built billion-dollar infrastructures around high-throughput screening, infrastructures that these companies are not going to mothball simply because new technologies have arrived.

Thus, he suggests, HemoShear and the nanofluidic device companies are going to have to evolve their systems to figure out how to plug into the high-throughput world.

Wamhoff calls that the biggest challenge in the near future. —

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**Strong statement**

Monoclonal antibody HIV drug succeeds in monotherapy clinical trial

**BY ILENE SCHNEIDER**

VANCOUVER, Wash.—According to the U.S. Centers for Disease Control and Prevention (CDC), some 1.14 million people aged 13 years and older are living with human immunodeficiency virus (HIV) infection. There are about 50,000 new HIV infections per year. Because HIV is such a big problem, the U.S. Food and Drug Administration (FDA) has given fast-track status to PRO 140, a drug candidate from CytoDyn Inc.

PRO 140 belongs to a new class of HIV/AIDS therapies—viral-entry inhibitors—that are intended to protect healthy cells from viral infection. PRO 140 is a humanized monoclonal antibody directed against CCR5, a molecular portal that HIV uses to enter cells. PRO 140 blocks the HIV co-receptor CCR5, and clinical trial results thus far indicate that it does not affect the normal function of the cell.

CytoDyn, a biotechnology company focused on developing subcutaneously delivered humanized cell-specific monoclonal antibodies as entry inhibitors for the treatment and prevention of HIV, recently announced the continuation of strong positive results for four weeks of monotherapy with PRO 140. Patients with HIV-1 are currently participating in the company’s Phase 2b treatment substitution trial. The company has requested an “end of Phase 2b meeting” with the FDA to discuss Phase 3 plans. The Phase 2b clinical study was designed PRO 140 CONTINUED ON PAGE 29

**Easing the pain**

Improved treatment for spasticity on the horizon

**BY ZACK ANCHORS**

LEXINGTON, Mass.—The first clinical study of a new drug under development by Concert Pharmaceuticals holds promise for patients who suffer from spasticity, a chronic condition that involves painful tensing and spasms of muscles. The biopharmaceutical company’s results from its Phase 1 study of CTP-354 suggest that the drug could present significant advantages over currently available treatments for spasticity.

Concert is one of several companies working to find a new and more effective treatment for spasticity. GW Pharmaceuticals is planning to launch a Phase 3 trial for its cannabis-based treatment this fall. “All of the current treatments for spasticity have substantial limitations, both in terms of dosing regimen and efficacy,” Roger Tang, CEO of Concert, tells DDNews. “We think there’s great potential for a medicine that’s easier to comply with and that doesn’t have the sedative effects of the most commonly used treatments.”

Roughly 12 million patients suffer from spasticity worldwide, according to a 2006 estimate by the American Association of Neurologic Surgeons. The condition can result from a wide range of disorders, including multiple sclerosis, spinal cord injury, cerebellar palsy, amyotrophic lateral sclerosis, stroke and hereditary spastic paraplegia. Symptoms range from mild muscle tightness to more severe symptoms, including crippling and painful inability to move limbs that can result in disability and diminished quality of life.

Concert’s recent study focused specifically on the treatment of patients suffering from spasticity as a result of spinal cord injury and multiple sclerosis. “We think there are about 250,000 patients in the U.S. that fit those two categories, and we think about half or so are not satisfied with their treatment or are not receiving adequate

**Progress on dementia**

Intra-Cellular Therapies announces topline safety results from Phase 1/2 trial of lead dementia drug candidate

**BY LLOYD DUNLAP**

NEW YORK—Intra-Cellular Therapies Inc., a biopharmaceutical company focused on the development of therapeutics for central nervous system disorders, has announced topline results from ITI-007-200, a Phase 1/2 clinical trial designed to evaluate the safety, tolerability and pharmacokinetics of low doses of its lead drug candidate, ITI-007, in healthy geriatric subjects (trial part one) and in patients with dementia, including Alzheimer’s disease (trial part two). The data presented at the 2014 annual meeting of the American Neurological Association relate to part one of the trial. Additional data, including part two of the trial, will be presented at a future scientific conference.

The initial results demonstrated that ITI-007 is safe and well tolerated in healthy geriatric subjects and met the primary objectives of the study. Further, the results indicate a
Hope for spinal injury?

StemCells Inc. takes step toward treating cervical spinal cord injury and possibly achieving a cure

BY LORI LESKO
NEWARK, Calif.—StemCells Inc. has launched its Pathway Study, a Phase 2 proof of concept clinical trial using its proprietary HuCNS-SC platform of human neural stem cells, for the treatment of cervical spinal cord injury (SCI). This is the company’s first study accessing the efficacy of neural stem cells for the treatment of paraplegics dependent on wheelchairs and breathing tubes.

“StemCells’ Pathway Study is reportedly the first clinical study designed to evaluate both the safety and efficacy of transplanting stem cells into patients with traumatic injury to the cervical spinal cord. “The expansion of this trial into patients with cervical injury is exciting because even a gain of one to two segments in cervical spinal cord injury patients can allow for additional function in the upper extremities,” Greg Schiffman, chief financial officer of StemCells, tells DDNews.

The decision to pursue a therapy for SCI “was based on the large unmet medical need combined with the strength of the preclinical science supporting the use of our HuCNS-SC cells to treat victims of spinal cord injury,” Schiffman said. “We showed the cells could repair and replace damaged or lost cells such as the myelinating oligodendrocytes or new neurons.”

Approximately 1.3 million people in the U.S. report being paralyzed due to an SCI, and there currently are no effective treatments available. Approximately 56 percent of the spinal cord injuries occur in the cervical region. Overall, approximately 13 percent of SCI patients have no mobility, and 35 percent have limited mobility after the traumatic injury.

The upcoming trial will be conducted in a randomized, placebo-controlled, single-blind study and efficacy will be primarily measured by assessing motor function according to the International Standards for Neurological Classification of Spinal Cord Injury. The primary efficacy outcome will focus on change in upper extremity strength as measured in the hands, arms and shoulders. The trial will follow the patients for one year from the time of enrollment. “StemCells Inc. has been evaluating our proprietary human neural stem cells (HuCNS-SC) for the treatment of spinal cord injury for over 10 years,” Schiffman says. “Our first preclinical work was published in the Proceedings of the National Academy of Sciences in 2005, demonstrating that our cells could promote locomotor recovery in spinal cord-injured mice.”

“Our first clinical trial in spinal cord injury was initiated in 2011 for patients with thoracic injuries to their spinal cord,” Schiffman adds. “The thoracic cord is responsible for sensory function. Earlier this year, the company completed enrollment and reported interim results from this trial on eight patients with at least six months of follow-up post-transplantation. Half of the patients transplanted had significant post-transplant gains in sensory function. The interim results also continue to confirm the favorable safety profile of the cells and the surgical procedure.”

“The key to its success so far has been the HuCNS-SC product candidate,” he continues. “We have conducted four clinical trials so far in disorders involving the brain, eye and spine. We have seen results consistent with our preclinical models in all of these studies. We believe that we have a platform in our HuCNS-SC human neural stem cells that has the ability to address a broad number of indications in the CNS, including spinal cord injuries. We see our HuCNS-SC platform as a next generation of cellular therapy and find that the vast majority of people seem to support the idea of using cells to treat serious disorders that have no other treatment options available.”

Schiffman believes that the cell therapy field is at a point “where clinical data is being generated and I think we will see several breakthrough therapeutic approaches validated over the next three to five years. This is a time of excitement and promise for the field of regenerative medicine, and I look forward to a time where we have several breakthrough stem cell-based therapies approved to treat serious disorders where there are no treatments available today.”

“The initiation of the Pathway Study represents a major milestone for StemCells Inc. as we pursue the development of a truly breakthrough therapy for spinal cord injury,” said Martin Glynn, president and CEO of StemCells. “While we are thrilled by the prospect that patients with thoracic level injuries might be able to regain lost sensory function below the site of the injury, the possibility of demonstrating improvements in sensory function across the cervical region of the cord might regain or improve lost motor function could be truly life-changing.”

ITI-007

Continued from page 27

The company believes that ITI-007 may provide additional benefits above and beyond selective 5-HT2A antagonism for treating agitation, aggression and sleep disturbances in diseases that include dementia, Alzheimer’s disease and autism spectrum disorders, while avoiding many of the side effects associated with more robust dopamine receptor antagonist. As the dose is increased, additional benefits are derived from the engagement of other receptors including modest dopamine receptor modulation and modest inhibition of serotonin transporters. The company believes that combined interactions at these receptors may provide additional benefits and tolerance profile of the drug and its pharmacokinetic profile. The results allow the future testing of a range of low doses of ITI-007 that offer the potential clinical benefits of optimal 5-HT2A antagonism and additional potential benefits offered by the gradual engagement of other receptors as the dose is increased. The outcome of ITI-007 holds the potential to make an important step forward in the clinical development of ITI-007 for the treatment of behavioral disturbances associated with dementia and related disorders.”

ITI-007 is Intra-Cellular Therapies’ lead product candidate, whose mechanism of action is believed to have the potential to yield a first-in-class antipsychotic therapy and, at lower doses, a first-in-class therapy for the behavioral disturbances associated with dementia. In preclinical and clinical trials to date, ITI-007 combines potent serotonin 5-HT2A receptor antagonist, dopamine receptor phospho-mephalin, glutamatergic modulation and serotonin reuptake inhibition into a single drug candidate. At dopamine D2 receptors, ITI-007 has been demonstrated to have dual properties and to act as both a post synaptic antagonist and a pre-synaptic partial agonist. ITI-007 has also been demonstrated to stimulate phosphorylation of glutamatergic NMDA NR2B, or GluN2B receptors, in a mesolimbic specific manner.

At the lowest dose studied to date (1 mg), ITI-007 has been demonstrated to act primarily as a potent 5-HT2A serotonin receptor antagonist. As the dose is increased, additional benefits are derived from the engagement of other receptors including modest dopamine receptor modulation and modest inhibition of serotonin transporters. The company believes that combined interactions at these receptors may provide additional benefits above and beyond selective 5-HT2A antagonism for treating agitation, aggression and sleep disturbances in diseases that include dementia, Alzheimer’s disease and autism spectrum disorders, while avoiding many of the side effects associated with more robust dopamine receptor antagonist. As the dose of ITI-007 is further increased, leading to moderate dopamine receptor modulation, inhibition of serotonin transporters and indirect glutamate modulation, clinical trials to completement the complete blockade of 5-HT2A serotonin receptors. In this dose range, ITI-007 may be useful in treating the symptoms of Huntington’s disease, Parkinson’s disease, Huntington’s chorea, bipolar disorder, major depressive disorder and other neuropsychiatric diseases.

