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Trends with benefits

By C. Simone Fishburn, Senior Editor

The FDA set up its adverse event database decades ago to capture the side effects of marketed drugs, but a group from the **Icahn School of Medicine at Mount Sinai** has now exploited the millions of entries to extract a different type of information—beneficial drug combinations that statistically reduce a drug's risk of toxicity. The positive interactions could reveal nodes at which pathways intersect, providing new targets to help guide drug discovery.

“Our strategy was to ask what if combining drugs could have some good effects,” team leader Ravi Iyengar told *SciBX*.

Using the **FDA Adverse Event Reporting System** (FAERS) database as its principal source, the group devised an approach to identify marketed drugs that produced fewer adverse events (AEs) when used in combination with other drugs than when used alone.¹

Iyengar's goal was to find pairs of drugs with beneficial interactions, explore the networks associated with each drug's target and then find points of intersection that might separate therapeutic effects from AEs to help guide drug discovery.

Iyengar is a professor of pharmacology and systems therapeutics at Mount Sinai and director of **Systems Biology Center New York**.

“The trick is to find the balance or mixture of drugs that will raise the therapeutic index.”

**—Ravi Iyengar,
Icahn School of Medicine
at Mount Sinai**

Better with Byetta

The group focused its first search on Avandia rosiglitazone, a diabetes drug with a label that warns of an increased risk of myocardial ischemia and cardiovascular effects.

The team expected a high number of reported cases of Avandia AEs and hypothesized that the large numbers of diabetics taking multiple drugs would increase the odds of finding significant trends.

A scan of about 4 million entries in the FAERS database revealed about 63,064 reports of AEs among patients using Avandia. Of these, 20,005 were associated with myocardial infarction (MI), representing about 32% of the Avandia AEs.

The group then searched FAERS and identified 10 drugs that, when taken with Avandia, were associated with MI incidence substantially lower than 32%.

Byetta exenatide emerged as the most effective drug in reducing the odds of Avandia-associated MI. The database contained 4,460 reports of AEs for patients taking both Byetta and Avandia, of which 95 were MIs. That 2% rate was comparable to the overall MI representation in FAERS.

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PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798United Kingdom
T: +44 (0)18 6551 2184Washington, DC
2008 Q Street, NW, Suite 100
Washington, DC 20009
T: +1 202 462 9582**Nature Publishing Group**New York
75 Varick Street, 9th Floor
New York, NY 10013-1917
T: +1 212 726 9200London
The Macmillan Building
4 Crinan Street
London N1 9XW
United Kingdom
T: +44 (0)20 7833 4000Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
Shinjuku-ku, Tokyo 162-0843
Japan
T: +81 3 3267 8751

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Combinations of Avandia and Seroquel quetiapine or Diamicon gliclazide reduced the MI-associated reports to 7% and 5%, although the sample size was small—each combination had less than 700 cases.

For another 7 drugs in combination with Avandia, the MI proportion ranged from 13% to 22% and the number of entries ranged from about 1,400 to 11,800.

Avandia is marketed by **GlaxoSmithKline plc**. Diabetes drugs Byetta and Diamicon are sold by **Bristol-Myers Squibb Co.** and **Servier**, respectively. **AstraZeneca plc** markets Seroquel to treat schizophrenia and other neurological disorders.

Networking

Iyengar's group then focused on finding molecular mechanisms that might explain the link between Avandia drug combinations and reduced MI risk.

As a first step, the team used systems biology to create cell biological interaction networks centered around Avandia's target, peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ).

Next, the group focused on fluid retention and blood clotting as two plausible pathways by which Avandia might cause MI.

For each pathological process, the team searched for transcriptional relationships and protein-protein interactions connected with PPAR γ and crafted a subnetwork that branched out from that target.

The team then looked for targets of the Avandia-interacting drugs within the two subnetworks and identified a node of convergence with Byetta in the clotting network at plasminogen activator inhibitor 1 (SERPINE1; PAI1).

Iyengar's group treated diabetic mice with Avandia and Byetta and found that the combination normalized Pai1 levels, and it decreased clotting dynamics compared with Avandia alone.

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The researchers did not take the next step and use the PAI1 node to design new drugs, but they think the overall strategy can identify previously unknown pathway interactions that can be incorporated into drug discovery screens.

Data were reported in *Science Translational Medicine*.

Strength in numbers

Iyengar acknowledged the drawbacks of AE databases, as they rely on self-reporting and have no denominator such as the total number of prescriptions. As such, it is not possible to know how significant any interaction is within the total number of patients taking a particular combination of drugs.

Nevertheless, he told *SciBX*, the large size of FAERS compensates for the lack of a denominator, and the large numbers of cases fed into the statistics far exceed the numbers used in clinical trials.

In addition, according to Iyengar, the strength of the approach for identifying new targets or nodes of interaction is that the hypotheses derive from human clinical data rather than *in vitro* or cell-based experiments.

Thus, he thinks that the approach can yield information about drug combinations that could guide clinical practice.

“The trick is to find the balance or mixture of drugs that will raise the therapeutic index,” he told *SciBX*.

Whereas Byetta and Avandia are both used to treat diabetes, other drug combinations from diverse indications were also identified in the FAERS database search.

Indeed, Iyengar’s group found more than 19,000 other combinations for which co-prescribing drugs could reduce the toxicity associated with one of them.

For example, a selective serotonin reuptake inhibitor (SSRI) and the histamine H2 receptor (HRH2; H2R) antagonist Zantac ranitidine significantly reduced the suicide rate from 3.1% for an SSRI alone to 0.6% for the combined drugs.

Iyengar said that pharma could use the information from his team’s screens to run prospective clinical trials to assess whether combinations might provide a significant therapeutic advantage over standard of care.

Mount Sinai has filed for patents covering data in the study, and the findings are available for licensing.

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REFERENCES

1. Zhao, S. *et al. Sci. Transl. Med.*; published online Oct. 9, 2013; doi:10.1126/scitranslmed.3006548

Contact: Ravi Iyengar, Icahn School of Medicine at Mount Sinai, New York, N.Y.

e-mail: ravi.iyengar@mssm.edu

COMPANIES AND INSTITUTIONS MENTIONED

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

Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.

Food and Drug Administration, Silver Spring, Md.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Icahn School of Medicine at Mount Sinai, New York, N.Y.

Servier, Neuilly-sur-Seine, France

Systems Biology Center New York, New York, N.Y.



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BETting on Th17 cells

By Lev Osherovich, Senior Writer

Researchers at **Constellation Pharmaceuticals Inc.** have established a connection between BET bromodomain proteins and pathogenic T helper type 17 cells.¹ The findings hint at therapeutic opportunities for this epigenetic target class in autoimmunity and inflammatory disease, but further details about tolerability and specificity of current BET inhibitors are needed.

BET bromodomains are protein modules that bind to acetylated lysine residues of histones, the principal components of chromatin. Small molecule BET inhibitors mimic acetylated lysine and prevent BET proteins from recognizing chromatin, leading to transcriptional changes that arrest cell proliferation and differentiation.

Most efforts to target BET proteins have focused on cancer. BET inhibitors from Constellation, **GlaxoSmithKline plc** and **Oncoethix S.A.** are in Phase I testing for a range of tumor types.

In 2010, an international team that included **The Rockefeller University** and GSK reported that GSK525762, a broad-spectrum BET inhibitor in Phase I testing for epithelial cancer, also had potent anti-inflammatory effects in macrophages.² Rab Prinjha, VP and head of the EpiNova epigenetics discovery performance unit at GSK, said that results of the trial are expected in 2014.

Now, a Constellation team has shown that BET proteins influence the development and activation of T helper type 17 (Th17) cells, which are dysregulated in autoimmune diseases including multiple sclerosis (MS) and rheumatoid arthritis (RA).

“There was already a good notion that this family of proteins controls inflammation,” said Jose Lora, team leader and executive director of preclinical sciences at Constellation. “The novelty of our recent paper is that these BET proteins control an important differentiation pathway in T cells.”

Lora previously was director and head of immuno-epigenetics biology at GSK.

He said that the findings suggest BET proteins regulate inflammation by controlling expression of Th17 cell-specific proinflammatory cytokines.

“We are showing that this pathway is a fundamental mediator of transcription of these cytokines and show in animal models that this is a reasonable entry point for therapeutics,” he added.

Lora’s team treated undifferentiated human T cells with JQ1, a broad-spectrum, small molecule BET inhibitor identified by researchers at **Harvard Medical School**,³ and then subjected the cells to conditions that promoted differentiation of various helper cell subtypes.

JQ1 prevented differentiation of Th17 cells but not of Th1, Th2 or T_{reg} cells, whereas vehicle had no effect.

In naïve T cells that had not yet developed Th17 cell characteristics, JQ1 blocked the expression of Th17 cell-associated cytokines including IL-17, IL-21 and granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2).

The team obtained a similar result in actual Th17 cells. That finding suggests that BET blockade not only could block the initiation of the Th17 cell response but also potentially could shut down active Th17 cells.

In mouse models of MS and RA, JQ1 decreased IL-17 production and disease severity compared with vehicle.

Results were reported in *The Journal of Experimental Medicine*.

Helping the helpers

Although the findings provide proof of concept for therapeutic intervention with BET inhibitors in Th17 cell-driven autoimmune diseases, the precise role of BET proteins in autoimmunity is still up for debate.

For example, the new findings contrast with last year’s report in the *Proceedings of the National Academy of Science* from a team led by Anjana Rao that found that GSK525762 prevented the initiation of the Th1 cell response but could not halt ongoing autoimmune activity.⁴ Rao is a professor of signaling and gene expression research at the **La Jolla Institute for Allergy & Immunology**.

In that study, GSK525762 blocked “the initial phases of T cell differentiation with specific and selective effects driven in a context-specific manner by signature cytokines more in Th1 than Th17 cells,” said Prinjha, who was a coauthor of Rao’s study.

