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By Tracey Baas, Senior Editor

Immunocore Ltd., Adaptimmune Ltd. and University of Pennsylvania researchers have determined that off-target toxicity most likely caused the two fatalities in a cancer trial of affinity-enhanced T cell receptors.¹ The results highlight the need in the cancer immunotherapy space for harnessing biologically appropriate cellular testing and deep molecular analysis approaches to minimize cross-reactivity-related toxicity in future adoptive immunotherapy trials.

A primary challenge in engineering T cells for adoptive immunotherapy is selecting a cancer-associated antigen that is absent on healthy tissues and lacks homology to other self-proteins.

Over the last few years, melanoma-associated antigen A3 (MAGEA3) emerged as one of the most promising targets for adoptive immunotherapy because it is highly expressed in a number of tumors and its expression in healthy individuals is limited to the testes.^{2,3}

Because the human immune system has evolved to avoid the generation of high-affinity T cell receptors (TCRs) against self-proteins to preclude autoimmune reactions, endogenous TCRs must be optimized for cancer antigen affinity. On the other hand, engineering TCRs with enhanced affinity for specific tumor antigens presents the challenge of minimizing affinity for other homologous self-proteins to prevent nonspecific binding of the TCRs.

Between 2008 and 2010, an Immunocore, Adaptimmune and UPenn team led by Carl June designed affinity-enhanced TCRs that target a nine-amino-acid MAGEA3 peptide. In functional analyses, a TCR called a3a was identified as the most potent MAGEA3-specific TCR, and extensive preclinical studies with a3a-transduced T cells showed no signs of toxicity.

June is a professor in the Department of Pathology and Laboratory Medicine at the **Perelman School of Medicine at the University of Pennsylvania** and director of the translational research program at the **Abramson Family Cancer Research Institute at the University of Pennsylvania**.

However, when the a3a-engineered T cells were used in two patients with melanoma or myeloma, both died of acute cardiac failure within five days of receiving the therapy.⁴ Analysis of autopsy samples showed T cell infiltration in the hearts of both patients but no *MAGEA3* expression, suggesting off-target toxicity.

Earlier this year, a **National Cancer Institute (NCI)**-led Phase I/II trial in patients with metastatic cancer given an affinity-enhanced TCR targeting three MAGEAs—MAGEA3, MAGEA9 and MAGEA12—resulted in fatal neurotoxicity in two of nine patients.⁵ In that instance, analysis of autopsy brain samples using real-time quantitative PCR,

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SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

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nanostring quantitation and deep sequencing showed that one of the antigens—MAGEA12—was expressed in the brain, indicating that toxicity may have stemmed from on-target effects in nontumor tissue.

This trial was led by Steven Rosenberg, chief of the surgery branch and head of the tumor immunology section at the NCI.

Although the NCI study showed that affinity-enhanced T cells could hit a target expressed in nontumor tissue at such low levels that they would be missed in standard preclinical studies, this did not solve the mystery of the UPenn study—quantitative RT-PCR confirmed the absence of *MAGEA3* in both patients' hearts.

Now, Immunocore, Adaptimmune and UPenn researchers, led by Bent Jakobsen, CSO of Immunocore, have uncovered the cause of infiltration by the a3a-engineered T cells and ensuing cardiac toxicity using functional analysis and amino acid scanning.

In 38 normal, cardiac-derived primary cells, the a3a-engineered T cells caused no T cell activation.

Next, the group explored a more biologically relevant cardiac cell culture—iCell cardiomyocytes from **Cellular Dynamics International Inc.** Unlike primary cells plated in a dish, iCell cardiomyocytes show biochemical, electrophysiological and mechanical characteristics of heart tissue, including spontaneous beating.

The cells did not show *MAGEA3* expression. Nevertheless, the a3a-engineered T cells killed the iCell cardiomyocytes within 24 hours, suggesting something other than *MAGEA3* was activating the T cells.