For more information, visit www.DDN-News.com
to investigate the potential of allowing patients to enjoy treat-
ment interruption from their cur-
rent highly active antiretroviral 
therapy (HAART) regimen con-
current with a monotherapy con-
sisting of weekly injections of PRO
140. The results from the treatment 
substitution trial to date have dem-
onstrated 100-percent success in 
suppressing the viral load among 
patients who had weekly injec-
tions of PRO 140 for four weeks 
of monotherapy. There were zero 
virologic failures among 21 patients 
who have reached four weeks of 
monotherapy, and 36 patients out 
of 40 have received at least the first 
injection of PRO 140. Now Cyto-
Dyn is requesting FDA clearance 
to conduct a larger, similar Phase 
3 licensing trial to demonstrate fur-
ther the efficacy of PRO 140.

As Dr. Nader Pourhassan, 
president and CEO of CytoDyn, 
explained, “Currently, there is no 
approved antibody therapy. We 
have the antibody … HIV patients 
will be able to stop taking pills and 
have a better quality of life while 
letting the body come back to itself. 
We believe we can suppress the 
infection for three months with the 
injections alone with low toxicity, 
low side effects and high patient 
acceptance.”

Comparing these results with 
previous studies used as histori-
cal controls supports the current 
study’s successful outcome. In a 
37-patient trial of treatment inter-
ruption from HAART, the use of 
multiple antiretroviral drugs in 
an attempt to control HIV infec-
tion, approximately 50 percent 
of patients experienced viral load 
breakout before four weeks, and 
approximately 100 percent showed 
viral load breakout at eight weeks. 
In another similar study, results 
indicated that 10 of 12 patients 
experienced viral load breakout 
after just two weeks of treatment 
interruption from HAART. 

According to Pourhassan, “We 
believe this is a very strong indica-
tion that PRO 140 is effective to 
allow four weeks of drug holiday 
with weekly injections. PRO 140’s 
safety has been well documented 
in previous studies, as well as our 
current study.” PRO 140 has been the subject of 
four Phase 1/1b and two Phase 2a 
clinical trials, each of which dem-
onstrated its ability to significantly 
reduce HIV viral load in human test 
subjects. The PRO 140 antibody 
appears to be a powerful antiviral 
agent, leading to potentially fewer 
side effects and less frequent dosing 
requirements as compared to daily 
drug therapies currently in use.

Pourhassan described the com-
mercial potential of PRO 140 as 
“huge.” CytoDyn acquired it from 
Progenix in 2012. Progenix, which 
worked on PRO 140 for more than a 
decade, chose to focus its efforts on 
cancer drugs. CytoDyn has received 
about $20 million for clinical tri-
als with the drug in the past and 
recently received $8.4 million 
from the U.S. National Institutes 
of Health for a testing program at 
Drexel University.

“We believe this drug could 
change the paradigm of HIV treat-
ment,” Pourhassan said. “The 
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Dr. Nader
Pourhassan, 
president and 
CEO of CytoDyn

PRO 140
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With more than 10 million building blocks and screening 
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Continued from page 27

CTP-354 is a novel, potentially first-in-class drug, but its development is built on a version of a drug initially developed by Merck. The compound L-838417, a subtype-selective GABAA receptor modulator, was discovered by Merck, which profiled the compound extensively in preclinical efficacy models and found potential efficacy against both inflammatory and neuropathic pain. But Merck ultimately abandoned the development of L-838417 because it also demonstrated substantial pharmacokinetic limitations.

Concert was able to apply its expertise in precision deuterium chemistry to use the failed Merck compound to create CTP-354, which it then patented. Concert was able to achieve more favorable pharmacokinetics with the new molecule, even though it typically need to take doses of most of these drugs three to four times a day, which is considered by many to be an overly burdensome dosing regimen. “We understand from talking to physicians and patients that this dosing regimen is very inconvenient for both caregivers and patients,” says Tung. Another shortcoming of current treatments involve their sedative effects, which can impair cognition and cause patients to have difficulty staying awake, preventing individuals from participating in many everyday activities.

Concert conducted a clinical trial that tested multiple dosing levels through a randomized, double-blind, placebo-controlled study of 30 healthy volunteers. The trial was designed to evaluate the safety, tolerability and pharmacokinetics of 10-day repeat dosing of three different amounts of CTP-354. Results showed that the molecule was generally well tolerated, with mild dizziness and drowsiness being the most common adverse effects. No sedation was observed.

“We found that the compound was very well absorbed, with the amount present in blood stream proportional to the amount taken orally,” Tung tells DDNews. “The compound had a very long half-life—about 20 hours—which is in great contrast to the available drugs, which have half-lives of three to four hours.” The study also examined the effect of food on the drug’s effect in patients and found that CTP-354 provided similar exposure under both fed and fasted conditions, suggesting that it can be dosed without regard to meals.

Concert presented the findings of its Phase 1 trial in July at the American Neurological Association’s annual meeting.

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ALIOS
CONTINUED FROM PAGE 1
and demonstrates a high barrier to the development of viral resistance. RSV is the most common cause of serious lower respiratory tract infections in infants, and though most healthy adults can recover from RSV infection fairly quickly, infection can also be severe for the elderly, immunocompromised infants and those with preexisting pulmonary issues. The U.S. Centers for Disease Control and Prevention note that “Almost all children will have had an RSV infection by their second birthday.” There is also a link between RSV infections and the later development of asthma in children. No effective treatments exist for RSV.

On Oct. 13, Alios announced results from a Phase 2 challenge study of AL-8176, a randomized, double-blind, placebo-controlled study conducted in healthy adult volunteers who had been infected with RSV intranasally. Sixty-two healthy volunteers received either placebo or one of three dosing regimens of AL-8176: 375 mg administered orally twice daily, or 750 mg given as a single loading dose followed by twice-daily maintenance doses of 350 mg or 500 mg. In the study, AL-8176 reached its primary and secondary endpoints of reduction in viral load and improvement in symptom scores compared to placebo. The drug candidate was found to be well tolerated, with no discontinuations and no clinically significant laboratory abnormalities.

All three dosage groups of AL-8176 demonstrated a rapid, significant reduction in RSV viral load following treatment, with a mean time to nondetectability of RSV load of 1.3 to 2.3 days for the AL-8176 treatment groups. At day 12, all subjects that received AL-8176 were RSV RNA undetectable, and remained so upon follow-up on days 16 and 28.

“Alios BioPharma’s pipeline is closely aligned with our vision to continue to address important unmet medical needs through scientific innovation,” Dr. Johan Van Hoof, global head of infectious diseases and vaccines at Janssen, noted in a statement. “This acquisition will allow us to combine their innovative compounds with our vast experience in viral diseases to deliver novel medicines and treatment options for patients worldwide.”

This could be a boost in Johnson & Johnson’s ability to compete with rival Gilead Sciences in another arena, as Gilead is also advancing an RSV drug candidate: GS-5806, an investigational oral RSV fusion inhibitor that saw positive results in a Phase 2a study earlier in the year. Michael Yee, an RBC Capital Markets analyst, noted that an RSV drug could potentially see annual sales of at least $1 billion.

The companies raced each other to be the first to get a hepatitis C compound approved last year, and while both got a horse to the track, so to speak—Gilead’s Sovaldi and Johnson & Johnson’s Olysio—Sovaldi has outperformed its competition, seeing better Phase 3 clinical trial results and becoming “the drug to most rapidly ever reach billion-dollar blockbuster status, with sales totaling more than $5 billion in the first six months of this year,” according to a Motley Fool article. Alios also has three liveratitis C compounds in its pipeline, in preclinical, IND and Phase 2 development.

Correction
The article “Cognitive computing in the clinic” in the October 2014 issue erroneously attributed several quotes and comments to Dr. Nicholas LaRusso of the Mayo Clinic that should have been attributed to Dr. Michael Weinr, director of healthcare strategic services at IBM. To see the corrected copy in the online version of the story, you can enter E101402 in the Edit-Connect Code window at http://ddn-news.com/15
A new universal in cell biology

Engineering, physics, computational modeling and quantitative methods are all part of this year’s ASCB special sessions

BY LLOYD DUNLAP

PHILADELPHIA—It is not by chance that the American Society for Cell Biology’s 54th ASCB Annual Meeting is co-hosted this year by the International Federation of Cell Biology (IFCB). Indeed not. “You are a cell biologist, whether you think of yourself that way or not,” notes Wallace Marshall, chair of the Program Committee for the 2014 ASCB Annual Meeting. “Regardless of what field is stamped on your union card, if you care about cell biology, you need to go to the ASCB Annual Meeting, which this year is being held jointly with the International Federation for Cell Biology.”

Cell biology and disease

The field of cell biology is constantly evolving, Marshall notes, “and an important goal of the annual meeting is to track new developments. In recent years, there has been a growing appreciation of the role of cellular dysfunction in diseases. Studies at the interface of medicine and cell biology have shed important light on both fields, and so for the past several years the ASCB Annual Meeting has devoted special attention to highlighting the cell biological basis of disease and medicine.”

“At this year’s ASCB/IFCB meeting, we will continue this trend in two ways,” Marshall observes. “First, we will have a special bench-to-bedside panel discussion on translation of cell biological discoveries to the understanding and treatment of disease. Second, we have included disease experts as organizers of many of the sessions, and these experts will help stimulate thinking about disease connections across the full spectrum of cell biological topics.”

“Another emerging trend in cell biology is the constantly increasing importance of quantitative concepts and approaches,” he adds. “The living cell is an emergent phenomenon, produced by the mutual interaction of huge numbers of molecules. The only way to begin to understand how such a complex system assembles and functions is to harness the same tools and conceptual approaches that have proven useful in engineering and physics.”

In recent years, Marshall notes, the importance of computational modeling and quantitative methods has been emphasized in special sessions, such as ones on mathematical modeling.
But having one or two special sessions on quantitative thinking also creates a sense that this is a different way of approaching cell biology, perhaps as a supplement to ‘real’ cell biology,” he says. “Indeed, I attended one session on the role of modeling in which it was implied that models are something to be added onto the end of a cell biology paper to increase publishability, much as a piece of parsley may be added as a garnish to a steak dinner. In my humble opinion, this approach is completely backwards and misses the most important value of a model, that it can be used to help design the experiments from the outset of a project.

“So this year, rather than isolating modeling and quantification in their own separate compartment, like toxic enzymes to be sequenced in the lysosome, we decided to let quantitative and physical sciences pervade the entire meeting by appointing quantitative cell biologists to co-chair many of the minisymposium sessions.”