Prinjha thinks that methodological differences between the two experiments could account for the divergent conclusions. He said that Rao’s team used adoptive T cell transfer for its *in vivo* work, whereas Lora’s team did much of its work *in vitro* in human T cells and in mouse disease models with relatively unmanipulated immune systems.

Alexander Tarakhovsky, a professor in the laboratory of immune cell epigenetics and signaling at Rockefeller University, said that the new findings underscore the limited ability of animal models to capture the full complexity of autoimmune disease.

“Current models of autoimmunity typically focus on a particular type of immune response, but such studies are not sufficiently inclusive of other aspects of immunity,” he said.

Thus, said Tarakhovsky, the two teams’ conclusions “are not mutually exclusive and could result from different experimental setups.”

Tarakhovsky led the team that first reported the anti-inflammatory effects of BET inhibitors.² He is collaborating with GSK to characterize the immunological effects of the company’s BET compounds.

Lora concurred that “the difference in models probably explains the differences” between the two studies.

Nevertheless, it is not certain that blocking Th17 cell activity is the main effect of BET inhibitors on the immune system.

“It is still unclear what is the most important site of action of the BET inhibitors,” said Prinjha. “Our adoptive transfer experiments in the Rao paper went some way to showing the importance of Th1 cells, but more work is needed to characterize other immune cell types.”

“To get an answer about which specific proteins and cells are involved in which aspects of autoimmune disease, we would need conditional genetic knockouts.”

—Hozefa Bandukwala, Pfizer Inc.

Hozefa Bandukwala, first author on last year's *PNAS* paper and now a principal scientist at **Pfizer Inc.**, said that BET inhibitors likely affect a broad range of immune cells besides T helper cells.

Red light

Tarakhovsky said that uncertainty about what exactly BET inhibitors do to immune function should serve as a warning against leaping into the clinic.

He said that BET proteins appear to affect the development and activity of multiple immune cells, and thus he thinks that current BET inhibitors are likely to have broad immunosuppressive effects.

Current BET inhibitors are relatively unselective and are likely to hit multiple members of the BET protein family.

"In fact, we know very little about the true spectrum of the effects of these compounds," he said.

Improving the selectivity of BET inhibitors is a logical way to help position the molecules in autoimmune diseases.

Humans have at least nine BET proteins, the best characterized of which include bromodomain containing 2 (BRD2) and BRD4. Many other proteins feature bromodomains that are potentially affected by BET inhibitors.

"One potential area for improving the safety profile of BET inhibitors is to narrow the specificity to BRD2 and BRD4, but because all bromodomains are very similar, it will be challenging to achieve selectivity for one over the other," said Lora.

Lora added that Constellation has a discovery-stage program to identify selective BET inhibitors for autoimmune and inflammatory disease. The company's lead product in the space, CPI-0610, is in Phase I testing for

lymphoma. Constellation did not disclose details about that compound's selectivity.

Meanwhile, genetic methods could help determine which BET proteins are working in which immune cells to drive autoimmunity.

"To get an answer about which specific proteins and cells are involved in which aspects of autoimmune disease, we would need conditional genetic knockouts," said Bandukwala.

Lora and Prinjha said that ongoing Phase I trials of pan-BET inhibitors in oncology should lead to insights about the immunological effects of blocking this protein family.

"The ongoing trials in oncology are going to be very informative. This is the first time that we'll see the safety profile of these compounds and how well they're tolerated," said Lora.

"I suspect the final choices of immuno-inflammatory disease indication will be driven by data that emerge from our ongoing clinical studies rather than more preclinical work," said Prinjha.

Constellation did not disclose whether it has filed patents in connection with the *JEM* study.

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REFERENCES

1. Mele, D.A. *et al. J. Exp. Med.*; published online Oct. 7, 2013; doi:10.1084/jem.20130376
Contact: Jose M. Lora, Constellation Pharmaceuticals Inc., Cambridge, Mass.
e-mail: jose.lora@constellationpharma.com
2. Nicodeme, E. *et al. Nature* **468**, 1119–1123 (2010)
3. Filippakopoulos, P. *et al. Nature* **468**, 1067–1073 (2010)
4. Bandukwala, H.S. *et al. Proc. Natl. Acad. Sci. USA* **109**, 14532–14537 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

Constellation Pharmaceuticals Inc., Cambridge, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
La Jolla Institute for Allergy & Immunology, La Jolla, Calif.
Oncoethix S.A., Lausanne, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
The Rockefeller University, New York, N.Y.

"There was already a good notion that this family of proteins controls inflammation. The novelty of our recent paper is that these BET proteins control an important differentiation pathway in T cells."

**—Jose Lora,
Constellation
Pharmaceuticals Inc.**

RSVing for site zero

By Tracey Baas, Senior Editor

Despite decades of research, respiratory syncytial virus (RSV) remains a highly prevalent childhood pathogen without an approved vaccine.¹ There is a marketed prophylactic—Synagis palivizumab—to prevent severe disease caused by RSV in at-risk infants, but the passive immunization provided by the antibody does not last from season to season, and its high cost precludes its use in other patient populations. Now, a team from the NIH has used structure-based design to generate RSV vaccines that showed strong neutralizing activity in both mice and macaques.²

The next step is picking a lead vaccine to advance into GMP production and clinical trials.

RSV is the most common cause of hospitalization in children under 5 years of age and results in more than 3 million hospital stays each year. RSV mortality in the elderly is comparable to that of influenza virus.^{3,4}

There are multiple barriers to developing RSV vaccines. These include the very young age of most patients, the lack of a good animal model that recapitulates human RSV infection, and the virus' ability to both evade innate and adaptive immunity and reinfect patients.

The most substantial barrier came to light decades ago when one of the first candidate vaccines—formalin-inactivated RSV (FI-RSV)—not only failed to protect children in early trials but also enhanced virus-induced respiratory disease and led to two deaths and a high hospitalization rate.

The vaccine-enhanced disease is thought to be caused by the induction of high levels of non-neutralizing antibodies.

Ideally, an effective vaccine would induce high levels of neutralizing antibodies.

Synagis is marketed by AstraZeneca plc's MedImmune LLC unit to prevent RSV in premature infants at high risk of infection. The humanized mAb targets RSV F, which is a trimeric glycoprotein the virus uses to enter host cells via membrane fusion. The mAb posted sales of \$1.04 billion in 2012.

Although RSV F is clearly a good starting point for vaccine development, the conformational diversity of the target makes engineering a good antigen difficult.

Before virus-cell interactions, RSV F exists in an unstable, lollipop-shaped conformation. After the merging of virus and cell membranes, RSV F exists in a stable, crutch-shaped conformation.

The stable, postfusion RSV F is currently being used to develop vaccine candidates⁵ (see Table 1, "RSV pipeline").

But in recent years, a team from the NIH and China identified 5C4 and another team from antibody company AIMM Therapeutics B.V. identified AM22 and D25—all three strongly neutralizing antibodies that target a site dubbed antigenic site zero in prefusion RSV F.⁶ Antibodies targeting site zero were 10- to 100-fold more potent than Synagis.

Based on that work, the NIH team suspected that vaccines able to induce neutralizing antibodies against prefusion RSV F could be a better approach than using postfusion RSV F.

Now, the NIH team has bridged the gap between site zero-targeting antibodies and an actual vaccine. The group used structure-based design to engineer antigens based on soluble variants of the prefusion RSV F protein that have stably exposed antigenic site zero.

The researchers modified F protein to include cysteine pairs, cavity-filling hydrophobic substitutions and a C-terminal trimerization domain dubbed a foldon. They constructed more than 100 such variants and looked for those that bound the D25 antibody for at least a week.

Among the top four variants, X-ray crystallography showed that the stabilized proteins included some version of the antigenic site zero fixed in a D25-bound conformation.

The team dosed mice and rhesus macaques with the variants plus the adjuvant poly inosine:cytosine formulated in polylysine carboxymethylcellulose (poly-ICLC) and then tested the ability of the animals' sera to prevent RSV infection in human cells.

In mice, the top variant elicited neutralizing activity that was 8-fold better than that caused by stable, postfusion F protein and 40 times the threshold for protection. In macaques, this same variant led to neutralizing activity that was 70 times greater than that of the postfusion F protein.

Results were published in *Science*.

Vaccine reality

The next step for the team is GMP manufacturing of a lead variant in preparation for a Phase I trial.

"It's not clear if additional improvements to the antigen are needed," said Jason McLellan, the study's lead author, who is now an assistant professor of biochemistry at the Geisel School of Medicine at Dartmouth. "Additional modifications will be made and tested. Removal of the foldon domain may be required."

JoAnn Suzich, VP of research for infectious diseases and vaccines at MedImmune, agreed. "Ideally, a vaccine for humans would not contain extraneous protein sequence such as a foldon. At the very least, the similarity of foldon sequence to any human protein sequences would need to be explored, and the potential for antibodies or T cell responses directed against this domain to cross-react with human tissues should be addressed."

Gregory Glenn, SVP and CMO of vaccine company Novavax Inc., said that it will be important to test the vaccine "with an adjuvant that is already approved for use in humans rather than the poly-ICLC adjuvant used in the study."

Glenn wanted to see the vaccine used in cotton rats challenged with RSV infection, but Peter Kwong said that such studies would yield little information. Kwong is chief of the Structural Biology Section at the NIH's Vaccine Research Center and one of the corresponding authors on the paper.

"In terms of challenge studies, there is unfortunately not an optimal animal study [or] challenge model for RSV," he said. "We will be moving forward toward clinical studies to evaluate safety."

Barney Graham said "that while mice and cotton rats are both semipermissive for RSV infection, they are commonly used for preclinical evaluation of RSV vaccine safety. However, when vaccination results in

"In terms of challenge studies, there is unfortunately not an optimal animal study [or] challenge model for RSV. We will be moving forward toward clinical studies to evaluate safety."