To identify what the T cells were targeting, each amino acid in the nine-amino-acid *MAGEA3* peptide was replaced in turn with either alanine or glycine residues. The process allowed the researchers to discover a motif essential for a3a TCR binding within that nine-amino-acid peptide. A search of genome databases found a trio of proteins that

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harbor that motif, and the group performed multiple cell line studies to narrow the culprit to the muscle protein titin (TTN).

Notably, titin activated MAGEA3-targeting T cells in human cell lines but not in mouse cell lines, suggesting preclinical toxicity testing would not have revealed the off-target effects.

Expression of titin was confirmed in 3D beating cultures of iCell cardiomyocytes and in five independent human cardiac tissue samples. The results suggest a3a-engineered T cells recognize a sequence motif within titin, resulting in off-target toxicity.

Results were published in *Science Translational Medicine*.

“The iPS [induced pluripotent stem] cell system that the authors have used is a beautiful way to demonstrate the reactivity of the TCR-modified cells against titin-expressing cells. In combination with the amino acid scanning approach, this appears a viable strategy to identify possible cases of off-target reactivity before they appear in the clinic,” said Ton Schumacher, a professor and group leader in immunology at **The Netherlands Cancer Institute**.

The findings should extend beyond titin and could be used to filter out engineered TCRs that might interact with proteins they were not designed to target.

Rooting out safety issues

Schumacher cautioned that because the procedure relies on primary sequence homology between the target epitope of interest and the cross-reactive epitope, “a fraction of potential off-targets may be missed” that are due to

secondary structural homologies.

Researchers also thought that a deeper understanding of how the enhanced affinity of TCRs can lead to off-target toxicity was required.

“The observed off-target possibility was due to the *in vitro* affinity maturation, and the use of TCR identification systems that do not rely on *in vitro* affinity maturation would provide a nice way around the issue,” noted Schumacher.

“Cameron and colleagues provide clear evidence that TCR degeneracy of antigen recognition represents a true risk for clinical TCR gene therapy. The chances that such degenerate recognition leads to autoimmunity, as in the case of the reported cardiotoxicity, significantly increases when TCRs have an enhanced affinity for their cognate antigen,” said Reno Debets, an associate professor of experimental tumor immunology at **Erasmus Medical Center**. “Although I would not argue against the benefit of affinity enhancement of TCRs, I would advocate for studies to define the potential rules to safely mutate complementarity-determining regions within the TCRs, and investigating means to improve this gene therapy without enhancing the affinity of TCR, such as enhancement of T cell fitness and introduction of strategies to counteract the immune-suppressive micro-milieu of the tumor.”

Debets also said that it should become standard practice to test TCR-transduced T cells against 3D cultures of differentiated cells.

“Clearly these cultures, and not standard cultures of primary cells, better represent human organs with respect to their immunogenicity,”

he said. “Inclusion of specialized cultures—representing, for instance, vital organs—as T cell targets further advances the safety tests of TCR gene therapy irrespective of whether TCRs are affinity enhanced or not.”

Going forward, the Immunocore, Adaptimmune and UPenn team will use a cellular screening panel that will include primary cells, cells grown in 3D cultures and iCells that represent organs most likely to be affected.

“The tools we used to identify titin continue to be developed and are now being used to safety test our new TCRs,” Nick Pumphrey, head of pipeline research at Adaptimmune, told *SciBX*. “To complement our cell testing, we also use RT-PCR data for expression analysis of potential targets and possible off-target peptides using different tissue samples, including brain sections. RT-PCR data can only tell you if the protein you are probing is present, whereas cell testing highlights on- or off-target toxicity regardless of whether the specificity is known or not.”

Pumphrey told *SciBX* that one limitation with iCell neuronal culture is that it is made up of inhibitory γ -aminobutyric acid (GABA)-ergic and glutamatergic neurons. “There is a whole array of other neuronal types in the brain too,” he said. “We cannot rely on any one cell line as being representative of a complex tissue, and [we] are working to make our cell testing panels as broad as possible and combining this approach with RT-PCR and peptide scanning information to select the best TCRs to the best targets.”

