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Debugging Crohn's disease

By Benjamin Boettner, Assistant Editor

The intestinal flora of patients with Crohn's disease is frequently populated by adherent-invasive *Escherichia coli*, which cause intestinal inflammation. Although this inflammatory response is typically treated with tumor necrosis factor-lowering therapies, University of Nantes Angers Le Mans researchers have gone right to the source and targeted the bacteria directly with modified mannosides.¹ The researchers are planning to assess the compounds in a chronic mouse model for the disease.

CD is caused by a group of infectious bacterial strains that trigger a tumor necrosis factor (TNF)-induced inflammatory response. Patients experience a shift in the composition of their enteric microbiota, called dysbiosis,^{2,3} that is associated with overexpression of *carcinoembryonic antigen-related cell adhesion molecule 6* (CEACAM6; NCA; CD66c).⁴

CEACAM6 presents oligomannosides on the surface of intestinal epithelial cells. These oligomannosides allow adherent-invasive *E. coli* (AIEC), which are part of the intestinal microbiome in about 33% of patients with CD, to bind to the cells via a surface adhesion protein called fimbrial adhesin (fimH).

Marketed CD drugs suppress the inflammatory response by lowering TNF levels. The three anti-TNF antibodies on the market for CD are Humira adalimumab from AbbVie Inc., Remicade infliximab from Johnson & Johnson and Cimzia certolizumab pegol from UCB Group.

Recent data have shown that about 60% of patients responded to Humira, and of those, only 25% remained in remission after 1 year.⁵

A team led by Sébastien Gouin, research investigator at the Centre National de la Recherche Scientifique (CNRS) at the University of Nantes Angers Le Mans (L'UNAM), hypothesized that targeting the CD-causing bacteria rather than the secondary inflammatory response could provide an alternative therapy.

Gouin's group is no stranger to AIECs. His team and others have used synthetic, mannoside-based antagonists to target fimH in a different condition caused by AIECs—urinary tract infection (UTI).^{6,7}

The L'UNAM team developed a new class of *N*-linked thiazolylamino-mannosides that antagonized fimH *in vitro* and inhibited AIEC attachment in an *ex vivo* model of CD. The new mannosides inhibited attachment of AIECs to colonic explants obtained from a mouse model for CD in which *Ceacam6* is overexpressed in the ileum.⁸

Data were published in the *Journal of Medicinal Chemistry*.

"As far as I know, our results suggest for the first time the possibility to use synthetic mannosides to treat CD," said Gouin.

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“This work approaches CD treatment from a microbiological lens—focusing on a pathogen potentially linked to the pathophysiology of the diseases instead of the current paradigm in the field of focusing primarily on blocking proinflammatory mediators,” said Bernat Olle, COO of **Vedanta Biosciences Inc.** and a principal at **PureTech Ventures**. “In this sense, the approach is differentiated from and could be complementary to current drugs.”

Vedanta is developing an oral formulation of enteric bacteria to reduce the proportion of inflammation-inducing agents that occur in inflammatory bowel disease (IBD).

“Mannosides, provided side effects are minimal or tolerable, could prove a major advance over current immune modulatory treatment strategies for CD, which can have long-term side effects,” said Renate Kain, a professor at the **Medical University of Vienna** who has studied fimH-expressing AIECs in necrotizing glomerulonephritis.⁹

Anti-TNF treatments can increase the risk of both infection and certain cancers such as melanomas and non-Hodgkin’s lymphoma.

“Mannosides, provided side effects are minimal or tolerable, could prove a major advance over current immune modulatory treatment strategies for CD, which can have long-term side effects.”

*—Renate Kain,
Medical University of Vienna*

Taking (manno)sides

Gouin’s team plans to enhance the potency of the mannosides by generating multivalent scaffolds that combine several individual mannosides in one molecule. The team has previously developed multivalent mannosides to target uropathic *E. coli*.¹⁰

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Although the mannosides described in the paper have shown strong effects in *in vitro* and *ex vivo* experiments, an unanswered question is whether resistance will develop.

Gouin's team plans to test the effects of the mannosides on chronic AIEC infection and other CD features in the *Ceacam6* mouse model for CD.

Alain Vicari and Yolande Chvatchko told *SciBX* that chronic AIEC infection in streptomycin-treated conventional mice, an alternative model for CD,¹¹ could complement the *Ceacam6* model in gauging the *in vivo* effects of the compounds independently of *Ceacam6* overexpression. Vicari and Chvatchko are founders of **Calypso Biotech S.A.** and share the title of VP of R&D.

Vicari wanted to see how the effects of the compounds translate from *in vitro* systems to *in vivo* animal models to humans, especially considering the differences in intestinal physiology and the complexity of the gut microbiome.

Calypso, a spinoff of Merck KGaA's Merck Serono S.A. unit, is developing an antibody-based therapy against an undisclosed target

for a fistulizing form of CD.

Olle said any *in vivo* studies should keep track of the effects of the mannosides on beneficial commensal bacteria.

Another potential complication is that variants of fimH that differ by specific point mutations could be differentially sensitive or even resistant to specific mannoside compounds. Mutations in fimH result in structural differences that affect colonization and thus the inflammation-inducing potential of AIECs.¹²

Gouin told *SciBX* that he plans to analyze the specificity of the published mannoside collection for different fimH variants and determine which mutants might be most sensitive to specific mannoside compounds.

"By analyzing genetic variants in the AIEC *fimH* from patients, in the future it could become possible to design tailored treatments for particular subsets of patients," said Chvatchko.

Olle added that future clinical trials and more personalized treatment options would also benefit from the discovery of intestinal biomarkers that indicate the presence of AIECs in patient samples. Prescreening for such biomarkers would help identify which patients could benefit from mannoside treatments.

Jim Janetka, professor at the **Washington University in St. Louis School of Medicine** and cofounder and scientific advisor of **Fimbrion**

Therapeutics Inc., told *SciBX* that achieving clinically useful bioavailability with compound sugars such as modified mannosides can be a considerable challenge because of their often insoluble nature.

Gouin confirmed to *SciBX* that the most promising compounds will be subject to complete cytotoxic and pharmacokinetic evaluation. He said that the most promising compound of the collection is water soluble. He added that less water-soluble compounds can be modified by the addition of hydrophilic groups.

Fimbrion is developing fimH-targeting therapies for UTI.

Gouin said CNRS has filed for a patent covering the findings and the IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Calypso Biotech S.A., Geneva, Switzerland
Centre National de la Recherche Scientifique, Nantes, France
Fimbrion Therapeutics Inc., St. Louis, Mo.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Medical University of Vienna, Vienna, Austria
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Merck Serono S.A., Geneva, Switzerland
PureTech Ventures, Boston, Mass.
UCB Group (Euronext:UCB), Brussels, Belgium
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"This work approaches CD treatment from a microbiological lens—focusing on a pathogen potentially linked to the pathophysiology of the diseases instead of the current paradigm in the field of focusing primarily on blocking proinflammatory mediators."

—Bernat Olle,
Vedanta Biosciences Inc.