Marshall explains that to balance the tasks of increasing coverage of disease and quantitative biology, while retaining the traditional core topics of cell biology, they assembled a tripartite Program Committee, consisting of a “core” subcommittee (Mohan Balasubramanian, Magdalena Bezanilla, Orna Cohen-Fix, Ana Maria Cuervo, Beatriz Fontoura, Cynthia Jensen, Franck Perez, William Prinz, Luis Weisman, Mark Winem, Richard Voyle and Xiaodong Wang); a “cell biology and disease” subcommittee (Helen Blau, Catherine Dulac, Tom Misteli, Gregory Pazour, Jody Rosenblit and Marino Zerial); and a “physical and quantitative cell biology” subcommittee (Marileen Dogterom, Aki Kusumi, David Odde and Jit Louie).

“Keeping all the conference calls between these groups organized was only possible through the tireless efforts of ASCB’s Meeting and Abstracts Manager Alison Harris,” he adds. “Three other participants deserve special mention. ASCB President Jennifer Lippincott-Schwartz and Executive Director R. Kennedy for Visit Philadelphia.

“We are truly blessed in our field to have a single unifying event each year that brings us all together in one place. The tradition of a single, recurring meeting in cell biology that has now been running for 54 years helps to create a group identity. This is particularly important for cell biology, an inherently interdisciplinary field that has historically drawn on methods and concepts from a wide range of disciplines, including molecular biology, cytology, genetics, microscopy and physics.”

Wallace Marshall, program chair for the 2014 ASCB Annual Meeting

Stefano Bertuzzi never failed to offer their own insights and perspectives, which we found invaluable as we grappled with difficult decisions about topics and organization. In addition, Cynthia Jensen of the IFCB has been one of the most active participants in all of our conference calls and has played an invaluable role in helping to organize this joint meeting.

Four reasons to attend ASCB 2014

“First of all,” the ASCB’s program chair emphasizes, “you need to go to the meeting because it is simply the most efficient way to learn about the latest thinking, methods and results in the field. Whether you are an established investigator or someone just starting out, you need to have access to this cutting-edge information.”

“The ASCB Annual Meeting was the first scientific conference I ever attended,” Marshall continues. “I had been in graduate school only a couple of years, and as an electrical engineer who had become interested in living cells, I had the sense that many of my classmates had some outside source of information about cell biology that I didn’t have access to. Gradually it emerged that this was the magic source of information was the ASCB Annual Meeting. So that year I signed up for the meeting and showed up with my poster. It was like a window onto a whole wider world that had been opened. Now I could see the people whose papers I had been reading, hear them discussing their latest results in their own words and even have the chance to talk about my own science with these same individuals when they came to my poster. I haven’t missed a single ASCB Annual Meeting since. I make sure to go every year because I can’t afford to miss it, and neither can you.”

“Second, he says, “We are truly blessed in our field to have a single unifying event each year that brings us all together in one place. The tradition of a single, recurring meeting in cell biology that has now been running for 54 years helps to create a group identity. This is particularly important for cell biology, an inherently interdisciplinary field that has historically drawn on methods and concepts from a wide range of disciplines, including molecular biology, cytology, genetics, microscopy and physics.”

Third, he notes, ASCB has a strong tradition of providing mentorship and career support for its members, especially students and postdocs. Again this year, the meeting will include a Professional Development thread comprised of activities that can help attendees get jobs or enhance their careers. These activities include a grant writing workshop, scientific career panels, one-on-one CV review, sessions on international training and funding opportunities, career discussion and mentoring roundtables, and much more.

“Finally, the ASCB as a society fights for science funding and helps all of us through its advocacy, outreach and career development activities,” Marshall points out. “The Annual Meeting provides a focal point for regrouping and discussing where these efforts are going. By attending the meeting you have access to workshops and special sessions in a range of important issues and topics. This is the best time and place to make your voice heard in guiding the future of the field and shaping its role in society.”

On the whole, I’d rather be in Philadelphia

The subhead above comes to us by way of late, great performer WC. Fields when he was contemplating his eventual death; also, movies like “Rocky” depict Philadelphia as a gritty, tough city, but this image belies the architectural beauty, cultural diversity and rich history of one of America’s oldest cities. Within cell biology, Philadelphia has long been a research hub, and that continues to be the case today. In that respect, there are few more appropriate cities for the ASCB/IFCB meeting. But if you are attending, you might want to ensure getting there early, because Saturday starts the meeting with member-organized special interest sessions. These intense sessions feature topics and speakers selected by the people who know cell biology best—the members of ASCB.

That night at 6 p.m., keynote talks from Steven W. Squyres and Robert M. Hazen will offer a panoramic view of reality that spans the history of the cosmos to the origin of life. Special award talks from Keith Porter Lecturer Michael Sheetz and E.R. Wilson Medals Bill Brinkley, John Heuser and Peter Satir will cap the program on Sunday and Tuesday evenings. But while these special talks will be exciting and thought-provoking, another important reason to go to a meeting is to learn detailed information that can help you in your own research. And for this purpose you just can’t beat posters. Posters provide the best way to learn the most cutting-edge information from the people actually doing the work and to engage in a back-and-forth discussion that is usually not possible just before, during or after lectures, no matter how interactive the format of some of them. Posters are the heart of any serious meeting, and this has always been particularly true at ASCB.

In recognition of the importance of posters, this year ASCB has carefully structured the meeting schedule to ensure that everyone has plenty of opportunity to view them and meet the presenters. The former concept of the exhibit hall has been transformed into the ASCB Learning Center, and from noon to 3 p.m., Sunday through Tuesday, all meeting activities will take place there. Poster presentations and ePoster talks are scheduled for that time slot. This will also provide an opportunity to interact with the exhibitors, who have been encouraged to provide attendees with a variety of learning experiences, not just “sales pitches.” Visit the exhibits and attend their tech tutorials and tech showcas- ses to learn about the latest advances that help move cell biology forward. Between the posters and exhibitors, Marshall insists, you really can learn a lot in the ASCB Learning Center.

Each day the posters are augmented with symposia and minisymposia on a range of topics that span all of cell biology. Between the special talks, workshops, posters, symposia and minisymposia, think of the ASCB/IFCB meeting as an all-you-can-eat buffet of cell biology for your mind to feast on—and all your favorite dishes are served each day. John Heuser is famous for his signature eating options, like cheesesteaks and soft pretzels, among its many other features. But they probably won’t help your career along as well as the ASCB/IFCB fare will.
Keynote speakers will span the origin of life to the cosmos

UNDERSCORING THE MULTIDISCIPLINARY FOCUS OF this year’s ASCB meeting, keynote speakers Robert M. Hazen and Steven W. Squyres bring career-long research specialties in the origins of life and exploration of space. “Mineral evolution, mineral ecology and the co-evolution of life and rocks” will be the subject of Hazen’s address, while “The habitability of Mars as revealed by the Mars Exploration Rovers Spirit and Opportunity” will be discussed by Cornell University's Squyres. The keynote talks occur on the evening of the meeting’s opening day, Saturday, Dec. 6, at 6 p.m. The event will be followed by an opening night reception and the International Research and Training Exchange Fair.

Robert M. Hazen
Carnegie Institution of Science and Deep Carbon Observatory

Dr. Hazen is a research scientist at the Carnegie Institution of Washington's Geophysical Laboratory and Clarence Robinson Professor of Earth Science at George Mason University. He received degrees in geology at the Massachusetts Institute of Technology in 1971 and a Ph.D. at Harvard University in earth science in 1975. After studies as NATO Postdoctoral Fellow at Cambridge University in England, he joined the Carnegie Institution’s research effort. Hazen is the author of more than 350 articles and 20 books on science, history and music. A Fellow of the American Association for the Advancement of Science, he has received the Mineralogical Society of America Award (1982), the American Chemical Society Ipatieff Prize (1986), the ASCAP Deems Taylor Award (1989), the Educational Press Association Award (1999), the Elizabeth Wood Science Writing Award (1998) and the Distinguished Public Service Medal of the Mineralogical Society of America (2009). Hazen's recent research focuses on the role of minerals in the origin of life, including such processes as mineral-catalyzed organic synthesis and the selective adsorption of organic molecules on mineral surfaces. He has also developed a new approach to mineralogy, called “mineral evolution,” which explores the co-evolution of the geosphere and biosphere.

In addition to his mineralogical research, he is principal investigator of the Deep Carbon Observatory, which is a 10-year international effort to achieve fundamental advances in understanding the chemical and biological roles of carbon in Earth's interior. Some of Hazen's books, such as The Music Men, Wealth Inexhaustible and Keepers of the Flame—all three co-authored with his wife, Margaret Hindle Hazen—explore ties between technology and culture. The Breakthrough, The New Alchemists, Why Aren’t Black Holes Black, The Diamond Makers and Genesis describe the forefront of scientific research. He has also written widely for popular audiences, including articles in Newswrok, Scientific American, Smithsonian Magazine, New Scientist and The New York Times Magazine. He appears frequently on radio and television programs on science, and he developed two popular video courses: The Joy of Science and The Origins of Life, both produced by The Teaching Company. In addition to his scientific activities, Hazen is a professional trumpeter. He is presently a member of the National Philharmonic, the Washington Bach Consort and the National Gallery Orchestra.

Steven W. Squyres
James A. Weeks Professor of Physical Sciences

Dr. Squyres' research focuses on the robotic exploration of planetary surfaces, the history of water on Mars, geophysics and tectonics of icy satellites, tectonics of Venus, planetary gamma-ray and X-ray spectroscopy. Research for which he is best known includes study of the history and distribution of water on Mars and of the possible existence and habitability of a liquid water ocean on Europa.

From 1978 to 1981 he was an associate of the Voyager imaging science team, participating in analysis of imaging data from the encounters with Jupiter and Saturn. He was a radar investigator on the Magellan mission to Venus, a member of the Mars Observer gamma-ray spectrometer flight investigation team and a co-investigator on the Russian Mars 6 mission. Squyres is currently the scientific principal investigator for the Mars Exploration Rover Project. He is also a co-investigator on the Mars Express mission and on the Mars Reconnaissance Orbiter's High-Resolution Imaging Science Experiment. He is a member of the Gamma-Ray Spectrometer Flight Investigation Team for the Mars Odyssey mission and a member of the imaging teams for the Cassini mission to Saturn.