**—Peter Kwong,
National Institutes of Health**

Table 1. RSV pipeline. Only one product is marketed to prevent serious lower respiratory tract disease caused by respiratory syncytial virus (RSV). At least 12 other compounds are being developed to prevent or treat RSV-induced respiratory disease.

Source: BCIQ: BioCentury Online Intelligence

Company	Product	Description	Status
Vaccines			
Novavax Inc. (NASDAQ:NVAX)	RSV F vaccine	RSV vaccine directed against RSV F protein and formulated in virus-like particles	Phase II
AstraZeneca plc's (LSE:AZN; NYSE:AZN) MedImmune LLC unit	MEDI-559	Live attenuated RSV vaccine	Phase I
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	GSK3003891A	Immunostimulant vaccine	Phase I
	Pan-adenovirus type 3 (PanAd3)/modified vaccinia Ankara (MVA) virus RSV vaccine	Heterologous prime-boost regimen with vectors encoding a string of RSV F, N and M proteins bearing both B and T cell epitopes	Phase I
	RSV vaccine	Vaccine based on the company's PanAd3/MVA virus RSV vaccine	Phase I
Antibodies			
AstraZeneca/AbbVie Inc. (NYSE:ABBV)	Synagis palivizumab	Humanized mAb against RSV F	Marketed
MedImmune	Motavizumab (MEDI-524)	Humanized mAb against RSV F	Phase III
Ablynx N.V. (Euronext:ABLX)	ALX-0171	Single variable domain antibody fragment against RSV F	Phase I
Other modalities			
Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY)/ Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151)	ALN-RSV01	Small interfering RNA targeting RSV nucleocapsid gene	Phase II
Gilead Sciences Inc. (NASDAQ:GILD)	GS-5806	Undisclosed	Phase II
Arrow Therapeutics Ltd./Novartis AG (NYSE:NVS; SIX:NOVN)	RSV604	Nucleoprotein inhibitor	Phase II
MicroDose Therapeutx Inc.	MDT-637	Inhalable, small molecule, antiviral fusion inhibitor delivered using dry powder nebulizer technology	Phase I
Alios BioPharma Inc.	ALS-8176	Oral RSV nucleoside analog	Phase I

such high neutralization titers, it is difficult to make an assessment of vaccine-enhanced disease because infection cannot be established.”

Graham is chief of the Clinical Trials Core and Viral Pathogenesis Laboratory at the NIH's Vaccine Research Center and the other corresponding author on the paper.

On the safety front, McLellan said that the group's variants are unlikely to aggravate RSV infection. “Unlike FI-RSV, our prefusion-stabilized molecules elicit high titers of neutralizing antibodies,” he said. “Also, our stabilized antigens are far less likely to elicit non-neutralizing antibodies since we're presenting the active form of the molecule to the immune system.”

“These studies suggest that vaccines with the stabilized prefusion F have the best chance for efficacy of RSV vaccines tested to date.”

—Larry Anderson,
Emory University School of Medicine

“These studies suggest that vaccines with the stabilized prefusion F have the best chance for efficacy of RSV vaccines tested to date,” said Larry Anderson, a professor of pediatrics in the division of pediatric infectious diseases at the **Emory University School of Medicine**.

There also was consensus that the NIH's vaccine would not compete with Synagis.

“I believe a population different than the palivizumab target population would be best for this novel vaccine,” said Suzich. “The immaturity of the newborn immune system makes vaccination in very young infants difficult.”

According to Kwong, “The vaccine could target other populations affected by RSV such as the elderly. One could also target women of childbearing age or pregnant women.” Vaccine-induced neutralizing antibodies from the mother would be actively transported to the newborn.

Graham said, “Eventually it may be possible to evaluate the vaccine in young children and perhaps, with an enlarged safety database, in infants. None of these vaccine approaches would really compete with Synagis.”

The findings are patented and available for licensing from the Office of the Director at the NIH.

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REFERENCES

- Anderson, L.J. *et al. Vaccine* **31 Suppl. 2**, B209–B215 (2013)
- McLellan, J.S. *et al. Science*; published online Nov. 1, 2013; doi:10.1126/science.1243283
Contact: Peter D. Kwong, National Institutes of Health, Bethesda, Md.
e-mail: pdkwong@nih.gov
Contact: Barney S. Graham, same affiliation as above
e-mail: bgraham@nih.gov
- Graham, B.S. *Immunol. Rev.* **239**, 149–166 (2011)
- Lozano, R. *et al. Lancet* **380**, 2095–2128 (2012)
- Swanson, K.A. *et al. Proc. Natl. Acad. Sci. USA* **108**, 9619–9624 (2011)
- McLellan, J.S. *et al. Science* **340**, 1113–1117 (2013)

COMPANIES AND INSTITUTIONS MENTIONED

AIMM Therapeutics B.V., Amsterdam, the Netherlands
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Emory University School of Medicine, Atlanta, Ga.
Geisel School of Medicine at Dartmouth, Hanover, N.H.
MedImmune LLC, Gaithersburg, Md.
National Institutes of Health, Bethesda, Md.
Novavax Inc. (NASDAQ:NVAX), Rockville, Md.

Scleroderma models: skin in the game

By Michael J. Haas, Senior Writer

Systemic scleroderma involves fibrosis of the skin and internal organs, but its etiology is poorly understood and it has no known genetic causes—factors that have hampered the development of models and, in turn, therapies.

Now, a North American team has shown that mice harboring a mutant form of the glycoprotein fibrillin 1 (Fbn1) recapitulated skin fibrosis and other symptoms seen in patients with systemic scleroderma.¹ Although the team showed the therapeutic effect of targeting different proteins whose expression was altered by the mutant glycoprotein, future studies will have to zero in on the best target for treating scleroderma in patients.

FBN1, a glycoprotein secreted by fibroblasts into the extracellular matrix, is an essential component of the microfibrils found in many types of connective tissue. FBN1 also interacts with integrins expressed on other cell types, such as dermal-infiltrating dendritic cells (DCs), to regulate adhesion.

FBN1 mutations can cause a number of different conditions and diseases that affect connective tissue, most notably Marfan syndrome.²

In 2006, a team at **The Johns Hopkins University School of Medicine** led by Harry Dietz showed that some *FBN1* mutations could upregulate signaling by transforming growth factor- β (TGF β ; TGF β)—a family of cytokines that is involved in the proliferation and differentiation of most cells—to cause aortic aneurysms that occur in some patients with Marfan syndrome.³

Dietz's team also identified a few patients harboring *FBN1* mutations who exhibited symptoms of both Marfan syndrome and stiff skin syndrome, a rare inherited form of skin fibrosis with only about 40 cases reported in the literature. Subsequently, another Dietz-led team determined that stiff skin syndrome was caused by mutations in the integrin-binding domain of *FBN1* and involved upregulation of TGF β signaling.⁴

Now, his newest team has hypothesized that mice with loss-of-function mutations in the integrin-binding domain of *Fbn1* might provide insights into the pathobiology of another fibrotic disease associated with increased TGF β signaling—scleroderma.⁵

Indeed, the team found that the *Fbn1*-mutant mice exhibited skin fibrosis, high levels of collagen in the skin and the high levels of anti-nuclear and anti-topoisomerase I (Top1) antibodies in circulation seen in patients with systemic scleroderma.

Plasmacytoid DCs isolated from the dermis of the mutant mice and fibroblasts from patients with systemic scleroderma had high surface levels of integrin β_1 (CD29) and activated integrin β_3 (GPIIIa; CD61).

In the *Fbn1*-mutant mice, a mouse Cd29-activating antibody—which mimicked Fbn1's interactions with Cd29—decreased skin fibrosis and

levels of circulating anti-nuclear and anti-Top1 antibodies compared with an inactive murine control antibody.

Knockout of *Cd61* or a pan-specific, anti-Tgf β antibody also decreased skin fibrosis in the mice compared with normal *Cd61* expression or a control antibody.

In the patient fibroblasts, a CD29-activating antibody, an anti-CD61 antibody or a small molecule against type I TGF β receptor decreased collagen expression compared with inactive control antibodies.

Additionally, patient fibroblasts and DCs from the dermis of the mouse models had elevated TGF β -dependent MAP kinase 3 (MAPK3; ERK-1) and/or MAPK1 (ERK-2) signaling. In the fibroblasts and models, a small molecule MEK inhibitor decreased collagen expression and skin fibrosis, respectively, compared with vehicle.

Collectively, the findings suggest that stiff skin syndrome and systemic scleroderma involve similar pathological mechanisms (see **Figure 1, “Restoring dermal integrity”**) and thus could potentially be treated with the same therapeutic strategies, the team wrote in its report in *Nature*.

There are no drugs approved to treat stiff skin syndrome or the underlying causes of systemic scleroderma. Therapies for the latter primarily involve topical or systemic immunosuppressive drugs to ameliorate symptoms.

Dietz is a professor of pediatrics, medicine, and molecular biology and genetics at the Johns Hopkins University School of Medicine and a professor of medicine and genetics at the school's McKusick-Nathans Institute for Genetic Medicine. He is also director of the school's William S. Smilow Center for Marfan Syndrome Research and an investigator at the **Howard Hughes Medical Institute**. His team included a researcher from **McGill University**.

Although stiff skin syndrome and scleroderma have differing or unknown causes, “Dietz has shown that, once initiated, the diseases appear to have similar biological processes that converge on the same pathways,” Luke Evnin, chairman of the **Scleroderma Research Foundation**, told *SciBX*. “These mouse models could help us study the biology behind scleroderma and identify therapeutic strategies for preventing or reversing skin fibrosis.”

Evnin, who is a managing director at life sciences VC **MPM Capital**, said that the Scleroderma Research Foundation recruited Dietz about six years ago to work on scleroderma and funded the research in the *Nature* study.

“Among the obstacles to understanding scleroderma are the heterogeneity of the disease—systemic sclerosis that affects multiple organs—and the variability of its clinical course. The *Nature* study helps reduce this complexity by focusing on a genetic model involving only pathological fibrosis of the skin,” said Gary Nabel, CSO of **Sanofi**.