Translational tidbits

By Lev Osherovich & Michael J. Haas, Senior Writers

Last month's public-private partnership with the highest total funding was the launch of the **Global Health Innovative Technology Fund**, an infectious disease initiative that plans to disperse \$100 million over 5 years. On the biotech side, **Onyx Pharmaceuticals Inc.** formed an alliance with the **University of California, San Francisco's** Helen Diller Family Comprehensive Cancer Center.

A table of selected public-private partnerships (PPPs) announced in June rounds out this edition of translational tidbits (see Table 1, "Selected public-private partnerships for June 2013").

Japan reaches out

The Global Health Innovative Technology Fund (GHIT Fund) launched its flagship funding program to partner Japanese pharma and academics with Western not-for-profit organizations to conduct research on tropical and neglected diseases.

GHIT Fund's plan is to distribute about \$100 million over 5 years for R&D in diseases that mostly occur outside of Japan, including tuberculosis, malaria and a range of tropical parasites.

About half of the committed funding comes from Japan's government, a quarter from the **Bill & Melinda Gates Foundation** and the rest from a consortium of five Japanese pharma—**Astellas Pharma Inc.**, **Daiichi Sankyo Co. Ltd.**, **Eisai Co. Ltd.**, **Shionogi & Co. Ltd.** and **Takeda Pharmaceutical Co. Ltd.**

In June, GHIT Fund handed out its first tranche of \$11.3 million to fund 13 separate partnerships between 3 Western not-for-profit groups and Japanese companies and academic institutes.

"This is the most significant investment both by the Japanese government and by the Japanese private sector in R&D in global health," said GHIT Fund CEO and executive director B.T. Slingsby.

Under the scheme, **Medicines for Malaria Venture** will partner separately with Eisai, Daiichi and Takeda to screen for antimalarial compounds from those companies' libraries. Academic collaborators in this project are at the **Institute of Microbial Chemistry (BIKAKEN)** and the **Kitasato Institute**.

The **Global Alliance for TB Drug Development** will work separately with Eisai, Daiichi, Shionogi and Takeda to screen for TB compounds.

Finally, the **Drugs for Neglected Diseases initiative** will collaborate separately with Eisai, Takeda, BIKAKEN and the Kitasato Institute to identify compounds for leishmaniasis, Chagas disease and human African trypanosomiasis (sleeping sickness).

"Initially the alliance will consider funding projects across the entire drug development spectrum, from drug discovery to the use of markers, novel statistical methods and surrogate endpoints to accelerate clinical development."

—Pablo Cagnoni,
Onyx Pharmaceuticals Inc.

Each grant will cover two years of work and is subject to annual progress evaluations.

Slingsby said that GHIT Fund will not take a stake in new IP coming out of the partnerships, and new discoveries will belong to their inventors.

Participating companies will retain rights to their existing compounds. Slingsby said that the pharma most likely will grant their not-for-profit collaborators royalty-free licenses to promising lead compounds.

GHIT Fund will work with the not-for-profit organizations and the **United Nations Development Programme** to help make the new compounds available to interested parties for further development.

"We're trying to ensure access, which is not always the same as IP," said Slingsby.

GHIT Fund has issued a second call for proposals for development of preclinical assays and clinical trial design in HIV, TB, malaria and neglected tropical diseases. The second round of funding also will pair Japanese and partners outside Japan but will not necessarily

require pharma participation.

Full-spectrum cancer innovation

The Oncology Innovation Alliance between Onyx and UCSF aims to discover and develop therapies to treat hematological cancers and solid tumors.

Pablo Cagnoni, Onyx's EVP of global R&D and technical operations, told *SciBX* that Onyx established the three-year alliance with UCSF "because of our physical proximity to one another, our shared commitment to cancer research and our existing and past research collaborations."

He added, "Initially the alliance will consider funding projects across the entire drug development spectrum, from drug discovery to the use of markers, novel statistical methods and surrogate endpoints to accelerate clinical development. We may refine the focus of the alliance according to the type of proposals we actually get."

A joint steering committee—composed of three members each from Onyx and UCSF—will oversee the alliance.

"I would like to have the first set of projects approved and ready to go by the end of the year," said Cagnoni.

The number of projects the alliance funds each year will be dictated by a fixed annual budget, although the financials are not disclosed.

Under the terms of the agreement, IP generated by the alliance could be owned jointly or by either party alone. Onyx will have options to license IP from the alliance, said Cagnoni.

In 2012, Onyx signed a nonexclusive, two-year deal with **The University of Texas MD Anderson Cancer Center** to research potential treatments for multiple myeloma (MM) and lymphoma, including the company's proteasome inhibitors carfilzomib and oprozomib (formerly ONX 0912).

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"This is the most significant investment both by the Japanese government and by the Japanese private sector in R&D in global health."

—B.T. Slingsby,
Global Health Innovative Technology Fund

Table 1. Selected public-private partnerships for June 2013. Significant public-private partnerships announced in June included the NIH's National Center for Advancing Translational Sciences (NCATS) award of \$12.7 million to 9 academic research groups to repurpose compounds from pharma partners.¹ Japan's Global Health Innovative Technology Fund program also disclosed a first tranche of \$11.3 million to support partnerships between Western not-for-profit organizations and Japanese companies and academic institutes.