His scientific publications include "The Athena Mars rover science investigation," "The Spirit rover’s Athena science investigation at Gusev Crater, Mars," "In-situ evidence for an ancient aqueous environment at Meridiani Planum, Mars," "The Opportunity rover's Athena science investigation at Meridiani Planum, Mars,” “Sedimentary rocks at Meridiani Planum: Origin, diagenesis and implications for life on Mars,” “Rocks of the Columbia Hills,” “Two years at Meridiani Planum: Results from the Opportunity rover," “Overview of the Opportunity Mars Exploration Rover mission to Meridiani Planum: Eagle Crater to Purgatory Ripple,” “Detection of silica-rich deposits on Mars” and “Exploration of Victoria Crater by the rover Opportunity.”

Visitors and locals use the Phlash to get to the city’s historic and cultural attractions easily and quickly. From May until Labor Day, the big purple bus transports people every day, every 15 minutes from 10 a.m. to 6 p.m., and then it runs on weekends until December 28. The Phlash is $2 per ride or $5 for an all-day pass, and its more than 20 stops are conveniently located near popular places—Independence Visitor Center, Independence National Historical Park, Philadelphia Museum of Art, Penn’s Landing, Reading Terminal Market, Pennsylvania Convention Center, Philadelphia Zoo and Please Touch Museum.

Introduced to the region by German (“Pennsylvania Dutch”) settlers in the 18th century, pretzels—dough twisted into three loops, then baked, salted and served hard—quickly became a favorite local snack. Now, of course, there’s the famous Philly soft pretzel, purchased from street vendors or from bakery storefronts such as the Philly Soft Pretzel Factory. No matter what form the pretzel takes—braided, sticks, nuggets and bagels—it’s often accompanied by mustard.
Metabolon taps Medtia for European marketing of prediabetes tests

The collaboration includes Metabolon’s Quantose IR and Quantose IGT tests

BY KELSEY KAUSTINEN

RESEARCH TRIANGLE PARK, N.C.— Metabolon Inc. and company Rockland Immunochemicals Inc. recently inked a partnership with Spanish biomedical company Medtia Biotech S.L. for the commercialization of Metabolon’s Quantose IR and Quantose IGT prediabetes tests in Europe. Under the collaboration, Medtia will market the tests to hospital and clinical laboratories in Spain, Portugal, France, Italy, the United Kingdom, Germany, Switzerland, Sweden, Norway, Denmark, Finland, the Netherlands, Belgium and Austria. Financial details for the partnership were not disclosed.

“Licensing our Quantose IR and Quantose IGT technology to Medtia in Europe is an important next step in expanding the availability of these obesity-related diagnostic tests outside the U.S.,” Dr. John Ryals, president and CEO of Metabolon, commented in a statement. “We are confident in Medtia’s broad knowledge of the molecular diagnostics market in Europe. Earlier this year, Quantose IR became commercially available in Mexico through Patia Biopharma, a leading Latin American diabetes public health company. We are delighted to see our technology available to contribute to the health of millions of people in these two major markets.”

Prediabetes, according to the American Diabetes Association, affects 25% of the adult population in the United States, or 50 million adults. The condition is characterized by elevated blood sugar levels and is a major risk factor for type 2 diabetes—a disease that affects over 29 million Americans, or 9% of the population.

Although only 35 to 40 percent of all breast cancers will ever metastasize, almost 85 percent of women with newly diagnosed breast cancer are treated with chemotherapy. MetaStat hopes to spare women from needless chemo with its MetaSite Breast diagnostic.
Advanced Cell Diagnostics receives major NCI grant

BY JIM CIRIGLIANO

HAYWARD, Calif.—The U.S. National Cancer Institute (NCI) has awarded a two-year, $1.4 million grant under its Small Business Innovation Research Phase II Program to Advanced Cell Diagnostics Inc. (ACD), a company with a focus on in-situ nucleic acid detection for life-sciences research and clinical diagnosis.

The grant will allow ACD, along with its academic partner Cleveland Clinic, to work toward the development and validation of a diagnostic test based on the company’s proprietary RNAscope technology for discriminating various B-cell non-Hodgkin lymphomas (NHLs) from benign lymphoproliferative diseases. The test would be an important advance in diagnosing B-cell lymphomas due to the shortcomings of conventional methods of establishing clonality in the majority of NHLs.

“Reliable in-situ detection of any RNA in routine clinical specimens has been an unmet need for over 40 years despite many efforts and improvements,” says Dr. Xiao-Jun Ma, chief scientific officer of ACD. “Traditional RNA in-situ hybridization (ISH) techniques are limited to the small fraction of highly expressed genes, leaving 95 percent of the expressed genes undetectable. ACD’s RNAscope technology addresses the need of detecting that 95 percent of the transcriptome.” RNAscope is said to be the first automated multiplex chromogenic and fluorescent in-situ hybridization platform capable of detecting and quantifying RNA biomarkers in situ at single-molecule sensitivity. An prime example of the potential of the RNAscope technology is in the detection of Ig kappa/lambda light chain mRNAs, which are expressed at extremely low levels in most B-cell lymphomas, falling into the undetectable 95 percent category for conventional techniques. Clinical laboratory detection of Ig light chain restriction (LCR) is a helpful tool in the differential diagnosis that includes lymphoid hyperplasia, atypical lymphoid hyperplasia, chronic inflammation and B-cell neoplasia.

“When fresh tissue is available for examination, LCR can be readily detected as an abnormal kappa/lambda surface immunoglobulin ratio using flow cytometry. However these samples are often unavailable in many clinical settings. Existing solutions, including chromogenic in-situ hybridization and immunohistochemistry (IHC), only address a small fraction of B-cell lymphomas, such as multiple myelomas and those lymphomas with chromosome hyperdiploid differentiation. ACD’s assay reportedly will be applicable to essentially all B-cell lymphoma variants.

“This breakthrough is achieved through a proprietary probe design and signal amplification strategy that allows robust signal generation for true target detection but not for nonspecific background,” says Ma. “This is in contrast to previous efforts focusing mainly on signal enhancement and little on the background problem.”

“Developing and validating an RNAscope-based diagnostic test is similar to that of the more familiar PCR or IHC-based assays. In some ways, it is actually simpler due to the rapid assay development time (new probes can be had within two weeks) and the assurance of probe sensitivity and specificity.”

Dr. Xiao-Jun Ma, chief scientific officer of ACD

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The biggest challenge may be that we need to be more vigilant about how samples are fixed and processed so we are detecting RNA, which is more labile than DNA and protein,” Ma says. “We have developed our technology to be compatible with established standards such as CAPASCO guidelines for clinical sample preparation. We also strongly recommend the inclusion of positive and negative control probes in the assay to assess RNA adequacy and sample quality. In our experience, most routinely processed clinical specimens, including archival materials that are more than 10 years old, are adequate for RNAscope staining.”

Cleveland Clinic will provide their expertise in pathology and clinical medicine to guide the development and validation of the assay to help ensure the final product is well-validated and suited for everyday clinical use by pathologists. Cleveland Clinic will also provide access to patient samples and corresponding reference data generated by standard of care testing.

The Small Business Innovation Research grant is a high priority program that encourages domestic small businesses to engage in research and development that holds promise for commercialization. ACD had previously received a one-year Phase I grant and completed the project in 2013, which made it eligible to apply for Phase II funding. The Phase II award will be applied to expenses to cover personnel, materials and supplies and facilities related to the proposed research.

“This award is a further validation of the clinical utility of RNAscope technology,” Dr. Yuling Liu, president and CEO of ACD, said in a news release announcing the receipt of the grant. “We are very pleased that NCI has recognized the diagnostic potential of RNAscope technology and are grateful for its continued support.”

“To stem the tide of the prediabetes/diabetes epidemic, we must get ahead of the development of these conditions and focus on prevention. That’s where Quantose IR comes in. The test is a tool that provides information to physicians, so they can identify at-risk patients and take steps to prevent the development of prediabetes and diabetes.”

Eric Button, senior vice president of diagnostics at Metabolon

METABOLON

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Diabetes Association (ADA), is characterized by “blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes.” It is sometimes referred to as impaired glucose tolerance or impaired fasting glucose.

Metabolon’s Quantose IR is a laboratory-developed test that reflects insulin resistance based on insulin and three non-glycemic biomarkers. It can determine an individual’s risk of progression to prediabetes earlier than traditional glycemic measures such as hemoglobin A1c. According to the ADA, the A1c test measures a patient’s average blood glucose over the past two to three months, with prediabetes diagnosed in the range of 5.7 to 6.4 percent and diabetes at 6.5 percent or higher.

Quantose IGT reflects the degree of impaired glucose tolerance in a patient, which is a core metabolic defect in dysglycemia and a known risk factor for prediabetes. Quantose IGT can be used as an alternative to an oral glucose tolerance test or to determine patients who may be candidates for such a test.

“Diabetes is a significant global health concern, and the costs to society are high and growing rapidly,” Oscar Rodriguez, director of Metdia Biotech, said in a news release. “According to the International Diabetes Federation, more than 55 million adults in the European Region are coping with diabetes every day. Another 66 million have impaired glucose tolerance, a known risk factor for prediabetes. Tests using Metabolon’s Quantose tool that provides an assessment of someone’s risk of not just type 2 diabetes, but also heart disease and stroke. Fortunately, if the condition is caught early, steps can be taken to avoid the development of diabetes; the ADA reports that an individual with prediabetes can lower their diabetes risk by 58 percent by losing 7 percent of their body weight and exercising moderately for 30 minutes a day, five days a week. The fact that early intervention can increase a person’s chances of avoiding a decline into diabetes provides significant support for tests like Metabolon’s.”

Eric Button, senior vice president of diagnostics at Metabolon

“To stem the tide of the prediabetes/diabetes epidemic, we must get ahead of the development of these conditions and focus on prevention. That’s where Quantose IR comes in. The test is a tool that provides information to physicians, so they can identify at-risk patients and take steps to prevent the development of prediabetes and diabetes.”

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For more information, visit www.DDN-News.com
METASTAT CONTINUED FROM PAGE 35

tumor through the bloodstream to other areas of the body—is responsible for about 90 percent of all solid tumor cancer-related deaths, according to Dr. Oscar Bronsther, MetaStat CEO.

Being able to predict the probability of systemic metastasis allows doctors to better customize cancer treatment decisions by identifying patients with a high-risk of systemic metastasis who need aggressive therapy, and sparing patients with a low-risk of systemic metastasis from the harmful side effects and expense of chemotherapy, Bronsther said.

“Some 240,000 women are newly diagnosed with breast cancer every year in America,” Bronsther tells DDNews. “Virtually all will have their tumors surgically removed. That is the first step in their journey. What comes after that is answering the question of whether there is a need for chemotherapy, traditionally used to prevent cancer from spreading through the rest of the body.”