Mark Dudley, a staff scientist and head of the cell production facility at the NCI, noted that “retrospectively identifying the mechanism of a known toxicity is much easier, and a very different problem, than prospectively determining whether a TCR will be safe for adoptive therapy. It is unlikely that any combination of preclinical tests will completely predict the behavior of novel T cell receptors and chimeric antigen receptors introduced into T cells.”

The upshot, he said, is that “engineered T cells are potent clinical agents, and some can only be fully evaluated by testing their antitumor effects in patients.”

Chiara Bonini, head of the Experimental Hematology Unit and a member of the cancer immunotherapy and gene therapy program and the bone marrow transplantation unit of the **San Raffaele Scientific Institute**, said measures to minimize toxicity could include “dose escalation of infused T cells, which could allow detection of toxicity of a milder and more controllable grade before increasing the T cell dose; nuclease-mediated knockdown of the endogenous TCR to avoid TCR mispairing and alloreactivity; and the incorporation of suicide genes, which might allow the elimination of activated T cells as soon as toxicity is observed.”

Debets was unsure about the suicide gene approach. “Although the suicide gene could provide the option to delete TCR-transduced T cells from patients once there are signs of toxicity, it is questionable whether such a switch could counteract the fast kinetics of toxicity reported in this study—four to five days following T cell infusion,” he said.

Michel Sadelain, director of **Memorial Sloan-Kettering Cancer Center’s** Center for Cell Engineering, also was unsure about the suicide gene. He thinks that an alternative safety feature would be to use T cells that transiently express the affinity-enhanced TCRs.

“The T cells can be transfected with mRNA that codes for the TCR, thereby generating T cells that have a limited lifetime within the recipient’s tissues,” he said.

“Inclusion of specialized cultures—representing, for instance, vital organs—as T cell targets further advances the safety tests of TCR gene therapy irrespective of whether TCRs are affinity enhanced or not.”

—Reno Debets,
Erasmus Medical Center

“The new study shows that strategies needed to evaluate TCR-induced toxicities will need to be extremely broad reaching and most likely very labor intensive,” added Sadelain. “And in the end, these strategies may still not be enough to identify all potential risks. Using T cells that are self-limiting is the only way to truly guard patients from off-target or on-target off-tissue toxicities when moving TCRs into first-in-man trials.”

Adaptimmune is recruiting patients with multiple myeloma and synovial sarcoma for trials using affinity-enhanced TCR-expressing T cells that target cancer/testis antigen 1B (CTAG1B; NY-ESO-1). The company said its products have shown no off-target toxicity and encouraging early data.

Immunocore is focused on the discovery and development of TCR-based therapies to treat cancer and viral diseases using their immune-mobilizing, monoclonal TCRs against cancer (ImmTACs). ImmTACs consist of a very high-affinity TCR linked to a CD3 receptor, a strong T cell activator.

Currently, UPenn is concentrating its efforts on clinical trials with chimeric antigen receptor-expressing T cells with **Novartis AG**, and Adaptimmune has entered into a cell therapy manufacturing services agreement with **NeoStem Inc.**'s Progenitor Cell Therapy subsidiary to enable their new clinical trials with affinity-enhanced TCR-expressing T cells to be run independently of UPenn.

Baas, T. *SciBX* 6(33); doi:10.1038/scibx.2013.879
Published online Aug. 29, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Abramson Family Cancer Research Institute at the University of Pennsylvania, Philadelphia, Pa.
Adaptimmune Ltd., Abingdon, U.K.
Cellular Dynamics International Inc. (NASDAQ:ICEL), Madison, Wis.
Erasmus Medical Center, Rotterdam, the Netherlands
Immunocore Ltd., Abingdon, U.K.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
National Cancer Institute, Bethesda, Md.
NeoStem Inc. (NASDAQ:NBS), New York, N.Y.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
The Netherlands Cancer Institute, Amsterdam, the Netherlands
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa.
San Raffaele Scientific Institute, Milan, Italy
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Collaborating against diabetes complications

By Michael J. Haas, Senior Writer

Pfizer Inc.'s diabetes deal with the **Sanford-Burnham Medical Research Institute** could help reverse a trend that has seen the pharma arriving late—or not at all—to the party with new targets for the indication. Indeed, the goal of the three-year collaboration is to identify and validate new drug targets to prevent and treat insulin resistance and organ damage in obesity-related diabetes.