Source: BCIQ: BioCentury Online Intelligence

Companies	Institutions	Business area	Disclosed value	Purpose
AstraZeneca plc (LSE:AZN; NYSE:AZN); Eli Lilly and Co. (NYSE:LLY); Johnson & Johnson (NYSE:JNJ); Pfizer Inc. (NYSE:PFE); Sanofi (Euronext:SAN; NYSE:SNY)	Baylor College of Medicine; Indiana University; Kennedy Krieger Institute; Mayo Clinic; University of Pittsburgh; The University of Rhode Island, Kingston; University of Virginia; University of Washington; Virginia Commonwealth University; Yale University	Cardiovascular disease; musculoskeletal disease; neurology; pulmonary disease	\$12.7 million	Repurposing compounds from pharma partners within NCATS's Discovering New Therapeutic Uses for Existing Molecules program
Astellas Pharma Inc. (Tokyo:4503); Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568); Eisai Co. Ltd. (Tokyo:4523; Osaka:4523); Shionogi & Co. Ltd. (Tokyo:4507; Osaka:4507); Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)	Bill & Melinda Gates Foundation; Drugs for Neglected Diseases initiative; Global Alliance for TB Drug Development; Medicines for Malaria Venture; United Nations Development Programme	Infectious disease	\$11.3 million in initial tranche; \$100 million in total funding over 5 years	Support partnerships to develop drugs, vaccines and diagnostics for HIV/AIDS, malaria, tuberculosis and neglected tropical diseases within the framework of the Global Health Innovative Technology Fund
Athera Biotechnologies AB	Leiden University Medical Center	Cardiovascular disease	€6 million (\$8 million)	Grant from EU's Seventh Framework Program to CARDIMMUN consortium for developing Athera's phosphorylcholine (PC) mAb through proof of concept
None	Duke University; University of California, San Francisco; NIH	Infectious disease	\$2 million received by Duke; up to \$62 million to entire consortium by 2019	Clinical research network focused on antibacterial resistance
Shionogi & Co. Ltd.	Research institutes in Ireland	Pharmaceuticals	Each Shionogi Science Program (SSP) project will receive up to ¥15 million (\$158,400) annually	SSP drug discovery competition in Ireland, in which academics apply to partner with Shionogi to discover and develop new drug therapies
Abcodia Ltd.	Cancer Research UK	Cancer; diagnostics	Unavailable	Developing blood tests to detect a range of cancers when they are still early stage and asymptomatic
Advinus Therapeutics Ltd.	H. Lee Moffitt Cancer Center & Research Institute	Cancer	Undisclosed	Developing a disruptor of the interaction between retinoblastoma (RB) and CRAF (RAF1), and developing an inhibitor of rho-associated coiled-coil containing protein kinase (ROCK)
AstraZeneca	Cancer Research UK; The University of Manchester	Cancer	Undisclosed	Developing a therapeutic targeting an undisclosed protein involved with DNA damage response and screening for compounds against an undisclosed target
Inflection Biosciences Ltd.	Spanish National Cancer Research Centre (CNIO)	Cancer	Unavailable	Developing preclinical kinase inhibitors to treat cancer
Johnson & Johnson	Icahn School of Medicine at Mount Sinai	Autoimmune disease	Undisclosed	Launch of Johnson & Johnson Boston Innovation Center and new collaboration with Icahn School of Medicine to investigate triggers of inflammatory bowel disease (IBD)
Latitude Pharmaceuticals Inc./Xeris Pharmaceuticals Inc.	JDRF	Endocrine/metabolic disease	Undisclosed	Develop formulations of soluble glucagon for use in infusion pumps
Onyx Pharmaceuticals Inc. (NASDAQ:ONXX)	University of California, San Francisco	Cancer	Undisclosed	Oncology Innovation Alliance to discover and develop therapies for hematologic cancers and solid tumors
Sanofi	Curie Institute	Cancer	Undisclosed	Identifying targets to treat ovarian cancer
Theradiag (Euronext:ALTER)	Unicancer Group	Cancer; diagnostics	Undisclosed	Developing microRNA-based theranostic tools to screen and monitor treatment response to radiotherapies and chemotherapies for colorectal cancer

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Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Global Alliance for TB Drug Development, New York, N.Y.
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Targeting TB persistence

By Lauren Martz, Staff Writer

A group of researchers from California and New York has identified a small molecule with activity against currently intractable nonreplicating stages and drug-resistant strains of *Mycobacterium tuberculosis*.¹ The compound, which works by blocking a cell wall biosynthesis enzyme and a cofactor biosynthesis enzyme, could be combined with existing tuberculosis drugs to help shorten treatment duration and prevent or eliminate the emergence of resistant bacteria.

One of the major challenges of treating TB is bacterial persistence, which occurs when the bacteria enter a dormant, nonreplicating phase. Most marketed drugs are not effective against dormant TB, and new compounds are still mostly screened against growing bacteria, which have different metabolic properties and requirements than latent bacteria and only represent a fraction of the life cycle of *M. tuberculosis*.

As a result, the duration of standard care administration regimes spans from several months to years, leading to poor compliance and the emergence of resistant strains.

To identify new therapeutics for TB, Peter Schultz, William Jacobs, Feng Wang and colleagues created a *Mycobacterium* biofilm formation screen. The team hypothesized that measuring bacterial growth as a biofilm might mimic *in vivo* conditions during bacterial infection better than other cell culture models and could help identify molecules with new mechanisms of action.

Schultz is professor of chemistry at **The Scripps Research Institute** and founding director of the **California Institute for Biomedical Research** (Calibr). Jacobs is professor in the Department of Microbiology and Immunology and the Department of Genetics at the **Albert Einstein College of Medicine of Yeshiva University**. Wang is a principal investigator at Calibr.

The screen of 70,000 molecules used *M. smegmatis*, a nonpathogenic bacterium that is more suitable for preclinical screening than *M. tuberculosis*. Bacterial biofilm growth assays testing the most promising hits showed that TCA1 potently and selectively inhibited *Mycobacterium*-genus bacteria over other pathogenic bacteria.

In bacterial killing assays using drug-sensitive *M. tuberculosis*, TCA1 had comparable efficacy to the generic TB drugs isoniazid and rifampicin, and a combination of TCA1 and either drug eradicated the bacteria. In assays using multidrug-resistant strains of the bacteria, TCA1 was more effective than isoniazid, rifampicin or no treatment, and the combination of TCA1 and isoniazid eliminated a multidrug-resistant strain.

TCA1 also was effective against extensively drug-resistant *M. tuberculosis*, suggesting it has a different mechanism of action than currently available drugs.

Moreover, TCA1 was effective in a nutrient-starvation *M. tuberculosis* assay, which measures the effect of therapeutics against bacteria in a dormant, nonreplicating state.

In mouse models for chronic and acute *M. tuberculosis* infection, oral treatment with TCA1 decreased bacterial burden compared with no treatment and was as effective as treatment with isoniazid and rifampicin. TCA1 did not cause weight loss or other adverse effects.

Genetic and affinity-binding studies identified TCA1's targets as *M. tuberculosis* decaprenylphosphoryl- β -D-ribose 2'-oxidase (dprE1) and *M. tuberculosis* molybdopterin biosynthesis protein (moeW). dprE1 is involved in cell wall biosynthesis, and moeW plays a role in molybdenum cofactor biosynthesis.

The team also found evidence that dprE1 inhibition contributes to bactericidal activity in replicating bacteria, and moeW inhibition may contribute to bactericidal activity in latent bacteria.

Data were published in the *Proceedings of the National Academy of Sciences*, and the team included researchers from the **University of Birmingham**, **Comenius University in Bratislava**, the **Swiss Federal Institute of Technology Lausanne**, the **Global Alliance for TB Drug Development** and the **University of Illinois at Chicago**.

"TCA1 has a relatively unique mechanism of action that appears to function differently from all previous

antimicrobials for tuberculosis examined, making it quite an exciting compound," said Jeffrey Cirillo, professor in the Department of Microbial and Molecular Pathogenesis at the **Texas A&M Health Science Center College of Medicine**. "The great benefits of TCA1 appear to be its high potency under nearly any conditions, including where bacteria are not replicating, which is a condition where very few drugs currently work."

Analog data

Calibr has partnered with the TB Alliance to develop TCA1 and related molecules.

Schultz told *SciBX* that his group has developed significantly more potent analogs of TCA1. "We have reasonable pharmacokinetics for oral dosing of some analogs," he said.

"Being from a novel class, these compounds are expected to help reduce and combat drug resistance, as they should be effective in treating both drug-sensitive tuberculosis and drug-resistant tuberculosis," said Takushi Kaneko, senior research fellow at the TB alliance.

He added that "killing nonreplicating *M. tuberculosis* cells is considered to be the most critical in shortening tuberculosis treatment duration."