“Because we lack a good (approved) cancer diagnostic, we lack the ability to effectively treat women with no progression or metastasis at all,” he continues. “That was a tough nut to crack. It never was a logical question that would tell a woman with breast cancer whether the risk of metastasis was nearly zero. Then the sword of Damocles wouldn’t have to hang over her head for a decade.”

If oncologists had access to MetaSite Breast, its diagnostic ability could dramatically improve lives and give the future back to most breast cancer survivors, Bronsther says, because only 35 percent of all breast cancers will ever metastasize. Unfortunately, at present “almost 85 percent of women with newly diagnosed breast cancer are treated with chemotherapy. Yet, only a fraction of these patients can actually benefit from chemotherapy, because only a fraction of these tumors have the biological potential to spread through the bloodstream,” he notes.

A complete course of chemotherapy is extremely expensive and, more importantly, takes at least six months and is associated with significant morbidity and a small mortality, he says. Thus, “Having the ability to identify those patients whose tumors are unlikely to metastasize, we can therefore spare those patients the complications.”

The journal paper, titled “Tumor Microenvironment of Metastasis and Risk of Distant Metastasis of Breast Cancer,” states how the MetaSite Breast test, a diagnostic assay that quantifies the number of tumor microenvironments of metastasis (TMEM) in tumor specimens, showed a strong and statistically significant association with the risk of distant spread—or metastasis—for the most common type of breast cancer.

The test performed well in assessing metastasis risk for the study’s most populous cancer subgroup: women with estrogen receptor-positive (ER+) / HER2- / HER2-negative (HER2-) disease (i.e., their cancer cells possess estrogen receptors but lack HER2 protein).

Women with ER+ / HER2- disease account for approximately 60 percent of all cases of breast cancer, according to the study. When women with this common type of breast cancer were divided into three groups based on their TMEM scores, the risk of distant metastasis turned out to be 2.7 times higher for women with the highest risk of systemic TMEM or MetaSite group compared with women with tumors in the lowest-scoring group.

The findings confirmed results from a smaller study of the test involving 30 pairs of biopsy specimens that was published in 2009. For comparison, TMEM predictions were compared on the same tumor samples to predictions from the IHC test, a diagnostic that assesses risk of recurrence by measuring levels of several proteins (ER,PR, HER2 and Ki-67) involved in tumor cell proliferation and response to hormone therapy in breast tumor tissue, the journal study reported.

As for assessing metastatic risk in the study’s most common type of breast cancer (ER+ / HER2-), “TMEM results were highly statistically significant, while IHC4 scores were borderline significant at best,” the study stated.

“MetaStat believes this is due to its unique understanding of the mechanics and the function-based processes of tumor cell migration and entry into the bloodstream.”

MetaStat is currently developing a commercially viable version of the MetaSite Breast test with automated systems to facilitate rapid repeatable implementation in a high-throughput clinical lab setting, Bronsther says.

“We are thrilled to see additional positive validation of the MetaSite Breast test,” Bronsther stated in a news release. “We believe it confirms the path-breaking approach that our function-based diagnostics, based on the biology of the mena protein and its isoforms, provide an understanding in cancer metastasis.”

“We believe our suite of breast cancer diagnostic tests, comprised of MetaSite Breast and MenaCalc, will offer women and their oncologists highly prognostic and actionable information,” Bronsther continued. “These diagnostic tests aim to empower patients with the information they seek to create the most personal and appropriate approach to their unique tumors.”

MetaStat plans on commercializing its suite of breast cancer diagnostics in December 2015 or January 2016, based on CLIA and GLP certification. The company’s commercialization efforts will be headed by Heiner Dreisemann, former president and CEO of Roche Molecular Systems.

IBA CONTINUED FROM PAGE 35

cancer. No finite time has been set, and both IBA and Philips see this as an enduring collaboration.

IBA proton therapy solutions are scalable and adaptable, offering universal full-scale proton therapy centers as well as next-generation compact, single-room solutions. IBA also focuses on the development and supply of dosimetry solutions for quality assurance of medical equipment and increased patient safety as well as particle accelerators for medical and industrial applications. Royal Philips offers products in the areas of cardiac care, acute care and home healthcare, energy-efficient lighting solutions and new lighting applications, as well as grooming and oral healthcare products.

According to Olivier Legrain, CEO of IBA, the two companies have been partners for some time, working together to improve the patient experience of proton therapy. As he explained, “This new collaboration was a natural next step for both IBA and Philips, allowing the two companies to exploit their leading positions in proton therapy and image guidance systems to provide advanced diagnostic and therapeutic solutions for the treatment of cancer.”

The collaboration aims to transform cancer care and will provide clinicians with more efficient, effective and personalized treatment for their patients, while also dramatically reducing the time to start of treatment and the cost of that treatment.

The collaboration covers sales, marketing and research and development of imaging and therapy solutions in oncology. By merging their respective expertise, IBA and Philips plan to innovate with an integrated vision for more efficient, personalized cancer care. The companies believe that leveraging high-quality imaging and proton therapy offers the potential to increase confidence in the diagnosis and treatment of cancer, reduce short- and long-term side-effects and potentially enhance the quality of life of the patient before, during and after treatment, while reducing costs.

Additionally, the collaboration will enable both organizations to mutually leverage technologies and solutions: IBA will benefit from Philips’ diagnostic imaging products offered to oncology care centers, while Philips will leverage IBA proton therapy solutions within its offering for customers in select markets around the world. The commercial collaboration also includes an integrated offering for Molecular Imaging Centers, combining IBA’s expertise in PET/CT/positron emission tomography and diagnostics expertise.

Gene Saragoni, executive vice president and CEO of imaging systems at Royal Philips, added, “Proton therapy is one of the most exciting technological advancements in the oncology field. We look forward to collaborating with IBA to enhance access to best-in-class technology for both Proton Centers and Molecular Imaging Centers, as well as to accelerate the development of our informed therapy guidance vision in ways that can change the future of care, and improve the quality of life for patients.”

Legrain concludes, “This is an exciting and important step for IBA. A closer collaboration with a company of Philips’ caliber and global reach, where we are able to combine both companies’ expertise and excellence in oncology care, will accelerate innovation and provide more efficient and effective solutions in molecular imaging and treatment solutions. This collaboration is an important step toward adaptive treatment of cancer and a personalized treatment approach to enable the best possible result for cancer patients across the globe.”
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A ‘win-win’ in women’s health

AMAG Pharmaceuticals to acquire Lumara Health, propelling company into women’s health

BY LLOYD DUNLAP

WALTHAM, Mass.—AMAG Pharmaceuticals Inc. has entered into a definitive agreement to acquire Lumara Health Inc., a privately held pharmaceutical company specializing in women’s health, for $675 million ($600 million in cash and $75 million in stock) and additional contingent consideration of up to $350 million based on achievement of certain sales milestones. Lumara Health also announced recently that the company signed a separate agreement to divest certain other assets to a third party.

Lumara Health markets the fast-growing product Makena (hydroxyprogesterone caproate injection), which was granted seven-year Orphan Drug exclusivity in February 2011 and is the only U.S. Food and Drug Administration (FDA)-approved product indicated to reduce the risk of preterm birth in women who are pregnant with one baby and who have delivered one preterm baby spontaneously in the past. Preterm birth is defined as the delivery of a baby at less than 37 weeks.

AMAG gains by acquiring Lumara, was granted seven-year Orphan Drug exclusivity in 2011 as the only FDA-approved product indicated to reduce the risk of preterm birth in women who are pregnant with one baby and who have delivered one preterm baby.

AMAG Pharmaceuticals, a generic pharmaceutical company specializing in women’s health products, recently reported the expansion of its product portfolio with the acquisition of Lumara Health. The acquisition is expected to be completed within the next three months, subject to regulatory approval and other customary conditions.

Unde the terms of the original acquisition agreement, Shire is entitled to a break fee of $350 million based on achievement of certain sales milestones. Lumara Health also announced recently that the company signed a separate agreement to divest certain other assets to a third party.

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AMAGCONTINUED ON PAGE 41

AbbVie aborts plan to acquire Shire

After U.S. tax officials begin to put up roadblocks to inversion deals, deal falls apart

BY JEFFREY BOULEY

NORTH CHICAGO, Ill.—The IRS has claimed its first victory with anti-inversion rules—or perhaps its first victim, depending on your perspective—in AbbVie with the scuttling of an intended acquisition by the company of Dublin, Ireland-based Shire plc.

It was just in August that, after months of wooing, AbbVie and Shire came to a roughly $55 billion agreement. But then, in late September, the U.S. Department of Treasury proposed unilateral changes to the tax regulations designed to prevent or deter U.S. companies from re-domiciling in other countries—technically headquarters in Ireland. The move is a response to a growing trend of companies reincorporating to an tax haven to avoid paying taxes on profits made in the U.S.

The announcement came just a few weeks after the U.S. Supreme Court ruled in Actavis v.碌rit. The court’s decision was a significant victory for U.S. companies in their efforts to avoid paying taxes on profits made in the U.S.

AbbVie and Shire had been in talks for months about a deal that would create a global pharmaceutical giant with a market capitalization of more than $200 billion. The deal would have been one of the largest in recent history and would have made AbbVie the largest pharmaceutical company in the world.

However, the talks fell apart after the U.S. Department of Treasury proposed unilateral changes to the tax regulations designed to prevent or deter U.S. companies from re-domiciling in other countries—technically headquarters in Ireland. The move is a response to a growing trend of companies reincorporating to an tax haven to avoid paying taxes on profits made in the U.S.

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Can Plasticell’s massively parallel approach help transform regenerative medicine?

STEVENAGE, U.K.—Stem cell bio-tech Plasticell Ltd. announced recently the publication of a scientific research which it says demonstrates how the company’s innovative high-throughput Combinito-

rial Cell Culture (CombiCult) technology allows a single scientist to carry out hundreds of stem cell biology experiments in parallel. The scien-

tific paper points to the potential of high-throughput technologies “Discovery of robust methods to differentiate stem cells remains a serious bottleneck for the industry. This is a major reason why only two pluripotent stem cell therapies have progressed to clinical trials despite the spending of many hundreds of millions of dollars on pluripotent stem cell translation,” said Chris Mason of University College London such as CombiCult to accelerate painfully slow biomedical research, which has hampered the development of new therapies ever since human embryonic stem cells were developed in 1998.

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those nations while often not actually moving any operations out of the U.S., but instead creating paper transactions to answer IRS burdens, a process known as inversion.