The only diabetes drug in Pfizer's product line is Actos pioglitazone, a thiazolidinedione that the company co-markets with **Takeda Pharmaceutical Co. Ltd.** Actos came off patent in 2008, and in 2011, the FDA required the warnings section of the drug's label to state that use of pioglitazone for more than a year may be associated with an increased risk of bladder cancer.

Pfizer's late-stage pipeline for the disease includes ertugliflozin, an oral sodium-glucose cotransporter 2 (SGLT2) inhibitor that is partnered with **Merck & Co. Inc.** and is slated to start Phase III testing. The compound likely will be the fifth or sixth SGLT2 inhibitor to hit the market.¹

However, Pfizer's earlier stage development efforts—the new deal with Sanford-Burnham and PF-05190457, a first-in-class ghrelin receptor (GHSR) antagonist in Phase I testing—look to reverse its late-to-the-party trend in diabetes.

Under the deal with Sanford-Burnham, Pfizer will use the institute's Conrad Prebys Center for Chemical Genomics to conduct high throughput screening for new targets using investigational compounds from Pfizer and a compound library from the NIH.

The partners plan to elucidate the mechanism of action for hit compounds to identify previously unknown disease targets involved in insulin resistance and damage to the heart, kidneys, retina and other organs caused by obesity-related diabetes, said Rick Vega, research assistant professor at Sanford-Burnham's Lake Nona campus in Orlando, Fla.

The collaborators also will draw on Sanford-Burnham's metabolomics capabilities and research facilities “to better understand the mechanism of action of the compounds that we identify and to make comparisons to known agents and reference compounds,” he said. “These comparisons should help us prioritize the compounds of the highest interest.”

The screening hits will serve as probes for validating the targets and for guiding the development of new therapies to prevent and treat insulin

resistance and diabetes-induced organ damage, Vega said. Drugs that prevent or treat organ damage would have an advantage over the current standard of care for obesity-related diabetes.

Vega declined to disclose the financial terms of the deal or how ownership of any new IP generated by the collaboration will be handled.

“There is a clear need to translate innovative science into potential new medicines for people living with diabetes,” said Tim Rolph, VP and head of the cardiovascular and metabolic diseases research unit at Pfizer. “This collaboration with Sanford-Burnham is one example of how we approach the discovery and development of much-needed therapies.”

In 2011, Sanford-Burnham partnered with Pfizer to discover mechanisms and therapies for undisclosed diseases under the pharma's Global Centers for Therapeutic Innovation initiative.

Under that initiative, Pfizer provides its partners with funding for preclinical and clinical development programs and offers IP and ownership rights in return for options to license exclusive rights to drug candidates. Academic partners have access to Pfizer's antibody libraries and research and are eligible for milestones and royalties on advanced programs.²

Sanford-Burnham's push into the underpinnings of metabolic diseases dates to 2009. That year, the institute and **Florida Hospital** founded **The Translational Research Institute for Metabolism and Diabetes** (TRI), a joint venture aimed at identifying new markers that reflect subsets of heterogeneous metabolic diseases better than current markers.

TRI conducts clinical studies in patients with metabolic disease and healthy individuals,

whereas a team at Sanford-Burnham's Lake Nona campus conducts preclinical research and provides metabolomics analyses.³

In 2010, Sanford-Burnham and TRI signed a two-year deal with Takeda to support the clinical development of an undisclosed obesity compound from the pharma. The two institutes renewed the deal with Takeda in February and are open to forming partnerships with other drug companies, said Sanford-Burnham spokesperson Patrick Bartosch.

Haas, M.J. *SciBX* 6(33); doi:10.1038/scibx.2013.880
Published online Aug. 29, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Florida Hospital, Orlando, Fla.

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Sanford-Burnham Medical Research Institute, La Jolla, Calif.