"TCA1 has a relatively unique mechanism of action that appears to function differently from all previous antimicrobials for tuberculosis examined, making it quite an exciting compound."

—Jeffrey Cirillo,
Texas A&M Health Science Center
College of Medicine

"Being from a novel class, these compounds are expected to help reduce and combat drug resistance, as they should be effective in treating both drug-sensitive tuberculosis and drug-resistant tuberculosis."

—Takushi Kaneko,
Global Alliance for TB Drug
Development

According to Schultz, it is too early to predict how much TCA1 or related molecules could decrease treatment time.

“It is usually difficult to project the treatment time *in vivo* according to the *in vitro* activities. For *M. tuberculosis*, it is even more difficult due to the lack of good animal models for latent infection. However, based on the performance of known tuberculosis drugs, those drugs that have good activity against nonreplicating *M. tuberculosis in vitro* do have potential to shorten treatment time in humans,” he said.

Schultz added that in addition to killing multidrug-resistant and extensively drug-resistant *M. tuberculosis* strains, his team has found that TCA1 shows a very low frequency of inducing resistance mutations. “This may be related to the dual mechanisms of action of this compound,” he said.

Schultz said the work has been patented by Calibr and the IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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California Institute for Biomedical Research, La Jolla, Calif.
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Global Alliance for TB Drug Development, New York, N.Y.
The Scripps Research Institute, La Jolla, Calif.
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Texas A&M Health Science Center College of Medicine, Bryan, Texas
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Attenuating attrition

By C. Simone Fishburn, Senior Editor

High drug attrition rates from poor safety have spawned numerous efforts to use *in silico* methods to improve molecule design, but none of the algorithms created so far has emerged as a true game changer. Now, **AstraZeneca plc** and **Roche** have concluded that better prediction requires more data, and they are pooling their information via an intermediary cheminformatics company, **MedChemica Ltd.**, to produce a new set of design rules.

In 1997, Christopher Lipinski created the first widely recognized set of rules to guide the optimization of physicochemical properties, such as solubility and lipophilicity, and facilitate the generation of drug-like compounds.

Since then, computational chemists have created numerous algorithms to aid molecule design, most of which have improved upon Lipinski's rule of five. Fewer advances have been made that help medicinal chemists optimize biological properties such as toxicity and ADME.

MedChemica, created by three former AstraZeneca scientists, believes it can jump-start progress by analyzing how changing a molecule's structure affects its behavior in biological assays.

Although other algorithms try to relate structure to biological function, most of the analyses look at modifications across a wide array of diverse structures. MedChemica's approach is to look at modifications in a set of similar structures and see how minor differences affect the compounds' biological activity.

Al Dossetter, managing director of MedChemica, said the advantage of the company's platform is the WizePairZ algorithm that looks at pairs of fragments that are similar in structure but differ by a chemical group, such as a change from chlorine to fluorine or the addition of a methyl group.

This platform, he told *SciBX*, captures the chemical environment of the fragment change. For example, it incorporates the fact that the effect of changing chlorine to fluorine on a molecule will depend on the surrounding structure. The result is a rule that is context dependent.

The MedChemica approach applies to small molecules and uses only partial chemical structures, thus keeping compound identities out of the picture.

Because the platform does not reveal compound identities, AstraZeneca and Roche can share knowledge without disclosing proprietary information.

By collaborating to produce a new set of design rules, the pharma are aiming to reduce lead optimization time in drug discovery, during which compounds from screening hits are modified to improve their pharmacokinetics and reduce their potential for toxicity.

The lead optimization process generally requires the synthesis of 500–1,000 molecules that differ by minor chemical modifications and undergo testing in a battery of preclinical assays. With the aid of an improved set of rules, they hope to reduce the number of compounds that need to be synthesized to reach the optimal clinical candidate.

Although each pharma has rich compound libraries with millions of molecules and large amounts of experimental data, AstraZeneca and Roche believe that detecting significant trends requires even greater

statistical power, which will come with consolidating their databases and increasing the number of matched pairs.

Dossetter said smaller databases only allow researchers to extract one to five matched pairs, which have a low fidelity of prediction. Ten matched pairs are sufficient to draw a prediction, but reliability increases significantly with 20 matched pairs.

The MedChemica database contains 1.2 million datapoints, each of which represents a single molecule fragment in a single assay. It includes 31 different assays, although more are likely to be added in the future, and not all molecules have been tested in all assays.

Prior to partnering with MedChemica, AstraZeneca and Roche each had large libraries of compounds with corresponding experimental data. MedChemica is compiling those data into a single integrated database.

The proportion of the full MedChemica database contributed by each partner was not disclosed. The Roche data includes molecules and results from studies at its **Genentech Inc.** unit.

Compatibility of the datasets from Roche and AstraZeneca was key to forming the collaboration. The two companies are in discussions with other big pharma that also may join the partnership and would need to provide complementary datasets.

Mike Snowden, head of discovery sciences innovative medicines at AstraZeneca, said that the compatibility requirements for joining are having a database with a diverse compound background, large numbers of molecule pairs and biological data that are produced by similar techniques to those of Roche and AstraZeneca.

"By pooling datasets, we believe predictions of the platform will get better and better," he told *SciBX*.

Each partner will get a copy of the resulting database, dubbed the Grand Rule Database. MedChemica also will offer molecule optimization consulting services to nonpartners.

Snowden is not concerned about losing a competitive advantage or leveling the playing field. Although the rules can benefit all medicinal chemists, he said success in drug development depends on having a good molecule at the starting point.

The principal limitation of the collaborative effort may be that the assay data are entirely based on *in vitro* and cell-based experiments. As yet, no *in vivo* data either from animals or clinical trials have been included. Since *in vitro* data often do not translate directly to results in the clinic, the rules MedChemica derives may shorten the time to selecting a clinical candidate but may not alter its chances of success in human trials.

Snowden acknowledged that the tool may have limitations but said the goal is to learn how to predict the compounds that should not be made.

The shared database should be up and running by year end.

Fishburn, C.S. *SciBX* 6(26); doi:10.1038/scibx.2013.647
Published online July 11, 2013

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Genentech Inc., South San Francisco, Calif.

MedChemica Ltd., Newcastle-under-Lyme, U.K.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

"By pooling datasets, we believe predictions of the platform will get better and better."