Thus, this high-fidelity model of skin scleroderma could be used to screen for new compounds to treat the disease or possibly repurpose those in development for other diseases, he said.

Sanofi's SAR100842, an antagonist of lysophosphatidic acid receptor 1 (LPAR1; EDG2; LPA1) and LPAR3 (EDG7; LPA3), is in Phase II testing to treat scleroderma. LPA antagonists are thought to modify TGF β activity indirectly, Nabel said.

“These mouse models could help us study the biology behind scleroderma and identify therapeutic strategies for preventing or reversing skin fibrosis.”

—Luke Evnin,
Scleroderma Research Foundation

InterMune Inc. (NASDAQ:ITMN), **Ildong Pharmaceutical Co. Ltd.** and **Shionogi & Co. Ltd.** (Tokyo:4507) market Esbriet pirfenidone, a small molecule inhibitor of profibrotic cytokines such as transforming growth factor- β (TGF β ; TGF β) and proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), to treat idiopathic pulmonary fibrosis (IPF); **Eli Lilly and Co.** (NYSE:LLY) has LY2382770, a neutralizing mAb against TGF β 1 (TGFB1) in Phase II for diabetic nephropathy; **Digna Biotech S.L.** has disitertide (P144), a topical formulation of peptide 144 TGF β 1 inhibitor, in Phase II for systemic sclerosis and Phase I for actinic keratosis (AK); **Isarna Therapeutics GmbH** has trabedersen (AP 12009), a TGF β 2 (TGFB2) antisense oligonucleotide, in Phase II for pancreatic cancer and melanoma and Phase I/II for colorectal cancer; **Yuhan Corp.** has YH14618, a TGF β 1 antagonist, in Phase I/II for degenerative disc disease.

Exelixis Inc. (NASDAQ:EXEL), **Roche** (SIX:ROG; OTCQX:RHHBY) and **Genentech Inc.** have the MEK inhibitor cobimetinib (GDC-0973; RG7421; XL518) in Phase III for melanoma; **Array BioPharma Inc.** (NASDAQ:ARRY) and **AstraZeneca plc** (LSE:AZN; NYSE:AZN) have selumetinib (ARRY-886; AZD6244), a small molecule MEK inhibitor, in Phase III for non-small cell lung cancer (NSCLC) and Phase II for multiple other cancers; Array and **Novartis AG** (NYSE:NVS; SIX:NOVN) have MEK162 (ARRY-162), an oral MEK inhibitor, in Phase III for melanoma and ovarian cancer, Phase II for solid tumors and hypertrophic cardiomyopathy (HCM) in patients with Noonan syndrome, Phase I/II for biliary tract cancer and Phase I for colorectal cancer; **Bayer AG** (Xetra:BYN) and AstraZeneca have refametinib (BAY 86-9766; RDEA119), a selective MEK inhibitor, in Phase II for hepatocellular carcinoma (HCC) and Phase I/II for pancreatic cancer; **UCB Group** (Euronext:UCB) and **Wilex AG** (Xetra:WL6) have MK-554 (WZ-554), an orally available small molecule MEK inhibitor, in Phase I/II for solid tumors.

Figure 1. Restoring dermal integrity. A study from Gerber *et al.* has elucidated potential mechanisms by which mutations in the integrin-binding domain of fibrillin 1 (Fbn1) produce symptoms of stiff skin syndrome and systemic sclerosis. The findings suggest that the biological processes of the two diseases converge on shared signaling pathways that offer common intervention points.

In mouse dermis, mutant Fbn1 induces two distinct pathways that produce activated transforming growth factor- β (Tgfb; Tgf β) and activated (*) integrin β_3 (Gp113a; Cd61), respectively—two components required for collagen expression and consequent skin fibrosis.

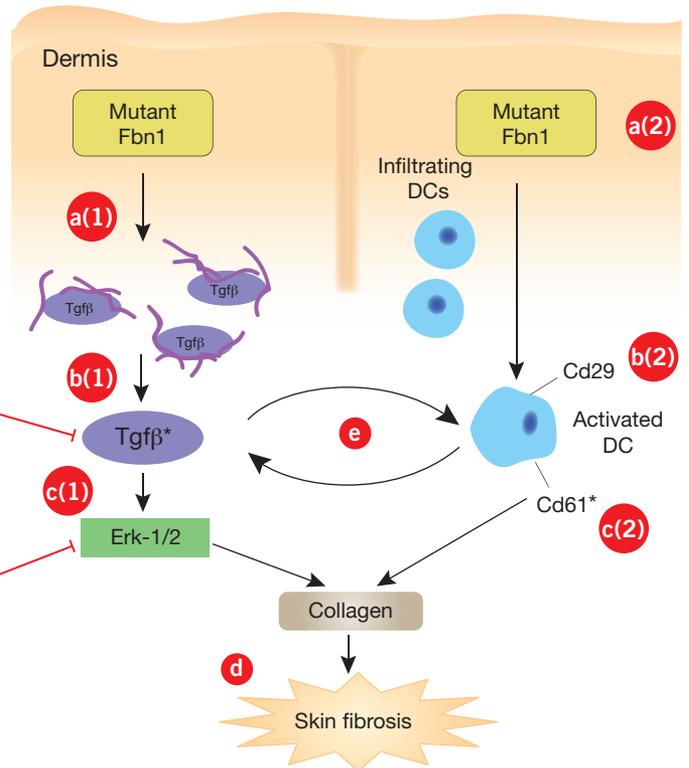
Mutant Fbn1 [a(1)] secreted by fibroblasts into the extracellular matrix binds Tgf β [b(1)] normally but forms a large number of

Going more than skin deep

Further work is needed before deciding which therapeutic strategy—targeting CD29, CD61 or TGF β —has the best chance in scleroderma.

“A large body of evidence points to a role of TGF β in scleroderma, and Dietz’s team’s work further supports this,” said Thomas Hultsch, senior medical director of translational medicine at Sanofi’s **Genzyme Corp.** unit. “Unraveling the mechanisms that control TGF β activation in the microenvironment of the dermis will be central for further development” of the team’s findings.

Added Nabel, “Our reading is that Dietz suggests the integrin



abnormal microfibrillar aggregates, resulting in high levels of latent Tgf β that become activated and upregulate Tgf β *-dependent MAP kinase 3 (Mapk3; Erk-1) and/or Mapk1 (Erk-2) signaling [c(1)].

Also in the dermis, Fbn1 cannot interact normally with infiltrating plasmacytoid dendritic cells (DCs) [a(2)], causing them to upregulate surface expression of integrin β_1 (Cd29) [b(2)] and Cd61* [c(2)].

Together, increased Tgf β -dependent Erk-1/2 signaling and high Cd61* levels lead to excessive collagen production and consequent skin fibrosis [d].

The two pathways also may be involved in a feedback loop [e] by which Tgf β * induces infiltrating DCs to produce additional Tgf β .

Fibroblasts from patients with systemic sclerosis also express high levels of TGF β [b(1)], have high surface levels of CD29 [b(2)] and CD61* [c(2)] and upregulate ERK-1/2 signaling [c(1)] to induce collagen production [d].

Inhibition of Tgf β , activation of Cd29, inhibition or deletion of Cd61 or inhibition of Erk1/2 in the mouse models and patient fibroblasts decreased skin fibrosis and collagen production, respectively, compared with controls.

pathways may allow modulation of TGF β in a more controlled way, spatially and temporally, than targeting the cytokine directly. However, this claim remains preliminary at the present time.”

Evnin agreed and said that targeting integrins β_1 or β_3 would probably be a better strategy than inhibiting TGF β “because the cytokine is involved in many biological processes and thus is not a good target for a chronic disease like scleroderma.”

He added, “An obvious next step would be to compare the relative efficacy and safety of the integrin β_3 -blocking and integrin β_1 -activating approaches in the *Fbn1*-mutant mouse models.”

Hultsch said that it also would be interesting to dissect the role of the specific TGF β isoforms TGF β 1 (TGFB1), TGF β 2 (TGFB2) and TGF β 3 (TGFB3) in skin fibrosis using isoform-specific antibodies, inhibitors or knockout models.

Evnin said that one drawback of the *Fbn1*-mutant models is that they do not exhibit the potentially life-threatening internal organ fibrosis seen in patients with systemic sclerosis. “That does leave open to question whether targeting integrins or TGF β would also prevent or reverse that fibrosis. While this question can’t be answered in mice, our hope is that the therapeutic effect would indeed be the same,” he said.

According to Evnin, **The Johns Hopkins University** has filed a patent application covering the findings reported in *Nature*.

Dietz did not respond to queries about his team’s follow-on studies in the *Fbn1* models.

This week, **Biogen Idec Inc.** and the BioFocus subsidiary of **Galapagos N.V.** announced a three-year collaboration to identify and validate new targets in scleroderma. Under the terms of the deal, BioFocus will use its technology platform and human skin models to deliver new assays and previously unknown, validated targets to Biogen

Idec. Galapagos said that the deal could net BioFocus up to \$31 million. Other terms were not disclosed.

Haas, M.J. *SciBX* 6(44); doi:10.1038/scibx.2013.1248
Published online Nov. 14, 2013

REFERENCES

1. Gerber, E.E. *et al. Nature*; published online Oct. 9, 2013; doi:10.1038/nature12614
Contact: Harry C. Dietz, The Johns Hopkins University School of Medicine, Baltimore, Md.
e-mail: hdietz@jhmi.edu
2. Dietz, H.C. *et al. Nature* **352**, 337–339 (1991)
3. Habashi, J.P. *et al. Science* **312**, 117–121 (2006)
4. Loeys, B.L. *et al. Sci. Transl. Med.* **2**, 23ra20 (2010)
5. Varga, J. & Pasche, B. *Nat. Rev. Rheumatol.* **5**, 200–206 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
The Johns Hopkins University, Baltimore, Md.
The Johns Hopkins University School of Medicine, Baltimore, Md.
Galapagos N.V. (Euronext:GLPG; Pink:GLPYY), Mechelen, Belgium
Genzyme Corp., Cambridge, Mass.
Howard Hughes Medical Institute, Chevy Chase, Md.
McGill University, Montreal, Quebec, Canada
MPM Capital, South San Francisco, Calif.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Scleroderma Research Foundation, San Francisco, Calif.