That got AbbVie to rethinking the deal and its potential profitability, and on Oct. 14, the company announced that it would not proceed with the direct - tion. “To reconsider the recommendation made on July 18, 2014, that AbbVie stockholders adopt the merger agree- ment needed to complete the pro- posed combination of AbbVie and Shire and “consider whether to withdraw or modify its recommendation.”

Some market-watchers had specu - lated that the deal would simply be modiﬁed, as both companies, particu- larly AbbVie, had been emphasizing their excitement about the potential synergies rather than the tax beneﬁts to AbbVie. The theory was that AbbVie had too much of its reputation invested in the deal and would take a hit to its cred- ibility if it backed off the acquisition. Those analyses proved to be wrong when, just a day after the announce- ment that the board would reconsider the deal, AbbVie noted that Shire had waived a three-day notice period and the AbbVie board had made a “detailed consideration of the impact of the U.S. Department of Treasury’s unilateral changes to the tax rules” and recom- mended that shareholders reject the merger and acquisition (M&A) deal, as “the breadth and scope of the changes, including the unexpected nature of the exercise of administrative authority to impact longstanding tax principles, and to target specifically a subset of compa- nies that would be treated differently than other inverted companies or foreign domiciled entities, introduced an unacceptable level of uncertainty to the transaction. Additionally, the changes eliminated certain of the finan- cial beneﬁts of the transaction, most notably the ability to access current and future global cash ﬂows in a tax-efﬁcient manner as originally contemplated in the transaction. This fundamentally changed the implied value of Shire to AbbVie in a signiﬁcant manner.”

“Although the strategic rationale of combining our two companies remains strong, the agreed-upon valuation is no longer supported as a result of the changes to the tax rules, and we did not believe it was in the best interests of our stockholders to proceed,” said AbbVie Chairman and CEO Richard G. Divis. Under the terms of the original acquisition deal, AbbVie will have to pay a break fee of approximately $1.64 billion.

While that is the third-largest fee on record to break an M&A deal, the sting might not be as hard felt for AbbVie in the end, as analysts have noted the fee—like many other related costs of the M&A negotiations and now breakup—is tax-deductible. A contrib- uted by M&A expert Donald S. Worth on the Forbes website estimates that AbbVie could realize at least $650 million in tax savings.

AMAG CONTINUED FROM PAGE 39

37 weeks of pregnancy. Approximately one in every nine babies is born preterm, or 11.7 per- cent of births in the United States. Premature birth alone costs $26.1 billion annu- ally, and average first-year medical costs are approximately 10 times greater for preterm infants than for full-term infants.

“This is a truly transformative transaction that will propel AMAG into a proﬁtable, high- growth multiproduct specialty pharmaceutical company positioned for what we expect to be continued revenue and bottom-line growth, further business diversiﬁcation and share- holder value creation,” says William Heiden, president and CEO of AMAG. Invoking what is often cliché, he refers to the deal as a “win,” but in this case there may be good reason for the characterization. Heiden and Lumara’s CEO Greg Divis have a 10-year-old relationship dating back to their days at Shering-Plough. Divis notes that AMAG “shares our commitment,” and that Makena and AMAG’s Feraheme (ferumoxytol) are a good ﬁt.

“We believe the Lumara Health transac- tion will facilitate future product acquisitions in an attractive new therapeutic area and is an excellent strategic ﬁt with our Feraheme market expansion plans,” Heiden adds. The acquisition of Lumara Health provides AMAG with a strategic commercial entry into the women’s health segment. Women’s health includes one of the largest pools of patients with iron deﬁciency anemia (IDA). Accordingly, if AMAG is successful at gaining FDA approval to expand the label of Fer- aheme beyond the current chronic kidney dis- ease indication, the 75-person strong Lumara commercial sales force could become a meaningful contributor to the growth of Feraheme in the future.

Of the 1.5 million patients with IDA, AMAG estimates that fewer than 10 percent are now treated with IV iron such as Feraheme. Thus, an expanded label for the product could pro- duce a signiﬁcant uptick in sales.

Net sales of Makena over the 12 months ending August 31, 2014, were greater than $130 million, a 72-percent increase compared to the prior-year period. In addition, based on the three months ended August 31, 2014, Makena topline health maternal health-business would be on pace to exceed annualized net sales of $180 million and EBITDA of $110 million. AMAG believes that positive market dynamics, including a favorable regu- latory environment, and implementation of a new patient- centered business strategy con- tributed to the signiﬁcant recent growth of Makena.

Heiden continued, “Makena is a unique product with clear clinical beneﬁts that serves an important medical need for at-risk pregnant mothers and their unborn children. The consequences of preterm birth are sig- niﬁcant public health issue, and we believe that Makena will be a tremendous addition to our portfolio and will be complementary to AMAG’s in-office injectables commercial experience. We’re also looking forward to wel- coming to AMAG the talented Makena com- mercial team, which has put Makena on a remarkably strong sales growth trajectory. We believe that our combined larger-scale, com- bined portfolio diversiﬁcation, new resources and broader commercial expertise will allow AMAG to create new long-term growth oppor- tunities and allow us to better serve patients.”

Another arrow in the new company’s quiver is the Drug Quality and Security Act that placed new restrictions on compounding pharmacies. Heiden notes that 46 per- cent of the competition for Makena comes from compounders, and he expects AMAG to whittle away at this business. In addition, he points out that the physicians who spe- cialize in women’s care frequently prescribe off-label drugs out of a perceived lack of a better alternative.

“I strongly believe AMAG is the right partner to support the continued growth of Makena and our maternal health business,” said Lumara’s Divis. “This transaction is a great reﬂection of the outstanding work our team has done to build the maternal health franchise to what it is today, and I am pleased that this same team will continue to grow the brand within AMAG. It has been clear from the start of our discussions that AMAG shares our commitment to at-risk pregnant mothers, their babies and their healthcare providers.”

The transaction is expected to result in projected combined 2015 product sales of $350 million and is expected to be immedi- ately accretive to adjusted earnings per share, with cost synergies of at least $20 million per year. Following the closing of the transac- tion, AMAG expects to have approximately $100 million in cash and $25.4 million basic shares outstanding. AMAG intends to pro- vide additional ﬁnancial guidance for 2015 as promptly as practicable following comple- tion of the transaction.

Upon closing, Lumara Health’s commercial operations will function as a separate business unit within AMAG, reporting directly to Heiden. AMAG intends to name current Lumara Health executives who will be joining AMAG’s leadership team at or prior to closing.

The transaction has been unanimously approved by both companies’ boards of direc- tors. The transaction has also been approved by the stockholders of Lumara Health. It is expected to be completed in the fourth quar- ter of 2014, following termination or expira- tion of the waiting period under the Hart- Scott-Rodino Antitrust Improvements Act of 1976 and completion of ﬁnancing.

In addition to the $675 million at closing, the terms of the agreement provide for con- tingent consideration of up to $350 million based on the achievement of various sales milestones for Makena, including sales achievement of $300 million, $400 million, and $500 million in consecutive 12-month periods. AMAG believes that its tax attributes following the closing of the transaction rep- resent an important corporate asset that can provide long-term shareholder beneﬁts.

I

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November 2014 || DDNews 41
Horizon Discovery acquires Sage Labs

CAMBRIDGE, U.K. & ST. LOUIS—There are a number of reasons for Horizon Discovery Group plc to acquire Sage Labs Inc. For one thing, it would enhance Horizon’s U.S. footprint and strengthens both its U.S. and European Union (EU) sales force, and it would strengthen Horizon’s intellectual property (IP) with regard to CRISPR technology as it gains exclusive rights for in-vivo zinc finger nuclease (ZFN) applications.

And all this for the price of $48 million, according to Horizon’s late-September announcement of a deal to acquire Sage. This deal “builds upon the acquisition of Combina-Tox in July and makes Horizon the world’s leading gene-editing company and the go-to company for the provision of integrated product, service and research solutions at all stages of translational genomics and personalized medicine research from sequence to therapist,” according to Horizon. Horizon will gain exclusive access to ZFN for in-vivo model generation and certain exclusive and non-exclusive CRISPR-related IP to add to its extensive in-vitro IP in CRISPR, ZFN and RNAi, the latter of which is a worldwide exclusive to Horizon.

According to Horizon, it will focus on expanding Sage’s pre-dominantly U.S. customer base by increasing its presence in Europe, Japan and beyond via access to Horizon’s business development and commercial infrastructure. The acquired business will continue to be known as Sage Labs Inc., and will operate as a wholly owned subsidiary of Horizon Discovery Group.

The acquisition was expected to be complete by Oct. 2, though there was, as of press time, no confirmation that the deal had been finalized officially—however, Sage Labs was posting news dated Oct. 23 from Horizon on its website, which said that Horizon had “announced the launch of its patient-derived xenograft (PDX) models of breast cancer under its Sage Labs brand. The new panel is the largest available collection of highly characterized PDX models, and is licensed from Washington University.”

ENDO
Continued from page 1

Transaction will include an election to pay for Auxilium stockholders to elect cash and stock, all-stock or all-cash consideration, subject to proration in accordance with terms of the definitive agreement. The per-share consideration represents a premium of 55 percent to Auxilium’s closing price on Sept. 16, 2014, the day Endo made public its proposal for Auxilium.

Immediately prior to entering the merger agreement with Endo, Auxilium terminated its proposed merger agreement with QLT Inc., in accordance with the terms of the QLT merger agreement.

According to Endo, the addition of Auxilium’s leading men’s health products and development portfolio should “significantly enhance Endo’s branded pharmaceutical business.”

“We are pleased to have reached this agreement with Auxilium, which we believe will create value for both Endo and Auxilium shareholders, as well as for patients, customers and employees,” said Rajjo De Silva, president and CEO of Endo.

“By adding Auxilium’s complementary commercial portfolio, we believe this transaction is aligned with our strategy of pursuing accretive, value-creating growth opportunities. We intend to leverage Auxilium’s leading presence in men’s health, as well as our R&D capabilities and financial resources, to accelerate the growth of Xiaflex and Auxilium’s other products. We look forward to working with the Auxilium team to achieve the growth and synergy potential of this compelling strategic combination.”

Xiaflex seems to be a big selling point in the acquisition. It is a collagenase clostridium histolyticum (CCH) biologic compound currently approved in the United States, European Union, Canada and Australia for the treatment of adult Dupuytren’s contracture patients with a palpable cord and in the United States for the treatment of adult men with Peyronie’s disease with a palpable plaque and penile curvature deformity. Xiaflex is currently in a Phase 2a study for the treatment of edematosus fibrosclerotic panniculopathy, commonly known as cellulite.