**—Mike Snowden,
AstraZeneca plc**

This week in therapeutics

THE DISTILLERY brings you this week's most essential scientific findings in therapeutics, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Breast cancer	Fatty acid binding protein 5 psoriasis-associated (FABP5; EFABP)	<i>In vitro</i> and mouse studies suggest FABP5 inhibition could help treat breast cancer. In mouse embryonic fibroblasts, vector-mediated overexpression of FABP5 caused oncogenic transformation and increased cell proliferation, migration and invasion compared with normal FABP5 expression. In a transgenic mouse model for epidermal growth factor receptor (EGFR)-driven breast cancer, <i>Fabp5</i> knockout suppressed mammary tumor development and decreased EGFR signaling compared with no knockout. Ongoing studies include creating FABP5 inhibitors in sufficient quantities for preclinical testing.	Patent application filed covering FABP5 inhibitors and their use in cancer; available for licensing	Levi, L. <i>et al. Cancer Res.</i> ; published online May 30, 2013; doi:10.1158/0008-5472.CAN-13-0384 Contact: Noa Noy, Case Western Reserve University School of Medicine, Cleveland, Ohio e-mail: nxn51@case.edu
		SciBX 6(26); doi:10.1038/scibx.2013.648 Published online July 11, 2013		
Cancer	PTEN (MMAC1; TEP1); phosphoinositide 3-kinase (PI3K)	Cell culture and mouse studies identified a secreted variant of PTEN that could help treat cancer. PTEN is a tumor suppressor that regulates PI3K signaling and was not thought to be secreted. Computational analysis and studies in mouse and human cells identified a translational variant of PTEN that is expressed, secreted and taken up by normal and cancer cells. In a xenograft mouse model for cancer, intraperitoneal injection of the PTEN variant decreased tumor growth compared with injection of a control protein. Next steps include studying the loss of function of the secreted PTEN variant in mice.	Patent application filed by Columbia University; available for licensing from Columbia Technology Ventures Contact: Peter Golikov, Columbia Technology Ventures, New York, N.Y. e-mail: peter.golikov@columbia.edu	Hopkins, B.D. <i>et al. Science</i> ; published online June 6, 2013; doi:10.1126/science.1234907 Contact: Ramon Parsons, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: ramon.parsons@mssm.edu
		SciBX 6(26); doi:10.1038/scibx.2013.649 Published online July 11, 2013		
Cancer	Ras; rho guanine nucleotide exchange factors (ARHGEFs; GEFs)	An <i>in vitro</i> study suggests prolonged inhibition of interactions between Ras and GEFs could help treat cancer. Oncogenic mutations in Ras fix the protein in an active, GTP-bound conformation. In multiple cancer cell lines, prolonged treatment with andrographolide (AGP), a compound that is predicted to block Ras-GEF interaction, inhibited GTP loading, oncogenic Ras signaling and cell growth. Next steps include optimizing AGP derivatives for potency and <i>in vivo</i> application.	Patent and licensing status undisclosed	Hocker, H.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 4, 2013; doi:10.1073/pnas.1300016110 Contact: Alemayehu A. Gorfe, The University of Texas Health Science Center at Houston, Houston, Texas e-mail: alemayehu.gabebe@uth.tmc.edu Contact: John F. Hancock, same affiliation as above e-mail: john.f.hancock@uth.tmc.edu Contact: Johnson Stanslas, University Putra Malaysia, Selangor, Malaysia e-mail: jstanslas@yahoo.co.uk
		SciBX 6(26); doi:10.1038/scibx.2013.650 Published online July 11, 2013		