“Unraveling the mechanisms that control TGF β activation in the microenvironment of the dermis will be central for further development.”

– Thomas Hultsch, Sanofi



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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
Autoimmune disease				
Multiple sclerosis (MS)	G protein-coupled receptor 17 (GPR17)	Cell culture studies suggest inhibiting GPR17 could help promote remyelination in MS. In oligodendrocyte cultures from <i>Gpr17</i> heterozygous mice, a <i>Gpr17</i> agonist inhibited differentiation into mature, myelin-producing cells, whereas it had no effect in cultures from <i>Gpr17</i> knockout mice. Next steps include investigating GPR17 function in human induced pluripotent stem cell-derived oligodendrocytes and developing a GPR17 antagonist in partnership with an undisclosed pharma company. Omeros Corp. has a GPR17 antagonist in preclinical development to treat MS.	Patent application filed; unavailable for licensing	Hennen, S. <i>et al. Sci. Signal.</i> ; published online Oct. 22, 2013; doi:10.1126/scisignal.2004350 Contact: Evi Kostenis, University of Bonn, Bonn, Germany e-mail: kostenis@uni-bonn.de Contact: Jesus Gomeza, same affiliation as above e-mail: jgomez@uni-bonn.de
		SciBX 6(44); doi:10.1038/scibx.2013.1249 Published online Nov. 14, 2013		
Primary immunodeficiency disease (PID)	Phosphoinositide 3-kinase catalytic subunit δ -polypeptide (PI3KCD; p110 δ)	Sequencing and <i>in vitro</i> studies identified a specific PID called activated phosphoinositide 3-kinase- δ (PI3K δ) syndrome and suggest selective inhibitors of p110 δ could help treat the condition. Sequencing of RNA from patients with PID identified 17 subjects who carried a gain-of-function E1021K mutation in <i>p110δ</i> that increased kinase activity compared with the wild-type subunit. <i>In vitro</i> , two isoform-selective inhibitors of p110 δ decreased the activity of the mutant enzyme compared with baseline. Next steps include identifying additional patients who have activated PI3K δ syndrome and recruiting them for clinical trials to evaluate selective p110 δ inhibitors. Gilead Sciences Inc.'s p110 δ inhibitor, idelalisib, is under review for non-Hodgkin's lymphoma (NHL). The compound also is in Phase III testing to treat chronic lymphocytic leukemia (CLL). At least 10 other companies have compounds that inhibit p110 δ in Phase II testing or earlier to treat various cancers and inflammatory and autoimmune diseases.	Unpatented; licensing status not applicable	Angulo, I. <i>et al. Science</i> ; published online Oct. 17, 2013; doi:10.1126/science.1243292 Contact: Sergey Nejentsev, University of Cambridge, Cambridge, U.K. e-mail: sn262@cam.ac.uk
		SciBX 6(44); doi:10.1038/scibx.2013.1250 Published online Nov. 14, 2013		

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Cancer	CC chemokine receptor 4 (CCR4; CD194)	<i>In vitro</i> and mouse studies suggest anti-CCR4 mAbs could increase antitumor immunity by depleting a subset of T _{reg} cells. In peripheral blood mononuclear cells (PBMCs) from patients with melanoma, depletion of CCR4 ⁺ effector T _{reg} cells using an anti-CCR4 antibody followed by exposure to tumor antigen induced antigen-specific T cells. In a patient with T cell leukemia/lymphoma, the anti-CCR4 mAb Poteligeo mogamulizumab depleted effector T _{reg} cells and stimulated a T cell response against the antigen. Next steps include clinical testing of an anti-CCR4 mAb combined with a cancer vaccine. Kyowa Hakko Kirin Co. Ltd. markets Poteligeo to treat T cell lymphoma. Affitech A/S has the CCR4 mAb AT008 in preclinical testing for cancer and autoimmune diseases. SciBX 6(44); doi:10.1038/scibx.2013.1251 Published online Nov. 14, 2013	Patent and licensing status unavailable	Sugiyama, D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 14, 2013; doi:10.1073/pnas.1316796110 Contact: Shimon Sakaguchi, Osaka University, Osaka, Japan e-mail: shimon@ifrec.osaka-u.ac.jp Contact: Hiroyoshi Nishikawa, same affiliation as above e-mail: nishihiro@ifrec.osaka-u.ac.jp
Cancer	Indoleamine 2,3-dioxygenase 1 (IDO1)	Mouse and cell culture studies identified IDO1 inhibitors derived from the natural compound tryptanthrin that could be useful for treating cancer. In culture, compounds in the series inhibited IDO1 and reversed IDO1-mediated suppression of T lymphocytes. In a mouse model of Lewis lung carcinoma, the lead compound decreased tumor growth and immunosuppressive T _{reg} cell numbers compared with vehicle. Next steps could include testing the lead inhibitor in combination with other cancer therapeutics in animal models. NewLink Genetics Corp.'s IDO (INDO) pathway inhibitor, NLG8189, is in Phase I/II testing to treat solid tumors. Incyte Corp.'s IDO1 inhibitor, INCB24360, is in Phase II testing to treat solid tumors. SciBX 6(44); doi:10.1038/scibx.2013.1252 Published online Nov. 14, 2013	Patent and licensing status unavailable	Yang, S. <i>et al. J. Med. Chem.</i> ; published online Oct. 7, 2013; doi:10.1021/jm401195n Contact: Qing Yang, Fudan University, Shanghai, China e-mail: yangqing68@fudan.edu.cn
Melanoma	Protein kinase N1 (PKN1)	Cell culture studies suggest inhibiting PKN1 could help increase the efficacy of BRAF inhibitors in treating melanoma. In samples from patients with melanoma, lower wingless-type MMTV integration site (WNT) signaling was associated with higher PKN1 levels. In melanoma cells, small interfering RNA against PKN1 increased WNT pathway signaling and apoptosis triggered by wingless-type MMTV integration site family member 3A (Wnt3a) or a BRAF inhibitor compared with control siRNAs. Next steps include testing the effects of PKN1 inhibitors in animal models of melanoma growth and developing PKN1-specific inhibitors. Zelboraf vemurafenib, a small molecule BRAF inhibitor, is marketed by Roche and Daiichi Sankyo Co. Ltd. to treat metastatic melanoma in patients expressing the V600E BRAF mutation. Tafinlar dabrafenib, a small molecule BRAF inhibitor from GlaxoSmithKline plc, is marketed to treat metastatic melanoma in patients expressing mutant BRAF. SciBX 6(44); doi:10.1038/scibx.2013.1253 Published online Nov. 14, 2013	Patent and licensing status not applicable	James, R.G. <i>et al. J. Biol. Chem.</i> ; published online Oct. 10, 2013; doi:10.1074/jbc.M113.500314 Contact: Randall T. Moon, University of Washington School of Medicine, Seattle, Wash. e-mail: rtmoon@uw.edu Contact: Richard G. James, same affiliation as above e-mail: rickerj@uw.edu

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Deep vein thrombosis (DVT); venous thromboembolism (VE)	Thrombin (factor IIa; F2)	<i>In vitro</i> and mouse studies identified a nonpeptide thrombin inhibitor that could be used as an anticoagulant to help treat DVT and VTE. <i>In vitro</i> , a 1-(pyridine-4-yl)piperidine-4-carboxamine-based compound selectively inhibited human thrombin with low nanomolar K_i values over factor Xa and other serine proteases. In a clotting assay in human plasma, the inhibitor had anticoagulant activity at low micromolar concentrations. Next steps could include testing the anticoagulant in additional animal studies. SciBX 6(44); doi:10.1038/scibx.2013.1254 Published online Nov. 14, 2013	Patent and licensing status unavailable	De Candia, M. <i>et al. J. Med. Chem.</i> ; published online Oct. 8, 2013; doi:10.1021/jm401169a Contact: Cosimo Altomare, University of Bari Aldo Moro, Bari, Italy e-mail: cosimodamiano.altomare@uniba.it
Ischemia/reperfusion injury	TNNI3 interacting kinase (TNNI3K)	Patient tissue sample and rodent studies suggest inhibiting TNNI3K could help treat cardiac reperfusion injury. In human tissues, TNNI3K was expressed specifically in cardiomyocytes, and its expression was higher in patients with ischemic cardiomyopathy than in healthy individuals. In ischemic mice, small molecule inhibitors of Tnni3k decreased infarct size compared with vehicle. In a mouse model of extended ischemia, intraperitoneal injection of a Tnni3k inhibitor at reperfusion and six hours after reperfusion decreased cardiac dysfunction and fibrosis compared with vehicle injection. Next steps include testing the compounds in a canine model of cardiac dysfunction. GlaxoSmithKline plc collaborated on and has filed for a patent covering the composition of TNNI3K inhibitors. SciBX 6(44); doi:10.1038/scibx.2013.1255 Published online Nov. 14, 2013	Patent application filed; licensing status undisclosed	Vagnozzi, R.J. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 16, 2013; doi:10.1126/scitranslmed.3006479 Contact: Thomas Force, Temple University School of Medicine, Philadelphia, Pa. e-mail: thomas.force@temple.edu
Endocrine/metabolic disease				
Diabetes	Cannabinoid CB ₁ receptor (CNR1)	Cell culture and mouse studies suggest inhibiting CNR1 could help treat hyperinsulinemia in type 2 diabetes. In cultured rat pancreatic β cells, a CNR1 antagonist suppressed endocannabinoid-induced insulin secretion compared with a control compound. In mice, knockout of <i>Cnr1</i> inhibited endocannabinoid-induced insulin secretion in pancreatic islets. Next steps include determining the underlying mechanism in mouse models of diabetes and patient samples and developing CNR1 antagonists with improved pharmacological properties. SciBX 6(44); doi:10.1038/scibx.2013.1256 Published online Nov. 14, 2013	Unpatented; licensing status not applicable	Malenczyk, K. <i>et al. J. Biol. Chem.</i> ; published online Oct. 2, 2013; doi:10.1074/jbc.M113.478354 Contact: Agnieszka Dobrzyn, Nencki Institute of Experimental Biology, Warsaw, Poland e-mail: a.dobrzyn@nencki.gov.pl Contact: Tibor Harkany, Karolinska Institute, Stockholm, Sweden e-mail: tibor.harkany@ki.se