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan

The Translational Research Institute for Metabolism and Diabetes, Winter Park, Fla.

“This collaboration with Sanford-Burnham is one example of how we approach the discovery and development of much-needed therapies.”

— Tim Rolph, Pfizer Inc.

Going stromal with docetaxel

By Chris Cain, Senior Writer

Abraxane nab-paclitaxel is the model example of how an old microtubule-stabilizing chemotherapy can be revitalized through a new nanoparticle formulation. Now, **Ontario Institute for Cancer Research** scientists have developed glycopolymer-conjugated docetaxel nanoparticles that outperform Abraxane in mouse models of breast cancer.¹

The Ontario Institute for Cancer Research (OICR) is backing the program with \$1.5 million to take it to the clinic. The expectation is that the product's ability to target the tumor stroma rather than the tumor itself will differentiate it from Abraxane and other chemotherapeutic formulations.

The toxicity of the tubulin-stabilizing cancer chemotherapeutics paclitaxel and docetaxel has led numerous companies to attempt to develop new versions with better safety profiles that enable their use at higher and thus more efficacious doses.

The poster child for these efforts is **Celgene Corp.**'s Abraxane, which is marketed to treat metastatic breast cancer and non-small cell lung cancer (NSCLC) and is under review in the U.S. to treat metastatic pancreatic cancer.

Abraxane consists of albumin-bound paclitaxel that is assembled into nanoparticles. This permits its delivery at higher doses without the use of toxic solvents, and its nanoparticle formulation leads to higher accumulation in tumor tissue.

Other next-generation paclitaxel formulations in clinical development include **NanoCarrier Co. Ltd.**'s NK-105, a liposomal formulation that is in Phase III testing to treat breast cancer, and **Cell Therapeutics Inc.**'s Opaxio paclitaxel poliglumex, a formulation of paclitaxel covalently linked to a polyglutamate polymer that is in Phase III trials to treat ovarian cancer.

In 2005, Opaxio, then known as Xyotax, failed to show superiority to paclitaxel in Phase III NSCLC trials.

Bind Therapeutics Inc. is pursuing an improved version of docetaxel. The company's BIND-014, a polymeric nanoparticle containing docetaxel that is targeted to prostate-specific membrane antigen (PSMA; FOLH1; GCP11), is in Phase II testing to treat prostate cancer.

Nanoparticle formulations of docetaxel in preclinical development include **Cerulean Pharma Inc.**'s CRLX301, which consists of docetaxel covalently linked to a cyclodextrin polymer.

In 2011, Shyh-Dar Li, a principal investigator of drug delivery and formulation at OICR and an assistant professor at the **University of Toronto**, threw his hat into the ring with Cellax, a nanoparticle formulation of docetaxel and polyethylene glycol (PEG) that is covalently linked to a cellulose derivative called acetylated carboxymethylcellulose.

Li chose to link docetaxel to the cellulose derivative because it is relatively stable in blood, is biologically inactive and has many available sites for drug or PEG linkage. His team showed that Cellax increased the half-life of docetaxel in the blood more than fivefold compared with unmodified Taxotere docetaxel.² **Sanofi** markets Taxotere, which went off patent in 2010.

Last year, Li's group published a detailed preclinical comparison of Cellax with Abraxane. In multiple xenograft mouse models of cancer, Cellax had a higher maximum tolerated dose and lower tumor growth and metastasis than Abraxane.³

Now, Li's team has shown that a key reason for Cellax's increased efficacy could be its pronounced effect on the tumor stroma.¹

In two orthotopic mouse models of breast cancer, Cellax reduced the number of actin $\alpha 2$ smooth aorta muscle (ACTA2; α -SMA)-expressing tumor cells by 70%–80%, whereas Abraxane or Taxotere had no significant effect on α -SMA-expressing cells. Cellax also significantly increased vascular permeability of the tumors and decreased metastases compared with Abraxane or Taxotere.

α -SMA is a marker of the tumor stroma.

In line with earlier studies, mice receiving Cellax did not have neutropenia or elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels and did not lose body weight. Side effects included mild inflammation in the liver and lungs.