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Tubulin	<p>Mouse studies suggest conjugates of paclitaxel and β-cyclodextrin polyrotaxane polymers could help treat cancer and have improved safety profiles. In mice with murine hepatic tumors, a β-cyclodextrin polyrotaxane and paclitaxel conjugate preferentially accumulated in tumor tissue and decreased tumor growth and increased survival compared with free paclitaxel. The conjugate did not cause observable toxicity to the liver or other organs. Planned studies include optimizing and testing the conjugate in animal models for other cancers.</p> <p>The tubulin inhibitor paclitaxel is a generic chemotherapeutic.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.651 Published online July 11, 2013</p>	Patent application filed; unlicensed	<p>Yu, S. <i>et al. Angew. Chem. Int. Ed.</i>; published online June 5, 2013; doi:10.1002/anie.201301397 Contact: Xiqun Jiang, Nanjing University, Nanjing, China e-mail: jiangx@nju.edu.cn Contact: Wei Wu, same affiliation as above e-mail: wuwei@nju.edu.cn</p>
Chronic myelogenous leukemia (CML)	MAP kinase interacting serine-threonine kinase 1 (MKNK1; MNK1); MKNK2 (MNK2); eukaryotic translation initiation factor 4E (eIF4E)	<p><i>In vitro</i> and mouse studies suggest inhibiting MNK1 and MNK2 could help treat the blast crisis phase of CML by reducing eIF4E activation. Self-renewal of granulocyte macrophage progenitors (GMPs) is associated with blast crisis. In GMPs from patients with CML, MNK1 and MNK2 inhibition decreased eIF4E activation and self-renewal capacity compared with no inhibition. In xenograft mouse models for CML blast crisis, an MNK1 and MNK2 inhibitor decreased GMP engraftment compared with vehicle. Ongoing work includes testing dual MNK and BCR-ABL tyrosine kinase inhibitors in cellular and animal models for CML.</p> <p>Isis Pharmaceuticals Inc.'s ISIS-EIF4ERx, a second-generation antisense oligonucleotide targeting eIF4E, is in Phase I/II testing to treat non-small cell lung cancer (NSCLC) and prostate cancer.</p> <p>Clavis Pharma ASA and Translational Therapeutics Inc. have ribavirin elaidate (CP-4033; TRX-201), a Lipid Vector Technology derivative of ribavirin that inhibits eIF4E, in preclinical testing to treat thyroid cancer.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.652 Published online July 11, 2013</p>	Unpatented; available for partnering	<p>Lim, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online June 4, 2013; doi:10.1073/pnas.1301838110 Contact: S. Tiong Ong, Duke-NUS Graduate Medical School Singapore, Singapore e-mail: sintiong.ong@duke-nus.edu.sg</p>
Lung cancer	Deoxythymidylate kinase (DTYMK); serine/threonine kinase 11 (STK11; LKB1)	<p>Cell culture studies suggest inhibiting DTYMK could help treat <i>LKB1</i> mutant lung cancer. A small hairpin RNA screen in mouse cells derived from lung tumors showed that <i>Dtymk</i> deficiency was lethal in <i>Lkb1</i> mutant cells. In a panel of <i>LKB1</i> mutant lung cancer cell lines, <i>DTYMK</i>-targeting shRNA decreased growth compared with control shRNA. Next steps could include developing pharmacological inhibitors of DTYMK.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.653 Published online July 11, 2013</p>	Patent and licensing status unavailable	<p>Liu, Y. <i>et al. Cancer Discov.</i>; published online May 28, 2013; doi:10.1158/2159-8290.CD-13-0015 Contact: Kwok-Kin Wong, Dana-Farber Cancer Institute, Boston, Mass. e-mail: kwong1@partners.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pancreatic cancer	DNA	<p>Mouse and cell culture studies suggest decreasing extracellular DNA levels could help prevent pancreatic cancer metastasis. In two human pancreatic cancer cell lines, compared with normal pancreatic cells, extracellular DNA levels in culture medium were increased. In a mouse xenograft model for human pancreatic cancer, injection of DNase I decreased metastasis compared with saline injection. Next steps include determining whether extracellular DNA is associated with pancreatic cancer metastasis in humans.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.654 Published online July 11, 2013</p>	Unpatented; licensing status not applicable	<p>Wen, F. <i>et al. Cancer Res.</i>; published online May 30, 2013; doi:10.1158/0008-5472.CAN-12-3287 Contact: Fushi Wen, The University of Arizona, Tucson, Ariz. e-mail: fwen@email.arizona.edu</p>
Endocrine/metabolic disease				
Diabetes	Peptidylprolyl <i>cis-trans</i> isomerase NIMA-interacting 4 (PIN4; PAR14)	<p>Cell culture and mouse studies suggest increasing PIN4 expression could help treat diabetes. In a human liver cell line, PIN4-targeting small interfering RNA decreased insulin signaling compared with control siRNA. In this cell line, PIN4 overexpression increased insulin signaling compared with overexpression of a control protein. In a mouse model for diabetes, Pin4 overexpression normalized hyperglycemia and decreased expression of gluconeogenic genes compared with control protein overexpression. Next steps could include studying PIN4 expression in additional preclinical models of diabetes.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.655 Published online July 11, 2013</p>	Patent and licensing status unavailable	<p>Zhang, J. <i>et al. J. Biol. Chem.</i>; published online May 29, 2013; doi:10.1074/jbc.M113.485730 Contact: Tomoichiro Asano, Hiroshima University, Hiroshima, Japan e-mail: asano-tyk@umin.ac.jp</p>
Infectious disease				
Bacterial infection	Unknown	<p><i>In vitro</i> studies identified small molecule inhibitors of <i>trans</i>-translation that could help treat bacterial infections. <i>Trans</i>-translation, a process that uses transfer-messenger RNA (tmRNA) to repair stalled ribosomal complexes, is required for bacterial survival against stress. A high throughput screen of 663,000 compounds in <i>Escherichia coli</i> identified multiple lead small molecules that inhibited <i>trans</i>-translation. <i>In vitro</i>, the compounds inhibited the growth of multiple strains of pathogenic bacteria at low micromolar concentrations. Next steps include identifying the mechanism of action for the lead compounds and developing more potent derivatives.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.656 Published online July 11, 2013</p>	Patent applications filed covering compounds with increased potency; available for licensing	<p>Ramadoss, N.S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online June 3, 2013; doi:10.1073/pnas.1302816110 Contact: Kenneth C. Keiler, Pennsylvania State University, University Park, Pa. e-mail: kkeiler@psu.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Ebola	Ebola glycoprotein GP1	<p>Studies in primates suggest rabies (RABV)-based vaccine vectors expressing GP1 could be used to prevent Ebola infection. In macaques immunized with replication-competent, replication-deficient or inactivated RABV-GP1 vaccines, neutralizing antibodies against both GP1 and RABV glycoproteins were detected. In immunized macaques challenged with Ebola virus, the replication-competent vaccine protected 100% of the primates, whereas the replication-deficient and inactivated vaccines protected about 50% of the primates. Next steps could include optimizing a prime-boost vaccine strategy.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.657 Published online July 11, 2013</p>	<p>Patented; available for licensing from the NIH Office of Acquisition Management and Policy Contact: Peter Soukas, National Institutes of Health, Bethesda, Md. e-mail: soukasp@od.nih.gov</p>	<p>Blaney, J.E. <i>et al. PLoS Pathog.</i>; published online May 30, 2013; doi:10.1371/journal.ppat.1003389 Contact: Matthias J. Schnell, Thomas Jefferson University, Philadelphia, Pa. e-mail: matthias.schnell@jefferson.edu</p>
Influenza virus	Influenza A virus hemagglutinin (HA)	<p>Mouse and ferret studies suggest an adeno-associated virus 9 vector that expresses the broadly neutralizing mAb FI6 (AAV9FI6) could be used to prevent influenza infection. FI6 is an HA-binding, recombinant antibody that protects mice from H1, H3 and H5 influenza virus infection. In mice challenged with lethal influenza infection, animals receiving nasal pretreatment with AAV9FI6 at least three days before challenge survived, whereas those pretreated one day before did not. In ferrets, nasal immunization with AAV9FI6 decreased viral replication and increased survival after lethal challenge with H1 or H5 influenza virus compared with immunization using empty vector. Next steps could include safety and immunogenicity studies in humans.</p> <p>FI6 is being developed by Humabs BioMed S.A., which has licensed the product to an undisclosed pharma.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.658 Published online July 11, 2013</p>	<p>Patent application filed; available for licensing</p>	<p>Limberis, M.P. <i>et al. Sci. Transl. Med.</i>; published online May 29, 2013; doi:10.1126/scitranslmed.3006299 Contact: Maria P. Limberis, University of Pennsylvania, Philadelphia, Pa. e-mail: limberis@mail.med.upenn.edu Contact: James M. Wilson, same affiliation as above e-mail: wilsonjm@mail.med.upenn.edu</p>
Influenza virus	Influenza A virus hemagglutinin (HA)	<p>Mouse studies suggest an adeno-associated virus (AAV) 2/8 vector that expresses a broadly neutralizing mAb against HA could help prevent influenza infection. Normal mice receiving intramuscular injection with an AAV vector encoding F10 or CR6261 were protected from challenge with at least three diverse strains of influenza virus. F10 and CR6261 are HA-targeting, recombinant antibodies that have been shown to protect mice from H1 and H5 influenza virus infection. In aged or immunocompromised mice, immunization with AAV encoding F10 resulted in protection from matched influenza virus challenge. Next steps include safety and immunogenicity studies in human systems.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.659 Published online July 11, 2013</p>	<p>Patent application filed; available for licensing</p>	<p>Balazs, A.B. <i>et al. Nat. Biotechnol.</i>; published online June 2, 2013; doi:10.1038/nbt.2618 Contact: David Baltimore, California Institute of Technology, Pasadena, Calif. e-mail: baltimo@caltech.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Malaria	Endothelial protein C receptor (EPCR)	<i>In vitro</i> and cell culture studies suggest disrupting the interaction between <i>Plasmodium falciparum</i> erythrocyte membrane protein 1 (PfEMP1) and EPCR could help prevent severe malaria. In an <i>in vitro</i> screen, EPCR was found to interact with a form of PfEMP1 containing a domain cassette 8 (DC8) variant, which is associated with severe malaria. <i>In vitro</i> , parasites expressing DC8-PfEMP1 bound EPCR with higher affinity than wild-type parasites. In coculture, an antibody that blocked interaction with EPCR or a soluble isoform of EPCR prevented parasite binding to epithelial cells. Next steps include better defining the PfEMP1-EPCR interaction to inform vaccine development. SciBX 6(26); doi:10.1038/scibx.2013.660 Published online July 11, 2013	Unpatented; licensing status not applicable	Turner, L. <i>et al. Nature</i> ; published online June 5, 2013; doi:10.1038/nature12216 Contact: Thomas Lavstsen, University of Copenhagen, Copenhagen, Denmark e-mail: thomasl@sund.ku.dk Contact: Louise Turner, same affiliation as above e-mail: lturner@sund.ku.dk
Neurology				
Addiction	Neuropeptide S receptor 1 (NPSR1; NPSR)	Rat studies suggest the NPSR antagonist NCGC84 could help treat alcoholism. In rats, NCGC84 prevented alcohol-induced activation of Mapk in addiction centers of the brain. In a rat model for addiction, NCGC84 decreased alcohol self-administration and alcohol-seeking behavior compared with vehicle. Next steps include optimizing NCGC84 and additional studies in models for alcohol dependence. SciBX 6(26); doi:10.1038/scibx.2013.661 Published online July 11, 2013	Patented; available for licensing	Thorsell, A. <i>et al. J. Neurosci.</i> ; published online Jun 12, 2013; doi:10.1523/JNEUROSCI.4742-12.2013 Contact: Markus Heilig, National Center for Advancing Translational Sciences, Bethesda, Md. e-mail: mheilig@mail.nih.gov Contact: Wei Zheng, same affiliation as above e-mail: wzheng@mail.nih.gov
Alzheimer's disease (AD)	β -Site APP-cleaving enzyme 1 (BACE1)	Rodent studies identified a BACE1 inhibitor that could help treat AD. In mice and guinea pigs, a single oral dose of the BACE1 inhibitor AZ-4217 potently inhibited BACE1 and decreased β -amyloid (A β) levels in the plasma, brain and cerebrospinal fluid compared with vehicle. In a mouse model for AD, Bace1 decreased amyloid deposition compared with vehicle. Next steps could include testing the inhibitor in additional AD models. Merck & Co. Inc. has the BACE1 inhibitor MK-8931 in Phase II/III testing to treat AD. At least five other companies have BACE1 inhibitors in Phase II testing or earlier to treat AD. SciBX 6(26); doi:10.1038/scibx.2013.662 Published online July 11, 2013	Patent and licensing status unavailable	Eketjäll, S. <i>et al. J. Neurosci.</i> ; published online June 12, 2013; doi:10.1523/JNEUROSCI.1165-13.2013 Contact: Susanna Eketjäll, AstraZeneca Translational Sciences Centre, Solna, Sweden e-mail: susanna.eketjall@astrazeneca.com