Leerink Partners, an investment bank specializing in health-care, forecasts pre- and post-deal five-year revenue compound annual growth rates of 3 percent and 8 percent, respectively.

“Key to the improved growth outlook is Auxilium’s ability to launch Xiaflex in Peyronie’s disease, where diagnosis rates remain low but Xiaflex offers a first-line alternative to surgery,” writes Jason Gerberry of Leerink.

“Based on a recent MEDAcorp survey of urologic surgeons, specialists see Xiaflex as a first-line treatment and plan to prescribe the drug to one-third of their patients within 12 months post-launch,” according to Leerink.

Global research and consulting firm GlobalData values Auxilium’s pharmaceutical assets at approximately $2.5 billion, which it says is in line with Endo’s offer.

Largely driving the company’s valuation is Xiaflex with a net present value of $920 million, followed by Testopel at $770 million and Stendra at $558 million, says Adam Dion, GlobalData’s analyst covering healthcare industry dynamics.

Dion also points out that Endo intends to leverage its resources to optimize and drive increased adoption of three key Auxilium drugs, which are Xiaflex, Testopel and Testim, the latter two both being hormone replacement agents.

“Testopel and Testim generated combined sales of $271 million in 2013, and will supplement Endo’s hypogonadism therapy Fortesta,” he explains.

However, GlobalData believes Endo’s purchase price might be slightly on the high side, “given that Auxilium was negotiating a position of weakness.”

“Auxilium’s top-line revenue was flat in 2013, and the company has been faced with slowing sales of Testim after the approval of a per- cent year-on-year drop in sales from Xiaflex,” Dion notes. “The company responded by announcing that it would cut about 150 jobs, or 30 percent of its work-force, as part of a plan to save $75 million per year. Auxilium was also considering purchasing the Canadian eye drugmaker QLT in an effort to save costs to a lower tax domicile, but recent changes to tax laws most likely thwarted those efforts.”

Dion says that Endo’s motivation behind the deal centers on cash generation and cost-cutting, remain low but Xiaflex offers a first-line alternative to surgery,” writes Jason Gerberry of Leerink.

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**People & Promotions**

**Perrigo Co. plc**
Clivety Martinez, Ph.D.
V.P. of Corporate Global Compliance & Chief Privacy Officer

**Myriad Genetics Inc.**
R. Bryan Riggsbee
Executive V.P., Chief Financial Officer & Treasurer

**Nurix Inc.**
Arthur T. Sands, M.D., Ph.D.
Chief Executive Officer

SAN FRANCISCO— Nurix, a company known for discovering and developing therapies that modulate the ubiquitin proteasome system, announced Sept. 18 that it had hired Dr. Clivety Martinez for the roles of vice president of corporate global compliance and chief privacy officer. Martinez will be responsible for overseeing the daily compliance program’s activities, driving awareness of Perrigo’s code of conduct and core values, identifying areas of compliance risk and guiding the efforts of the compliance teams at each Perrigo location worldwide. Martinez brings to Perrigo 14 years of global compliance experience in the healthcare and pharmaceutical industries.

**ICON plc**
In Spector, Ph.D.
Executive V.P. of Analytics and Consulting

**Aptose Biosciences Inc.**
Stephen B. Howell, M.D.
Chief Medical Officer

**Dimension Therapeutics**
Dr. Mark A. Goldsmith, M.D.
Chairman of the Board

**Theracan**
David Caumartin
Chief Executive Officer

**Aptose Biosciences Inc.**
SAN DIEGO and TORONTO— Aptose Biosciences, a clinical-stage company developing innovative small molecule therapeutics and molecular diagnostics that target the underlying mechanisms of cancer, recently announced that Dr. Stephen B. Howell will act in the capacity of chief medical officer. Howell is a renowned medical oncologist and leader in the development of novel drugs and drug delivery systems for the treatment of cancer and in the discovery of the molecular and genetic mechanisms underlying drug resistance. He holds the position of distinguished professor of medicine in the Division of Hematology-Oncology at the University of California San Diego Moores Cancer Center, where he also serves as the co-leader of the Solid Tumor Therapeutics Program and directs the Cancer Therapeutics Training Program.

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**Hemispherx Biopharma prevails in multimillion dollar federal lawsuit**

**San Diego Voice**

**ONLINE**

Here’s a tiny sampling of recent news stories on our main website and Cancer Research News site. Use the Editconnect number in the search windows on our homepages to reach the stories.

Genentech, NewLink deal could be worth more than $1B

The companies will work to further develop NewLink’s IDO inhibitor NLG919 and discover next-generation IDO/IDO compounds

EDITCONNECT: E10211401

Yale announces three-year extension of Gilead collaboration

Gilead will provide $10M in additional funding and gain a licensing option for resultant discoveries as the partners continue pursuing novel cancer therapies

EDITCONNECT: E10221400

Hemispherx Biopharma prevails in multimillion dollar federal lawsuit

All claims by Cato Capital were dismissed by a federal judge; company seeks $1-million award for fees and costs against losing party

EDITCONNECT: E10223401

AstraZeneca and University of Cambridge announce new collaborations

The agreements include a research collaboration, a Material Transfer Agreement, a doctoral training program and an entrepreneur-in-residence program

EDITCONNECT: E10161401

**People & Promotions**

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**NOVEMBER 2014 || DDNEWS 43**
IPSWICH, Mass.—In commemoration of its 40th anniversary, New England Biolabs Inc. (NEB) recently announced its Passion in Science Awards, which recognize members of the scientific community who are committed to making a difference through their science, humanitarian service, environmental stewardship or artistic and creative service—a set of awards that were given out in late October as part of a two-day international summit NEB held in Ipswich.

“We always believed that science is more than a vocation—it embodies an ethos that inspires acts of compassion, brilliance and originality. We want to celebrate the many unsung heroes of the lab, not just for their discoveries, but for their passions that contribute to making the world a better place,” said James Elard, CEO of NEB.

The awards are given in four categories: the Inspiration in Science Award, which recognizes scientists whose passion for their field motivates them to push the frontiers of knowledge on a daily basis; the Environmental Stewardship Award, which recognizes scientists who are working to preserve our natural resources or reduce waste either in the lab or outside of it; the Humanitarian Duty Award, which recognizes scientists who are improving the welfare and happiness of others; and the Arts and Creativity Award, which recognizes scientists who demonstrate a love of the arts and may also explore their creative side in the laboratory.

For DDNews readers, the five winners in the 2014 Inspiration in Science category of the Passion in Science Awards are probably the most pertinent. One of them is Ite Laird-Ofori of the Norris Cancer Center at the University of Southern California, who was honored for fighting lung cancer. Said Laird-Ofori: “We are tackling lung cancer in many ways. We are studying the epigenetic changes underlying lung cancer development and progression, focusing on DNA methylation.” A recent finding promises to improve the sensitivity of detection of methylated DNA in patients’ blood, and Laird-Ofori and colleagues are partnering with NEB to further develop this technology. The Norris team is also studying the epigenomes of alveolar epithelial cells and the cancer-associated immune response in the most aggressive type of lung cancer, small cell lung cancer. There is also Jasson Furrer of the University of Missouri, honored for inspiring by teaching, in large part because of his efforts to give opportunities for undergraduate students to participate in the research lab in which he works, and Laurie Doering of McMaster University in Ontario for research work on the role of astrocytes in autism.

Khalil Mathew of the International University was honored for work on understanding why certain pathogens (primarily Pseudomonas aeruginosa) are so refractory to antibiotic treatment in immunocompromised patients. Why the P. aeruginosa organism leads to the demise of patients with cystic fibrosis. Whitney Hagens of Massachusetts Biotechnology Education was recognized for work supporting science and biotechnology education in Massachusetts through educational programs, work-force development and lifelong learning.

In the Environmental Stewardship category, the winners of the Passion in Science Awards were Andrew Markley of the University of Wisconsin-Madison and Torin Kurrinian of Xiamen University in China. In the Humanitarian Duty category, NEB honored Karl Boock of the University of Detroit Mercy, Paul McDonald of the Virginia Tech Carilion Research Institute, Lori Baker of Baylor University and Peter Hotze of the Sabin Vaccine Institute in the Arts and Creativity category, the winners were Shelly Xie of the University of Texas Southwestern Medical Center in Dallas, Tal Danino of the Massachusetts Institute of Technology, Alia Qatarneh of Harvard University and Louise Hughes of Oxford Brooks University in the United Kingdom.

**Agilent Thought Leader Award supports cancer stem cell research at Mount Sinai**

SANTA CLARA, Calif.—Agilent Technologies Inc. announced Sept. 24 that Dr. Carlos Cordon-Cardo of the Mount Sinai Health System had received an Agilent Thought Leader Award in recognition of his groundbreaking work in molecular and translational pathology. Cordon-Cardo is the Irene Heinz Given and John LaForte Given Professor and chair of pathology at Mount Sinai.

The Agilent award will support ongoing cancer research conducted by Cordon-Cardo and his team, who are using a combination of genomic and proteomic technologies from Agilent to characterize tumor-initiating cells with stem cell-like properties derived from solid tumors taken from subjects with various types of cancer. The goal of studying this subpopulation of cancer cells is to better understand their ability to resist drug treatments and metastasize.

“Our goal is to bring in the outstanding measurement tools from Agilent to develop new diagnostic and predictive biomarkers,” said Cordon-Cardo. “This, in turn, will provide each patient a better chance of cure by defining their disease and optimizing treatment while offering a superior quality of life. This collaboration offers a unique opportunity to translate data into knowledge that maximizes personalized patient management, treatment efficacy and clinical outcomes.”

“We are very pleased to support Dr. Cordon-Cardo’s pioneering work in cancer stem cell research at one of the largest departments of pathology in the United States,” said Jacob Thaysen, vice president and general manager of Agilent’s Diagnostics and Genomics group. “Molecular characterization of these cells, using Agilent technologies and solutions, could result in the development of new cancer diagnostics.”

The Agilent Thought Leader Award promotes fundamental scientific advances by contributing financial support, products and expertise to the research of influential thought leaders in the life sciences, diagnostics and chemical analysis.

**Fibrocell Science receives 2014 Marcum Innovator of the Year Award**

EXTON, Pa.—Recognized for pioneering cell-based therapies for orphan skin diseases, Fibrocell Science Inc. recently received a 2014 Marcum Innovator of the Year Award. These awards recognize entrepreneurship and innovation by companies in the greater Philadelphia region that are pioneering new advancements in the biotech/healthcare, technology, manufacturing and business services sectors. David Pernock, chairman and CEO of Fibrocell Science, accepted the award at a ceremony in Philadelphia on Oct. 22.