Results were published in *Cancer Research*.

Stromal breakdown

Li said that the effect on the tumor stroma could be a key differentiator between Cellax and other nanoparticle formulations in development.

"The majority of cancer patients succumb to metastases and/or tumor drug resistance. Both these problems have been linked to tumor stroma," he said. "Stroma is a noncancerous component of the tumor that supports cancer cell growth and invasion. Stroma also makes tumors denser, reducing blood flow and making it harder for drugs to reach and kill cancer cells. Cellax acts directly on stromal cells, increases blood perfusion in tumors and inhibits the spread of cancer in mouse models of metastatic disease."

"The key aspect and finding of Cellax is that unlike existing clinically available taxane drug delivery systems, it targets and depletes tumor-associated stromal cells that play an important role in tumor growth and metastasis," said Sangyong Jon, head of the global research lab in the Department of Biological Sciences at the **Korea Advanced Institute of Science and Technology**.

Although one proposed reason for Abraxane's efficacy, particularly in pancreatic cancer, has been that the drug could disrupt tumor stroma, recent preclinical results have cast doubt on the mechanism.⁴

Jon added that a key unanswered question is precisely how Cellax preferentially affects the tumor stroma.

Triantafyllos Stylianopoulos, lecturer at the **University of Cyprus**, was impressed by the functional effect of stromal depletion in the mouse models.

"It is interesting that stromal depletion results in improved tumor perfusion and a lower interstitial fluid pressure," he said. "Hypoperfusion and the uniform elevation of interstitial fluid pressure in many breast cancers are major barriers to the effective delivery of chemotherapy and

"Unlike existing clinically available taxane drug delivery systems, it targets and depletes tumor-associated stromal cells that play an important role in tumor growth and metastasis."

— Sangyong Jon,
Korea Advanced Institute of
Science and Technology

nanomedicine. Overcoming these barriers can improve drug delivery and treatment outcomes not only for breast cancers but also for other desmoplastic tumors, such as pancreatic cancers.”

Cristianne Rijcken, cofounder and CEO of **Cristal Therapeutics**, said the covalent linkage of docetaxel to the carboxymethylcellulose polymer could provide advantages over formulations such as Abraxane, in which the drug is not covalently conjugated, because covalent linkage “provides more control over docetaxel release and distribution compared with current taxane formulations.”

She added that “the substantial increase in tolerability, combined with increased accumulation of drug in tumors, provides an opportunity to achieve improved therapeutic outcome in patients as compared to conventional taxane therapy.” Rijcken did say that she wants to see more characterization of safety in models including rats and additional studies to show that Cellax does not trigger an immune response.

In 2014, Cristal plans to start Phase I testing of its CriPec polymeric, covalently linked nanoparticle formulation of docetaxel to treat solid tumors.

Last November, Li received a \$1.5 million grant to develop Cellax from the OICR IP development and commercialization program, which funds early stage applied research and development at the institution.

Li said that he is using the funds to scale up Cellax production and to run additional preclinical studies in preparation for Phase I testing. He said that he is in discussions with potential partners.

OICR has filed for two patents covering Cellax’s composition

of matter, nanoparticle structure and method of use. The work is available for licensing from **MaRS Innovation**, the technology transfer organization for a consortium of 16 Toronto institutions including OICR.

Celgene did not respond to requests for an interview.

Cain, C. *SciBX* **6(33)**; doi:10.1038/scibx.2013.881

Published online Aug. 29, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Bind Therapeutics Inc., Cambridge, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Cell Therapeutics Inc. (NASDAQ:CTIC; Milan:CTIC), Seattle, Wash.
Cerulean Pharma Inc., Cambridge, Mass.
Cristal Therapeutics, Maastricht, the Netherlands
Korea Advanced Institute of Science and Technology, Daejeon, South Korea
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DISCerning schizophrenia in mice

By C. Simone Fishburn, Senior Editor

Despite genetic advances in schizophrenia research, a lack of predictive preclinical models has hampered the development of new therapeutics. Now, a team at **The Johns Hopkins University** has created a transgenic mouse model of prefrontal dysfunction involving disrupted networks of neurons that cause behavioral changes similar to those seen in patients with schizophrenia or mood disorders.¹

The model may represent a useful tool for preclinical characterization of candidate compounds. It centers on the schizophrenia risk marker disrupted in schizophrenia 1 (DISC1) and represents a departure from traditional models that approach the disease as one rooted in an imbalance of neurotransmitters and receptors. Instead, it puts disrupted connectivity in the brain as the cause of schizophrenia.