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cognitive dysfunction	Mitogen-activated protein kinase kinase 11 (MAP3K11; MLK3)	Cell culture and mouse studies suggest the MLK3 inhibitor URM-099 could be used to treat HIV-associated neurocognitive disorders (HAND). MLK3 has been associated with mediating neurotoxicity in mouse models for HIV-1 encephalitis. In cell-based and coculture models for HAND-associated neuroinflammation, URM-099 decreased inflammatory cytokine levels and phagocytosis of axons compared with saline. In mouse models for HAND, URM-099 decreased inflammatory cytokines and cortical dendritic spine elimination in the CNS compared with saline. Next steps include evaluating URM-099 in a humanized mouse model for active HIV infection. SciBX 6(26); doi:10.1038/scibx.2013.663 Published online July 11, 2013	Patent application filed; available for licensing	Marker, D.F. <i>et al. J. Neurosci.</i> ; published online June 12, 2013; doi:10.1523/JNEUROSCI.0598-13.2013 Contact: Daniel F. Marker, University of Rochester, Rochester, N.Y. e-mail: daniel_marker@urmc.rochester.edu
Huntington's disease (HD)	Brain-derived neurotrophic factor (BDNF); noggin (NOG)	Rodent and primate studies suggest overexpression of BDNF and NOG could help treat HD. In a mouse model for HD, intracerebroventricular injection of an adeno-associated virus (AAV) vector to induce BDNF and NOG overexpression resulted in recruitment of new medium spiny neurons that matured and functionally integrated with existing neurons. In the model, BDNF and NOG overexpression delayed disease progression and increased overall survival compared with AAV-mediated overexpression of a control protein. In normal nonhuman primates, the AAV vector also generated new neurons. Next steps could include developing a therapeutic strategy to upregulate BDNF and NOG in the CNS. SciBX 6(26); doi:10.1038/scibx.2013.664 Published online July 11, 2013	Patent and licensing status unavailable	Benraiss, A. <i>et al. Cell Stem Cell</i> ; published online June 6, 2013; doi:10.1016/j.stem.2013.04.014 Contact: Steven A. Goldman, University of Rochester Medical Center, Rochester, N.Y. e-mail: steven_goldman@urmc.rochester.edu Contact: Abdellatif Benraiss, same affiliation as above e-mail: abdellatif_benraiss@urmc.rochester.edu
Nerve damage	Nerve growth factor (NGF); tumor necrosis factor receptor 1 (TNFRSF1A; TNFR1; CD120a); tumor necrosis factor- α (TNF- α)	<i>In vitro</i> and mouse studies suggest activating membrane-tethered TNF- α could help promote nerve repair following injury. In cultured neurons, the known axon growth promoter NGF plus soluble TNFR1 or TNFR1-Fc increased axon growth and branching compared with NGF alone. In tissues from <i>Tnf</i> ^{-/-} or <i>Tnfr1</i> ^{-/-} mice, sympathetic innervation density was lower than that in tissues from wild-type mice. Next steps could include testing activation of TNF- α signaling in models for nerve injury. SciBX 6(26); doi:10.1038/scibx.2013.665 Published online July 11, 2013	Patent and licensing status undisclosed	Kisiswa, L. <i>et al. Nat. Neurosci.</i> ; published online June 9, 2013; doi:10.1038/nn.3430 Contact: Alun M. Davies, Cardiff University, Cardiff, U.K. e-mail: daviesalun@cf.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Ophthalmic disease				
Glaucoma	Cannabinoid CB1 receptor (CNR1); CNR2	<i>In vitro</i> and rat studies identified CNR1 and CNR2 agonist prodrugs that could help treat glaucoma. In biochemical studies, phosphonate ester derivatives of the topical CNR1 and CNR2 dual agonist SAD448 showed greater aqueous solubility and chemical stability than the parent compound. In rats receiving topical ocular prodrug delivery, the derivatives showed longer residence in the iris and ciliary body of the eye and lower plasma residence than the parent compound. Next steps could include studying the prodrugs in animal models for glaucoma. Novartis AG's SAD448 has completed Phase I testing for ocular hypertension. SciBX 6(26); doi:10.1038/scibx.2013.666 Published online July 11, 2013	Patent and licensing status unavailable	Mainolfi, N. <i>et al. J. Med. Chem.</i> ; published online June 5, 2013; doi:10.1021/jm4004939 Contact: Jeremy M. Sivak, The University of Toronto and the Toronto Western Research Institute, Toronto, Ontario, Canada e-mail: jsivak@uhnres.utoronto.ca Contact: Nello Mainolfi, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: nello.mainolfi@novartis.com
Various				
Atherosclerosis; hyperlipidemia	Variability in response to cholesterol enriched atherogenic diet (DIET1); fibroblast growth factor 19 (FGF19)	Mouse studies suggest inhibiting DIET1 could help treat atherosclerosis or hyperlipidemia. In a mouse strain previously shown to be resistant to atherosclerosis and hyperlipidemia, a loss-of-function mutation was identified in <i>Diet1</i> that decreased levels of an FGF19 homolog. In normal mice, <i>Diet1</i> knockout increased bile acid production and decreased cholesterol levels compared with no knockout. Next steps include using a human intestinal cell-based assay to identify DIET1 modulators. SciBX 6(26); doi:10.1038/scibx.2013.667 Published online July 11, 2013	Findings unpatented; available for licensing	Vergnes, L. <i>et al. Cell Metab.</i> ; published online June 4, 2013; doi:10.1016/j.cmet.2013.04.007 Contact: Karen Reue, University of California, Los Angeles, Calif. e-mail: reuek@ucla.edu
Atherosclerosis; inflammation; ischemia/reperfusion injury; sepsis	Sphingosine 1-phosphate receptor 2 (S1PR2; S1P2; EDG5)	Mouse studies suggest inhibitors of S1PR2 could help treat inflammatory vascular disorders. In mice, an S1PR2 antagonist decreased lipopolysaccharide (LPS)-induced increases in inflammation and vascular permeability compared with saline. In the same model, <i>S1pr2</i> -deficient mice showed lower expression of inflammation and coagulation mediators than wild-type mice in response to LPS. Next steps could include evaluating S1PR2 inhibitors in preclinical models for inflammatory vascular disorders such as atherosclerosis and ischemia/reperfusion injury. SciBX 6(26); doi:10.1038/scibx.2013.668 Published online July 11, 2013	Unpatented; licensing status not applicable	Zhang, G. <i>et al. Blood</i> ; published online May 30, 2013; doi:10.1182/blood-2012-11-467191 Contact: Teresa Sanchez, Harvard Medical School, Boston, Mass. e-mail: tsanchez@bidmc.harvard.edu