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Diabetes; obesity	Semaphorin 3E (SEMA3E); plexin D1 (PLXND1)	<p>Mouse studies suggest inhibiting SEMA3E could help treat obesity and diabetes. In a mouse model of diet-induced obesity, expression of <i>Sema3e</i> and its receptor, <i>Plxnd1</i>, was higher in adipose tissue than that seen in nondiabetic controls. In the mouse model, <i>Sema3e</i> inhibition with soluble <i>Plxnd1</i> or with <i>Sema3e</i> knockout decreased adipose inflammation and insulin resistance compared with no inhibition or knockout. Next steps could include testing SEMA3E inhibition in additional animal models of diabetes.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1257 Published online Nov. 14, 2013</p>	Patent and licensing status unavailable	<p>Shimizu, I. <i>et al. Cell Metab.</i>; published online Oct. 1, 2013; doi:10.1016/j.cmet.2013.09.001 Contact: Tohru Minamino, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan e-mail: t_minamino@yahoo.co.jp</p>
Obesity	Peroxisome proliferation-activated receptor- δ (PPARD; PPAR δ)	<p>Mouse studies suggest a form of phosphatidylcholine could help treat obesity. Compared with healthy controls, mouse models of diet-induced obesity had decreased serum levels of PC(18:0/18:1), a form of phosphatidylcholine that contains 2 18-carbon acyl chains and 1 acyl chain double bond. In healthy mice, signaling between <i>Ppard</i> in the liver and PC(18:0/18:1) in serum regulated serum triglycerides and fatty acid uptake in muscle cells. In mouse models of obesity, PC(18:0/18:1) decreased fasting serum levels of triglycerides, free fatty acids and glucose and increased glucose tolerance compared with vehicle. Planned work includes identifying and testing PC(18:0/18:1) mimics to treat obesity.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1258 Published online Nov. 14, 2013</p>	Patent application filed by Harvard University; unlicensed	<p>Liu, S. <i>et al. Nature</i>; published online Oct. 23, 2013; doi:10.1038/nature12710 Contact: Chih-Hao Lee, Harvard School of Public Health, Boston, Mass. e-mail: cle@hsph.harvard.edu</p>
Infectious disease				
Bacterial infection	DNA gyrase; topoisomerase IV	<p>Mouse and <i>in vitro</i> studies identified a pyridylurea-based DNA gyrase and topoisomerase IV inhibitor that could be useful for treating bacterial infections. In culture, the lead compound in the series inhibited growth of multiple Gram-positive and Gram-negative bacterial strains with nanomolar minimum inhibitory concentration (MIC) values. In a mouse model of <i>Staphylococcus aureus</i> infection in the thigh, the compound caused a 4.5 log decrease in colony-forming units compared with vehicle. Next steps could include evaluating the lead inhibitor in additional animal models of bacterial infection.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1259 Published online Nov. 14, 2013</p>	Patent application filed covering heterocyclic urea derivatives; licensing status unavailable	<p>Basarab, G.S. <i>et al. J. Med. Chem.</i>; published online Oct. 7, 2013; doi:10.1021/jm401208b Contact: Gregory S. Basarab, AstraZeneca R&D Boston, Infection Innovative Medicines, Waltham, Mass. e-mail: greg.basarab@astrazeneca.com</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
HIV/AIDS	HIV gag polyprotein; HIV p27 (nef); HIV pol; HIV env	<p>Macaque studies suggest mosaic HIV antigens delivered with a prime and boost vaccination regimen could protect against HIV infection. Mosaic antigens are bioinformatically optimized to increase coverage of HIV diversity. Macaques were vaccinated with combinations of modified vaccinia Ankara (MVA) and adenovirus serotype 26 (Ad26) vectors expressing HIV-1 mosaic env, gag and pol. The vaccines provided protection against repeated intrarectal inoculation with a highly virulent strain of simian immunodeficiency virus (SIV). The vectors have been tested in Phase I trials, and next steps include testing the vectors with the mosaic antigens in Phase I trials next year.</p> <p>Johnson & Johnson's Crucell N.V. unit coauthored the study and is manufacturing the mosaic vaccines based on this approach.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1260 Published online Nov. 14, 2013</p>	Multiple vaccine components used in study covered by patents held by various companies and institutions; licensing status undisclosed	<p>Barouch, D.H. <i>et al. Cell</i>; published online Oct. 24, 2013; doi:10.1016/j.cell.2013.09.061</p> <p>Contact: Dan H. Barouch, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: dbarouch@bidmc.harvard.edu</p>
HIV/AIDS	HIV gp120; HIV gp140; tenascin C (TNC; TN)	<p>Cell-based studies suggest the human breast milk-derived protein TNC could help prevent HIV-1 infection. In HIV-1 infected human cell lines, TNC showed dose-dependent, broad-spectrum neutralizing activity against the virus. In cell-based assays, TNC blocked the interaction between HIV-1 and epithelial cells by binding to HIV gp120 and HIV gp140. Next steps include defining the minimum region of TNC required for the HIV-neutralizing activity and conducting studies to determine whether the protein can prevent mucosal HIV transmission in animal models.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1261 Published online Nov. 14, 2013</p>	Patent pending covering prophylactic use of TNC; available for licensing from the Duke University Office of Licensing and Ventures Contact: Bilyana Georgieva, Duke University Medical Center, Durham, N.C. e-mail: bilyana.georgieva@duke.edu	<p>Fouda, G.G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 21, 2013; doi:10.1073/pnas.1307336110</p> <p>Contact: Sallie R. Permar, Duke University Medical Center, Durham, N.C. e-mail: sallie.permar@duke.edu</p>
Influenza virus	CD81	<p><i>In vitro</i> studies suggest inhibiting the interaction between CD81 and influenza virus could help treat or prevent infection. In a human lung cell line infected with various strains of influenza virus, small interfering RNA against CD81 decreased viral titers compared with control siRNA. A series of <i>in vitro</i> cellular assays showed that influenza virus relies on CD81 during the entry and budding stages of infection. Next steps could include developing pharmacological inhibitors that block the CD81–influenza virus interaction and evaluating them in infection models.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1262 Published online Nov. 14, 2013</p>	Patent and licensing status unavailable	<p>He, J. <i>et al. PLoS Pathog.</i>; published online Oct. 10, 2013; doi:10.1371/journal.ppat.1003701</p> <p>Contact: Xiaowei Zhuang, Harvard University, Cambridge, Mass. e-mail: zhuang@chemistry.harvard.edu</p>
Malaria	Not applicable	<p><i>In vitro</i> and mouse studies identified a series of 2-aminopyridines that could help treat malaria. <i>In vitro</i>, the compounds had low nanomolar IC₅₀ antimalarial activity against both drug-sensitive and multidrug-resistant strains of <i>Plasmodium falciparum</i> and were stable in human and rat liver microsomes. In the <i>P. berghei</i> mouse model of malarial infection, some of the compounds decreased parasitic burden compared with vehicle, and one cured the infection. Next steps could include toxicology testing.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1263 Published online Nov. 14, 2013</p>	Patent and licensing status unavailable	<p>Younis, Y. <i>et al. J. Med. Chem.</i>; published online Oct. 7, 2013; doi:10.1021/jm401278d</p> <p>Contact: Kelly Chibale, University of Cape Town, Rondebosch, South Africa e-mail: kelly.chibale@uct.ac.za</p>