“We are proud to be recognized for developing innovative cell-based therapies based on our proprietary fibroblast technology,” Pernock said. “These treatments have the potential to relieve the suffering of those with painful and debilitating skin and connective tissue diseases, such as recessive dystrophic epidermolysis bullosa, a rare genetic blistering disorder. We appreciate the recognition of our commitment to developing treatments for these patients, as well as our support of the Philadelphia business community.”

Fibrocell Science is an autologous cell therapy company focused on developing first-in-class treatments for rare and serious skin and connective tissue diseases with high unmet medical needs. Fibrocell’s lead orphan drug program is in late-stage preclinical development for the treatment of recessive dystrophic epidermolysis bullosa. Working in collaboration with Intrexon Corp., a leader in synthetic biology, Fibrocell is genetically modifying autologous fibroblast cells to express target proteins that are inactive or missing from patients with rare genetic skin and connective tissue disorders. Fibrocell is also pursuing medical applications for adflitox-T, the company’s proprietary autologous fibroblast technology, for restrictive burn scarring and vocal cord scarring. Both indications are currently in Phase 2 clinical trials.
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IDT launches modular NGS gene capture pools Integrated DNA Technologies These modular gene capture probes are the latest addition to IDT’s growing portfolio of high-quality, customizable next-generation sequencing (NGS) products. xGen Predesigned Gene Capture Pools and Plates are ideal for scientists who need to reduce the cost of their NGS experiments without sacrificing quality and specificity. xGen Predesigned Gene Capture Pools are available for the coding regions of any human RefSeq gene and are delivered premixed in tubes or in individual plate wells for selective mixing. Integrated DNA Technologies www.idtdna.com

New customer-driven format for quality-control standards portfolio ATCC ATCC announces the release of ATCC Minos—already the standard in the pharmaceutical and industrial labs. Only ATCC Genuine Cultures are authenticated and supported by ATCC polyphasic testing to ensure both microbial identity and phenotypic characteristics. To meet the needs of GC biologists, ATCC developed ATCC Minos—with the same high-quality ATCC Genuine Cultures—provided as a six-pack of ready-to-use QC strains preserved in glass-free “mini” cryovials containing glycerol stock. Each tube has a 2D barcode to allow for easy storage and tracking, and offers a peel-off label for fast and reliable recordkeeping. ATCC www.atcc.org


Bio-Rad introduces wet-lab validated real-time PCR assays for rat genome Bio-Rad Laboratories Inc. Bio-Rad’s PrimePCR Assays are fully wet-lab validated for specificity, efficiency and sensitivity, and they help researchers adhere to industry best practices known as MIQE. As part of this validation process, Bio-Rad scientists validate all PCR products using next-generation sequencing, verifying the percentage of on-target amplification. In addition, all of the validation raw data are available to the customer. Bio-Rad Laboratories Inc. www.bio-rad.com

New kit for performing neurite outgrowth studies Essen BioScience Inc. The Cell-Player NeuroPrime Cell Kit is the first commercially available cryopreserved neuronal/astrocyte co-culture kit. It is designed for long-term, kinetic live-cell measurement of neurite dynamics. Each kit cell contains cryopreserved cell vials of rat forebrain neurons and astrocytes and a vial of the novel, neuron-specific labeling reagent, NeuronLight Red. A fully validated protocol for thawing, labeling and measuring neurite outgrowth in a 96-well format using IncuCyte 2004 live-cell imaging system is also included. Essen BioScience Inc. www.esenbioScience.com

Phenomenex introduces first synthetic sorbent for simplified gpm-like extraction Phenomenex Inc. Novum Simplified Liquid Extraction (SLE) is a novel, simplified alternative to traditional diatomaceous earth SLE (also known as supported liquid extraction) products and a simplified approach to traditional liquid-liquid extraction (LLE). As the first of its kind, the synthetic Novum SLE sorbent (patent pending) can be used with the same procedure as traditional SLE sorbents while delivering improved lot-to-lot reproducibility. Supplies are readily available, compared to diatomaceous earth, which is a natural resource that must be mined. Phenomenex Inc. www.phenomenex.com

For more information, visit www.DDN-News.com
Celsus seeks to develop the anti-inflammatory drugs of the future

BY LLOYD DUNLAP

Celsus Therapeutics is a drug development company focused on novel anti-inflammatory, first-in-class synthetic drugs called multifunctional anti-inflammatory drugs (MFAIDs). Celsus’ proprietary drug technology platform potentially offers an answer to an urgent unmet need: the lack of satisfactory alternatives to corticosteroids in the treatment of a multitude of inflammatory diseases. The company has assembled an experienced team that shares its vision and is committed to making it a success. Dr. Gur Roshwald joined Celsus as CEO early last year, and DDNews interviewed him about his new company’s progress toward its goals.

DDNews: Dr. Roshwald, where did Celsus Therapeutics originate and how did it come to be U.S.-based?

Gur Roshwald: Celsus was spun out from technology developed at Hebrew University in Jerusalem and was incorporated in 2005 in the U.K. Celsus listed in the U.S. in 2013 with new management at the helm and is currently only traded on NASDAQ under the ticker symbol CLTX. As we advanced, the company required management with drug-development and public-market experience and access to greater institutional capital from well-established healthcare funds. We decided on listing in the U.S. where the biotech/specialty pharma market is active and well-funded. When the board of directors made the decision to go public, new, experienced management with deep healthcare and U.S. public company experience was brought on board.

“The market potential for MRX-6 in skin inflammation is more than $350 million per year in peak U.S. sales, with sales in Europe and Asia bringing in a likely equal amount. Cystic fibrosis and osteoarthritis are both potential multibillion-dollar markets.”

DDNews: Please describe your “First-in-class multifunctional anti-inflammatory program” and how and why it provides a potential alternative to corticosteroids.

Roshwald: Celsus’ lead products are first-in-class, novel, nonsteroidal, synthetic anti-inflammatory drugs termed multifunctional anti-inflammatory drugs (MFAIDs) that focus on one of the most sought-after pharmaceutical target classes in inflammation research: the sPLA2 family.

This extracellular family of enzymes is a universal early trigger in all of the inflammatory diseases studied that hydrolyze phospholipids on the cell membrane into two key inflammatory precursors: arachidonic acid (AA) and lysophospholipids (LysoPLs). AA is metabolized via the cyclooxygenase (COX) and lipoygenase (LOX) pathways to produce large families of eicosanoids; many of them are involved in the development of numerous pathological conditions, especially in inflammation-related processes. These include prostaglandins, thromboxanes and leukotrienes. LysoPLs induce white cell activation and extravasation, induce activation (by lypo-phosphatidylserine in particular), induce tissue damage, such as gastric ulceration, and act as growth factors (especially lyso phosphatic acid) to induce proliferation of cancer cells and tumor metastasis. Furthermore, LysoPLs are also the precursors of platelet activating factor (PAF), possibly the most potent mediator of inflammatory processes. MFAIDs inhibit sPLA2 with a different chemistry than corticosteroids and are generally specific to inhibiting cell surface sPLA2 activity, thus providing the benefit of inhibition, but, due to the different chemistry, none of the steroid side effects.

DDNews: You have characterized MFAIDs as a potential disruptive technology. How would you define disruptive technology?

Roshwald: As Clayton Christensen describes, it is a process by which a product or service takes root initially in simple applications at the bottom of a market and then relentlessly moves up market, eventually displacing established products or services.

A good example would be cell phones replacing landlines. For Celsus, it would be our products replacing corticosteroids for inflammation in the eye, lung, joints and bone.

DDNews: What class of molecule is MRX-6? How are your four current drugs related (or different)?

Roshwald: MRX-6 is made of a series of naturally occurring lipids conjugated to a glycosaminoglycan (hyaluronic acid). The glycosaminoglycan (GAG) is anchored on the cell surface through proteins known as adhesion (CD44, in an example), and provide antioxidant benefit, while the lipids conjugated to the GAG act as competitive inhibitors of sPLA2 at the cell surface.

Our pipeline products are similar in that we use various lipids, conjugated in different ways to a set of potential sugars (GAGs).

DDNews: Please describe your expectations for market potential and your patent position for each product.

Roshwald: The market potential for MRX-6 in skin inflammation is more than $350 million per year in peak U.S. sales, with sales in Europe and Asia bringing in a likely equal amount. Cystic fibrosis and osteoarthritis are both potential multibillion-dollar markets.

We have patent protection on our lead compounds and methods-of-use patents in the United States and major markets around the world. In addition to our pending applications, the other compounds in our pipeline are all new and have long-term composition of matter, formulation and method-of-use potential protection.

DDNews: Finally, what are the reasons you are confident of success when Lilly, Wyeth and Anthera have failed?

Roshwald: The key to successfully controlling this “universal inflammatory trigger” or sPLA2, has been demonstrated by the past clinical failures of several pharmaceutical companies. It can be summarized as follows: 1. Inhibit the entire sPLA2 family, not just one or two of its isomers.

2. Do not interfere with the cPLA2 family, a related group of enzymes that are located inside the cell (unlike the sPLA2s) and which have a vital homoeostatic role (unlike sPLA2) that must not be interfered with.

There are about 12 different isomers of sPLA2, and Lilly’s/Anthera’s compound inhibited the most ubiquitous—subtype IIA. Although they achieved good biomarker results, it is unclear if the compound failed due to an actual lack of benefit or simply because the indications pursued were too difficult (sepsis and post MI inflammation). The lesson learned is to only pursue indications where we know steroids have demonstrated a benefit.

In Wyeth’s case, the compound inhibited both sPLA2 and cPLA2, which was toxic.

Celsus’ MFAIDs were designed and synthesized to overcome these two critical, and previously insurmountable, problems: Lipids do not just single molecule but an entire new genus of compounds, each different but with a similar mechanism of action.

Q&A: Gur Roshwald, M.D., of Celsus Therapeutics

Gur Roshwald joined Celsus Therapeutics as CEO in March 2013. From April 2008 to February 2013, he was a vice president at Venrock, where he was an investment professional on the healthcare team investing in both private and public companies. From May 2004 to March 2008, he was a vice president and equity analyst at Piper Jaffray, publishing research on specialty pharmaceutical companies. Prior to Piper, Roshwald was in private practice in New York and board-certified in internal medicine.

He received his M.D. from Albert Einstein College of Medicine and his MBA from the New York University Stern School of Business.

DDNews: What are your four current drugs related (or different)?

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