This week in techniques

THE DISTILLERY brings you this week's most essential scientific findings in techniques, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Intestinal organoid model for cystic fibrosis transmembrane conductance regulator (CFTR) function	<p>An intestinal organoid model for CFTR function could help develop compounds to treat cystic fibrosis. Organoids were cultured from human intestinal stem cells and treated with forskolin, which activates CFTR and induces fluid influx and swelling. In organoids cultured from patients carrying mutant CFTR variants, forskolin-induced swelling was lower than that in patients carrying wild-type CFTR. In $\Delta F508$ mutant CFTR-expressing organoids, compounds that increased CFTR function also increased forskolin-induced swelling compared with vehicle. Next steps include using the organoids to model patient response to CFTR-targeted drugs.</p> <p>Vertex Pharmaceuticals Inc.'s VX-809, a CFTR corrector, is in Phase III trials to treat $\Delta F508$ mutant cystic fibrosis (CF) in combination with the CFTR potentiator Kalydeco ivacaftor (VX-770). Vertex markets Kalydeco to treat CF.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.669 Published online July 11, 2013</p>	Patent application filed; available for licensing	<p>Dekkers, J.F. <i>et al. Nat. Med.</i>; published online June 2, 2013; doi:10.1038/nm.3201 Contact: Jeffrey M. Beekman, University Medical Center Utrecht, Utrecht, the Netherlands e-mail: jbeekman@umcutrecht.nl</p>
Optogenetic models for obsessive compulsive disorder (OCD) in mice	<p>Mouse studies suggest optogenetic control of brain activity could be useful for studying OCD. In mice, repeated optogenetic activation of cortical glutamnergic neurons led to long-term repetitive grooming behavior. Also in the mice, the antidepressant Prozac fluoxetine decreased optogenetically induced grooming compared with vehicle. In a separate, genetically induced model for OCD, optogenetic activation of the lateral orbitofrontal cortex decreased grooming behavior compared with no optogenetic activation. Next steps could include testing therapeutic candidates in both models for OCD.</p> <p>Eli Lilly and Co. markets Prozac to treat major depressive disorder, OCD, bulimia nervosa and panic disorder.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.670 Published online July 11, 2013</p>	Patent and licensing status undisclosed for both studies	<p>Ahmari, S.E. <i>et al. Science</i>; published online June 7, 2013; doi:10.1126/science.1234733 Contact: Susanne E. Ahmari, Columbia University, New York, N.Y. e-mail: sea2103@columbia.edu</p> <p>Burguière, E. <i>et al. Science</i>; published online June 7, 2013; doi:10.1126/science.1232380 Contact: Ann M. Graybiel, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: graybiel@mit.edu</p>
Drug platforms			
Cow-derived antibody scaffolds	<p>Structural analysis of bovine complementarity-determining regions (CDRs) could guide the development of new antibody libraries. Cows have distinct immunoglobulin features including long CDRs and limited variable regions, and the molecular basis of their antibody diversity is not well understood. A series of computational and structural experiments demonstrated that these long CDRs can form numerous disulfide bonds that generate structural diversity through folding into unusual stalk- or knob-shaped structures. Next steps include constructing libraries of cow antibodies to identify hits against potentially difficult targets.</p> <p>Fabrus LLC, which coauthored the study and was cofounded by Vaughn Smider, is developing antibody screening platforms based on the technology.</p> <p>SciBX 6(26); doi:10.1038/scibx.2013.671 Published online July 11, 2013</p>	Patent applications filed; unavailable for licensing	<p>Wang, F. <i>et al. Cell</i>; published online June 6, 2013; doi:10.1016/j.cell.2013.04.049 Contact: Vaughn V. Smider, The Scripps Research Institute, La Jolla, Calif. e-mail: vvsmider@scripps.edu Contact: Ian A. Wilson, same affiliation as above e-mail: wilson@scripps.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Mammalian cell-based antigen display screening platform	A mammalian platform for surface antigen display could be used to screen for and discover therapeutic antibodies. A difficult step for <i>in vitro</i> antibody discovery is the cloning of candidates discovered via bacterial display systems into mammalian cell expression systems. In the current platform, human embryonic kidney 293 (HEK293) cells were transfected with a vector that caused them to display a protein on their surface and secrete it into culture media. The vector also was used to create HEK293 cell lines that displayed and secreted antibodies, antibody fragments and antibody fusion proteins. AnaptysBio Inc. has integrated this system into its SHM-XEL human antibody generation platform, and next steps include using the platform to develop therapeutic and diagnostic antibodies. SciBX 6(26); doi:10.1038/scibx.2013.672 Published online July 11, 2013	Covered by issued and pending patents; antibody discovery platform already partnered with multiple companies and government agencies	Horlick, R.A. <i>et al. J. Biol. Chem.</i> ; published online May 20, 2013; doi:10.1074/jbc.M113.452482 Contact: Robert A. Horlick, AnaptysBio Inc., San Diego, Calif. e-mail: rhorlick@anaptysbio.com

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Erratum: Analysis: Translational Notes

Haas, M.J. *SciBX* 6(25); doi:10.1038/scibx.2013.616
Published online June 27, 2013

The Analysis item “NCATS’s nine lives” erroneously included reference numbers as part of two compound names in Table 1. The correct compound names are JNJ-39393406 and SAR115740.

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