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Inflammation	Abhydrolase domain containing 6 (ABHD6)	Cell culture and mouse studies suggest inhibiting ABHD6 could help treat chronic inflammation. In several types of cultured lipopolysaccharide (LPS)-activated macrophages, ABHD6 inhibitors led to dose-dependent increases in endocannabinoid 2-arachinonylglycerol (2-AG) and decreases in prostaglandins compared with vehicle. In a mouse model of LPS-induced inflammation, inhibiting Abhd6 decreased the production of inflammatory cytokines compared with vehicle. Next steps could include developing specific inhibitors of ABHD6. SciBX 6(44); doi:10.1038/scibx.2013.1264 Published online Nov. 14, 2013	Patent and licensing status unavailable	Alhouayek, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 7, 2013; doi:10.1073/pnas.1314017110 Contact: Giulio G. Muccioli, Université Catholique de Louvain, Brussels, Belgium e-mail: giulio.muccioli@uclouvain.be
Inflammation	Hypoxia-inducible factor 1 α subunit inhibitor (HIF1AN; FIH1); hypoxia-inducible factor prolyl hydroxylase 1 (EGLN2; HIF-PH1; PHD1)	<i>In vitro</i> and mouse studies suggest inhibiting HIF1AN and HIF-PH1 could help treat inflammatory diseases by suppressing IL-1 β signaling. In cell culture, a pan-hydroxylase inhibitor or small interfering RNA knockdown of HIF1AN or HIF-PH1 decreased IL-1 β -induced activation of NF- κ B compared with vehicle or no knockdown. In mice, the pan-hydroxylase inhibitor prevented NF- κ B activation. Mass spectrometry analysis identified hydroxylated components of tumor necrosis factor receptor-associated factor 6 (Traf6) that linked IL-1 β to NF- κ B activation. Next steps could include testing hydroxylase inhibition in models of inflammatory diseases. SciBX 6(44); doi:10.1038/scibx.2013.1265 Published online Nov. 14, 2013	Patent and licensing status unavailable	Scholz, C.C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 21, 2012; doi:10.1073/pnas.1309718110 Contact: Cormac T. Taylor, University College Dublin, Dublin, Ireland e-mail: cormac.taylor@ucd.ie
Neurology				
Alzheimer's disease (AD); schizophrenia	Nicotinic acetylcholine receptor α_7 (CHRNA7)	<i>In vitro</i> and mouse studies identified a CHRNA7 ⁺ allosteric modulator that could help treat cognitive dysfunction associated with schizophrenia or AD. In <i>Xenopus</i> oocytes, a series of arylpyrid-3-ylmethanones were identified as positive allosteric modulators of CHRNA7. In mice, one of the compounds crossed the blood brain barrier. In a mouse model of cognitive dysfunction, the compound reversed cognitive impairment, whereas a CHRNA7 antagonist blocked the protective effects of the compound. Next steps include screening for off-target effects and toxicity. At least five companies have CHRNA7 agonists in Phase III testing or earlier to treat AD or schizophrenia. SciBX 6(44); doi:10.1038/scibx.2013.1266 Published online Nov. 14, 2013	Unpatented; not yet available for licensing	Hogenkamp, D.J. <i>et al. J. Med. Chem.</i> ; published online Oct. 4, 2013; doi:10.1021/jm400704g Contact: Derk J. Hogenkamp, University of California, Irvine, Calif. e-mail: dhogenka@uci.edu
Anxiety	Regulator of calcineurin 1 (RCAN1; DSC1)	Mouse studies suggest RCAN1 inhibition could help treat pathological and drug-induced anxiety. In mice, <i>Rcan1</i> knockout increased calcineurin phosphatase activity and anxiety compared with no knockout. In <i>Rcan1</i> knockout mice, the acute anxiety-causing effect of the selective serotonin reuptake inhibitor fluoxetine was inhibited. Next steps could include developing RCAN1 inhibitors and testing them in different anxiety models. SciBX 6(44); doi:10.1038/scibx.2013.1267 Published online Nov. 14, 2013	Patent and licensing status unavailable	Hoeffler, C.A. <i>et al. J. Neurosci.</i> ; published online Oct. 23, 2013; doi:10.1523/JNEUROSCI.3513-12.2013 Contact: Charles A. Hoeffler, New York University School of Medicine, New York, N.Y. e-mail: charles.hoeffler@gmail.com

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Excessive sleepiness	Vasopressin 1a (V1a) receptor; V1b receptor	<p>Mouse studies suggest antagonizing the V1a or V1b receptors could be useful for treating sleep disturbance caused by jet lag. In mice subjected to light-dark cycle changes, which alter circadian rhythms, <i>V1a receptor</i> and <i>V1b receptor</i> double knockout mice adapted more quickly to light-dark cycles than wild-type controls. In normal mice, infusion of V1a and V1b receptor antagonists accelerated adaption to a new light-dark cycle compared with vehicle infusion. Next steps could include further testing of V1a or V1b receptor antagonists in models of jet lag.</p> <p>Astellas Pharma Inc. markets Vaprisol conivaptan, a dual V1 receptor and V2 receptor antagonist, to treat hyponatremia.</p> <p>Vantia Therapeutics Ltd. has the V1a receptor antagonist VA111913 in Phase II testing to treat dysmenorrhea.</p> <p>Azevan Pharmaceuticals Inc.'s V1a receptor antagonist, SRX251, is in Phase I to treat dysmenorrhea.</p> <p>Roche's V1a receptor antagonist, RG7314, is in Phase I testing to treat autism spectrum disorder (ASD).</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1268 Published online Nov. 14, 2013</p>	Patent pending; licensing status undisclosed	<p>Yamaguchi, Y. <i>et al. Science</i>; published online Oct. 4, 2013; doi:10.1126/science.1238599</p> <p>Contact: Hitoshi Okamura, Kyoto University, Kyoto, Japan</p> <p>e-mail: okamurah@pharm.kyoto-u.ac.jp</p>
Fragile X syndrome	Cytoplasmic polyadenylation element binding protein 1 (CPEB1)	<p>Mouse studies suggest inhibiting CPEB1 could help treat fragile X syndrome. In a mouse model of fragile X syndrome, knockout of <i>Cpeb1</i>, an activator of translation expressed in the brain, restored normal protein translation and increased synaptic plasticity compared with no knockout. In the mouse model, <i>Cpeb1</i> knockout also decreased acoustic stimulation-induced seizures by 50% and decreased anxiety in social behavioral tests. Next steps could include developing CPEB1 inhibitors.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1269 Published online Nov. 14, 2013</p>	Patent and licensing status unavailable	<p>Udagawa, T. <i>et al. Nat. Med.</i>; published online Oct. 20, 2013; doi:10.1038/nm.3353</p> <p>Contact: Joel D. Richter, University of Massachusetts Medical School, Worcester, Mass.</p> <p>e-mail: joel.richter@umassmed.edu</p>
Pain	CD93 (C1QR); VGF nerve growth factor inducible (VGF)	<p><i>In vitro</i> and rat studies suggest inhibiting C1QR could help treat neuropathic pain. VGF and the VGF-derived neuropeptide TLQP-21 increase sensitivity to pain. <i>In vitro</i> analysis identified C1QR as a receptor for TLQP-21. In a rat model of neuropathic pain, a mAb targeting the globular heads of C1QR delayed the onset of mechanical hypersensitivity compared with control IgG. Next steps include studies to extend the duration of efficacy of the C1QR-targeted mAb.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1270 Published online Nov. 14, 2013</p>	Patented; licensing status available from Imperial Innovations Group plc, the technology transfer arm of Imperial College London	<p>Chen, Y.-C. <i>et al. J. Biol. Chem.</i>; published online Oct. 8, 2013; doi:10.1074/jbc.M113.510917</p> <p>Contact: Kenji Okuse, Imperial College London, London, U.K.</p> <p>e-mail: k.okuse@imperial.ac.uk</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pain	Nav1.7 (SCN9A)	<p>Studies in cell culture and mice identified a centipede venom-derived peptide antagonist of Nav1.7 that could help treat pain. In cultured rat neurons, a 46-residue peptide isolated from centipede venom prevented activation of Nav1.7. In human cell culture, the peptide had high selectivity for Nav1.7 over related sodium channels. In multiple mouse models of pain, the peptide decreased pain compared with saline. Next steps include further preclinical development of centipede-derived Nav1.7 inhibitors for pain indications.</p> <p>Nav1.7 antagonists in clinical development include Convergence Pharmaceuticals Ltd.'s CNV1014802, which is in Phase II testing to treat pain associated with trigeminal neuralgia and lumbosacral radiculopathy (LSR); Xenon Pharmaceuticals Inc. and Teva Pharmaceutical Industries Ltd.'s XEN042, which is in Phase II testing for postherpetic neuralgia (PHN); Pfizer Inc.'s PF-05089771, which is in Phase I testing for chronic pain; and Dainippon Sumitomo Pharma Co. Ltd.'s DSP-2230, which is in Phase I testing for neuropathic pain.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1271 Published online Nov. 14, 2013</p>	Patent pending; available for licensing	<p>Yang, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 30, 2013; doi:10.1073/pnas.1306285110 Contact: Glenn F. King, The University of Queensland, St. Lucia, Queensland, Australia e-mail: glenn.king@imb.uq.edu.au</p>
Post-traumatic stress disorder (PTSD)	Histamine H1 receptor (HRH1)	<p>Genetic screening and clinical studies suggest compounds including diphenhydramine could help treat aversive memory associated with PTSD. A screen combining the assessment of adverse memory with genomewide association studies and gene set-based methods in 2 large cohorts identified 20 genes clustering in 2 groups associated with long-term depression or neuroactive ligand-receptor interactions, including HRH1. In 349 severely traumatized patients, the generic antihistamine diphenhydramine decreased aversive memory recall compared with placebo. Next steps could include further investigating the effects of diphenhydramine on distinct phases of memory formation and retrieval.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1272 Published online Nov. 14, 2013</p>	Patent and licensing status unavailable	<p>Papassotiropoulos, A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 21, 2013; doi:10.1073/pnas.1314478110 Contact: Dominique J.-F. de Quervain, University of Basel, Basel, Switzerland e-mail: dominique.dequervain@unibas.ch Contact: Andreas Papassotiropoulos, same affiliation as above e-mail: andreas.papas@unibas.ch</p>
Ophthalmic disease				
Diabetic retinopathy	Semaphorin 3A (SEMA3A); neuropilin 1 (NRP1)	<p>Mouse studies suggest inhibiting SEMA3A could help treat diabetic retinopathy. In vitreous fluid from patients with edema, SEMA3A expression was higher than that in subjects without edema. In mice, intravitreal injection of SEMA3A increased vascular permeability and leakage compared with vehicle injection. Conditional knockout of <i>Sema3a</i>'s receptor, <i>Nrp1</i>, in the retinal vasculature or small hairpin RNA against <i>Sema3a</i> decreased permeability compared with no <i>Nrp1</i> knockout or control shRNA. Next steps include developing strategies to neutralize SEMA3A for ocular applications.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1273 Published online Nov. 14, 2013</p>	Provisional patent application filed; available for licensing	<p>Cerani, A. <i>et al. Cell Metab.</i>; published online Oct. 1, 2013; doi:10.1016/j.cmet.2013.09.003 Contact: Przemyslaw Sapiaha, University of Montreal, Montreal, Quebec, Canada e-mail: mike.sapiaha@umontreal.ca</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Other				
Poisoning	Unknown	<p>Rodent studies suggest 3,3'-diindolylmethane (DIM) could help prevent radiation poisoning. In irradiated rats, daily injections of DIM for 14 days resulted in up to 60% survival at 30 days, whereas all saline-treated controls died by day 10. In mice, daily injections of DIM for five days prevented radiation-induced decreases in red blood cell, white blood cell and platelet counts, whereas saline injection did not. Researchers did not disclose next steps, which could include generating optimized DIM derivatives and evaluating them in animal models of radiation poisoning.</p> <p>DIM is a metabolite of indole-3-carbinol, which is a phytochemical from cruciferous vegetables that is available as a nutritional supplement.</p> <p>SciBX 6(44); doi:10.1038/scibx.2013.1274 Published online Nov. 14, 2013</p>	Patent application filed covering use of DIM and DIM-related compounds as radioprotective agents; licensing status undisclosed	<p>Fan, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 14, 2013; doi:10.1073/pnas.1308206110 Contact: Eliot M. Rosen, Georgetown University Medical Center, Washington, D.C. e-mail: emr36@georgetown.edu</p>