An inherent problem in employing animal behavioral models in CNS drug development is the difficulty of recapitulating human higher functions such as decision making, emotion and adaptability. Indeed, the vast majority of compounds are evaluated in behavioral assays on normal rats, whose brains do not display the structural and biochemical changes that underlie the different psychoses in humans.

Creating representative models of diseases such as schizophrenia is particularly difficult because

of the involvement of multiple genetic factors and environmental triggers. Even when genetic breakthroughs are made, reproducing genetic changes in rats remains technically challenging because of the difficulties of making rat-derived embryonic stem cells despite recent progress in the field.²

Michela Gallagher, professor of psychology and neuroscience at Johns Hopkins, and her group at the university have taken a different approach with a model that involves overexpression of an inactive, mutant form of *Disc1*.¹

The gene has been strongly linked to schizophrenia predisposition following its identification in a Scottish family that suffered mental illnesses in several generations.³ The inactive mutant, a dominant negative form known as *DN-DISC1*, overrides the action of the regular DISC1 protein, which normally plays a role in the development and maintenance of synapses. Previous studies from other groups have suggested DISC1 is involved in synaptic regulation and the creation of networks that are disrupted in schizophrenia and mood disorders.⁴

“We want to understand how networks of genetically controlled pathways lead to common features of illnesses,” Gallagher told *SciBX*.

She said it is impossible to know whether animals can suffer diseases such as schizophrenia, but what is known is that animal neurons

behave electrophysiologically like human ones. She also said there is a large body of literature showing that many high-level systems in the prefrontal cortex are preserved from rodents to primates.

Previously, Gallagher’s group generated a heterozygous, transgenic *Dn-Disc1* mouse. The animals exhibited detectable biochemical changes in the brain, but behavioral changes were mild.⁵

Now the team has created a homozygous, transgenic *Dn-Disc1* mouse. To test higher-level functions of these mice, Gallagher’s group focused on activities that require advanced processing of information and that are controlled by the prefrontal cortex.

In a measurement of behavioral flexibility, *Dn-Disc1* mice were able to learn new tasks as efficiently as wild-type mice but were not able to adapt readily to a change and took longer to learn the new rules when a task was modified. Likewise, in an assay on outcome expectancy, *Dn-Disc1* mice could learn how to perform an action to receive a reward but could not change their actions even when they learned to expect that they would no longer receive the reward.

In tests relating effort to reward, *Dn-Disc1* mice were less motivated than wild-type animals to work hard for a pleasurable reward despite being able to learn the actions needed to receive it. In addition, in social interaction tests, *Dn-Disc1* mice were less inclined than wild-type animals to socialize with new mice, and when given a choice between a familiar mouse and a stranger mouse they selected the familiar one. In contrast, wild-type mice preferred the strangers (see Table 1, “Behavior DISCrmination”).

The team also observed a 10-fold increase in a marker of oxidative stress in *Dn-Disc1* mice specifically in the prefrontal cortex and not in the striatum.

Collectively, the data show that DISC1 affects complex cognitive functions that are controlled by the prefrontal cortex and that DISC1 plays a role in oxidative stress that could underlie damage caused to neurons in that region. The findings also support a role for DISC1 in neuronal networks related to schizophrenia as the altered behavior of the mice mimicked many of those represented in the disorder.

Results were reported in the *Proceedings of the National Academy of Sciences*.

A failure to communicate

Gallagher’s homozygous *Dn-Disc1* model reflects a shift in the CNS field toward the view that schizophrenia and some other CNS disorders are diseases of connectivity, in which a breakdown in communication occurs between neurons and between regions of the brain.