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			
Engineered bacterial LeuT to detail antidepressant binding mechanisms	An engineered bacterial homolog of eukaryotic biogenic amine transporters could be useful for informing how marketed antidepressants interact with their targets. Biogenic amine transporters are targeted by classes of drugs including selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors and tricyclic antidepressants. Bacterial LeuT was engineered to have human biogenic amine transporter-like pharmacology and then crystallized in complex with drugs from four classes of antidepressants. Crystallographic analysis showed that drugs from all four antidepressant classes have similar modes of binding to the engineered LeuT and lock the protein in an outward-facing, open conformation. Next steps could include generating additional crystal structures of LeuT in complex with additional drug classes and using this information to inform compound design.	Patent and licensing status unavailable	Wang, H. <i>et al. Nature</i> ; published online Oct. 13, 2013; doi:10.1038/nature12648 Contact: Eric Gouaux, Oregon Health & Science University, Portland, Ore. e-mail: gouaux@ohsu.edu
SciBX 6(44); doi:10.1038/scibx.2013.1275 Published online Nov. 14, 2013			
Drug delivery			
Ferrous iron (Fe ^{II})-dependent drug delivery system	Mouse studies suggest an Fe ^{II} -dependent delivery system could be useful for selectively targeting drugs to diseased tissues. The system involves conjugating a drug to a linker molecule and a 1,2,4-trioxolane ring that undergoes fragmentation in the presence of Fe ^{II} . In <i>Plasmodium berghei</i> -infected mice, a conjugate carrying an irreversible inhibitor of <i>Plasmodium</i> dipeptidyl aminopeptidase 1 (dpap1) selectively targeted infected red blood cells and showed more persistent inhibition of the parasitic enzyme than unconjugated inhibitor. In <i>P. berghei</i> -infected mice, the conjugate decreased parasitemia and showed increased safety compared with unconjugated inhibitor. Next steps include developing an optimized version of the delivery system and evaluating it for the delivery of drugs to treat malaria and cancer.	Patent application filed; available for licensing from the University of California, San Francisco Office of Innovation, Technology & Alliances	Deu, E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 21, 2013; doi:10.1073/pnas.1312782110 Contact: Matthew Bogyo, Stanford University School of Medicine, Stanford, Calif. e-mail: mbogyo@stanford.edu Contact: Adam R. Renslo, University of California, San Francisco, Calif. e-mail: adam.renslo@ucsf.edu
SciBX 6(44); doi:10.1038/scibx.2013.1276 Published online Nov. 14, 2013			
Drug platforms			
Predicting transplant rejection with a universal, common rejection module	Computational analysis of gene expression data from organ transplant patients identified an 11-gene signature that correlated with acute transplant rejection. In biopsies from a cohort of 120 renal transplant recipients, the signature predicted future transplant rejection in symptomless patients. In a mouse cardiac transplant model, Lipitor atorvastatin or Sprycel dasatinib, which reduced the levels or activity of different components of the signature, decreased the number of graft-infiltrating CD8 ⁺ T cells and increased transplant survival compared with no treatment. Next steps include validating the signature and immune benefits conferred by Lipitor on transplant survival in prospective clinical trials. Pfizer Inc. markets the HMG-CoA reductase inhibitor Lipitor to treat hypercholesterolemia, stroke, coronary artery disease (CAD), myocardial infarction (MI) and other cardiovascular indications. Bristol-Myers Squibb Co. markets the tyrosine kinase inhibitor Sprycel to treat hematopoietic cancers.	Patent applications filed by Stanford University; available for licensing	Khatri, P. <i>et al. J. Exp. Med.</i> ; published online Oct. 14, 2013; doi:10.1084/jem.20122709 Contact: Minnie M. Sarwal, Stanford University, Stanford, Calif. e-mail: msarwal@psg.ucsf.edu
SciBX 6(44); doi:10.1038/scibx.2013.1277 Published online Nov. 14, 2013			

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Markers			
Autoantibodies against BPI fold containing family B member 1 (BPIFB1) to diagnose autoimmune interstitial lung disease (ILD)	<p>Patient and mouse studies suggest autoantibodies against BPIFB1 may help diagnose autoimmune ILD. In a large cohort of patients with autoimmune polyglandular syndrome type 1 (APS1), an autoantibody to BPIFB1 was detected in 9.6% of patients with APS1 and 100% of patients with both APS1 and ILD. In additional subjects with idiopathic ILD, the antibody was detected in 12% of patients, whereas the antibody was not detected in age-matched controls. In <i>Bpifb1</i> knockout mice, immunization with recombinant BPIFB1 triggered an immune response, and transfer of these immune cells into immunodeficient mice led to the development of a lung disease similar to ILD. Next steps could include using <i>Bpifb1</i>^{-/-} mouse models to understand the mechanisms underlying autoimmune ILD and to identify therapeutics.</p> <p><i>SciBX</i> 6(44); doi:10.1038/scibx.2013.1278 Published online Nov. 14, 2013</p>	Patent and licensing status unavailable	<p>Shum, A.K. <i>et al. Sci. Transl. Med.</i>; published online Oct. 9, 2013; doi:10.1126/scitranslmed.3006998 Contact: Mark S. Anderson, University of California, San Francisco, Calif. e-mail: manderson@diabetes.ucsf.edu Contact: Anthony K. Shum, same affiliation as above e-mail: anthony.shum@ucsf.edu</p>

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IDO1	12
IL-1 β	16
IL-17	4
IL-21	4
INCB24360	12
INDO	12
Indole-3-carbinol	19
Indoleamine 2,3-dioxygenase 1	12
Integrin β_1	8
Integrin β_3	8

J

JQ1	4
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L

LeuT	20
Lipitor	20
Lipopolysaccharide	16
LPA1	8
LPA3	8
LPAR1	8
LPAR3	8

LPS	16	catalytic subunit	11	RSV F	6	Traf6	16
LY2382770	9	δ -polypeptide	11	S		Transforming growth factor- β	8
Lysophosphotidic acid receptor 1	8	Phosphoinositide 3-kinase- δ	11	SAR100842	8	Tryptanthrin	12
M		PI3KCD	11	SCN9A	18	Tumor necrosis factor- α	9
MAPK1	8	PI3K δ	11	Selumetinib	9	Tumor necrosis factor receptor-associated factor 6	16
MAPK3	8	Pirfenidone	9	SEMA3A	18	Tyrosine kinase	20
MAP kinase 3	8	PKN1	12	SEMA3E	14	V	
MDT-637	9	Plasminogen activator inhibitor 1	2	Semaphorin 3A	18	V1b receptor	17
MEDI-524	7	<i>Plasmodium</i> dipeptidyl aminopeptidase 1	20	Semaphorin 3E	14	V1 receptor	17
MEDI-559	7	Plexin D1	14	Serotonin	20	V2 receptor	17
MEK162	9	PLXND1	14	SERPINE1	2	VA111913	17
MK-554	9	Poly-ICLC	6	Sprycel	20	Vaprisol	17
Mogamulizumab	12	Poly inocine:cystosine formulated in polylysine carboxymethylcellulose	6	SRX251	17	Vasopressin 1a (V1a) receptor	17
Motavizumab	7	P		Synagis	6	Vemurafenib	12
N		Poteligeo	18	T		VGf	17
Nav1.7	18	PPAR δ	14	Tafinlar	12	VGf nerve growth factor inducible	17
Nef	15	PPAR δ	14	Tenascin C	15	W	
Neuropilin 1	18	PPARD	14	TGF β	8	Wingless-type MMTV integration site	12
NF- κ B	16	PPAR γ	2	TGF β 1	10	Wingless-type MMTV integration site family member 3A	12
Nicotinic acetylcholine receptor α_7	16	PPARG	2	TGF β 2	10	WNT	12
NLG8189	12	Prostaglandin	16	TGF β 3	10	Wnt3a	12
Noradrenaline	20	Protein kinase N1	12	TGFB	8	WZ-554	9
NRP1	18	Pyridylurea	14	TGFB1	10	X	
P		Q		TGFB2	10	XEN042	18
p110 δ	11	Quetiapine	2	TGFB3	10	XL518	9
P144	9	R		Thrombin	13	Y	
PAI1	2	Ranitidine	3	TLQP-21	17	YH14618	9
Palivizumab	6	RCAN1	16	Top1	8	Z	
Peroxisome proliferation-activated receptor- δ	14	RDEA119	9	Topoisomerase I	8	Zantac	3
Peroxisome proliferation-activated receptor- γ	2	Refametinib	9	Topoisomerase IV	14	Zelboraf	12
PF-05089771	18	Regulator of calcineurin 1	16	TN	15		
PHD1	16	RG7421	9	TNC	16		
Phosphoinositide 3-kinase	16	RG7314	9	TNF- α	17		
		Rosiglitazone	1	TNNI3 interacting kinase	13		
		RSV604	7	TNNI3K	13		
				Trabedersen	9		