This differs from the view of the disease upon which many current antipsychotics are based, which focused on correcting the over- or under-expression of specific receptors or transmitters.

“The locus of the deficit is not in a particular node but is distributed around the brain and should be thought of as a network problem. What is important is how one region interacts with other areas of the brain,” said Trevor Robbins, professor of cognitive neuroscience at the **University of Cambridge**.

According to Daniela Brunner, SVP of behavioral R&D at CNS CRO **PsychoGenics Inc.**, *DISC1* is one of the more interesting genes in schizophrenia and other mental disorders. She added that although there are several *DISC1* mutants, the dominant negative one, *DN-DISC1*, is one of the best for understanding the disorder.

“The mouse here is in a perturbed system based on the genetic model for a neuropsychiatric illness. The model provides for better drug testing than a cell in a dish or an *in vivo* model that is not a perturbed system.”

—Michela Gallagher,
The Johns Hopkins University

Table 1. Behavior DISCrmination. Experiments are based on fixed-period sessions in which animals are placed in an enclosed chamber, and the number of times they produce a response is counted during that time period. In behavioral flexibility, outcome expectancy and effort/reward assays, the animals are trained in a learning stage to perform an action that yields a food reward. In the test stage, the conditions are changed from their training, and their ability to adapt to the new change is measured.

Assay	Description	Result	
		<i>Dn-Disc1</i> mouse	Wild-type mouse
Behavioral flexibility	Mouse initially learns that pressing the left lever gives the reward; the sides are then switched so that the right lever gives the reward	Adapts to lever switch after multiple sessions	Adapts after one session
Outcome expectancy	Mouse learns to expect that an action will yield sucrose; the value of sucrose is then decreased by prefeeding the animal	Maintains interest in the reward	Loses interest in the reward
Effort/reward	Mouse learns to press a lever once for sucrose; the number of required lever hits then escalates over time	Loses motivation to hit the lever multiple times for a reward	Sustains motivation
Social interaction	Mouse given a choice of meeting a stranger mouse or being alone; it is then given a choice of meeting another new mouse or visiting a familiar mouse	No preference for meeting a stranger or being alone, then prefers the familiar mouse	Prefers meeting the stranger mouse in both stages of the test

Robbins thinks that the new model can be used to make valid inferences about DISC1 and its role in prefrontal dysfunction. “It has been hard to unravel deficits in DISC1 function, but this group has managed to do that,” he told *SciBX*.

One of the key strengths of the *Dn-Disc1* model, according to Gallagher, is that the deficits are only in higher-level functions, whereas other systems such as motor control, vision and hearing are not affected. This avoids a significant drawback of many other mutant models in which motor or sensory deficits can cloud the ability to interpret behaviors in tasks that require an animal to move, see or respond to a sound.

According to Brunner, advanced types of behavioral assessments that look at higher cognitive functions are a leap forward from the traditional earlier studies that used simple assays such as the open field test or the Morris water maze.

A low throughput tool

The translational potential of the model is yet to be determined, but Gallagher believes that the battery of behavioral tests in the *Dn-Disc1* background could be better predictors of human behavior than current models.

“The mouse here is in a perturbed system based on the genetic model for a neuropsychiatric illness. The model provides for better drug testing than a cell in a dish or an *in vivo* model that is not a perturbed system,” she told *SciBX*.

Gallagher cautioned that the model involves an intensive experimental paradigm of complex, multistep behavioral tests and thus

is best suited for testing late-stage lead preclinical compounds to help guide clinical studies rather than as a high throughput screening tool.

According to Robbins, one key problem that drug developers have when they employ models of neurological disorders is the failure to take into account behavioral side effects such as memory loss, which can be a major problem for schizophrenia drugs.

Thus, he said the model could have even greater translational utility if it were to include assays for behavioral side effects that involve other regions of the brain, most notably the hippocampus, which plays an important role in memory.

The work has not been patented.

Fishburn, C.S. *SciBX* 6(33); doi:10.1038/scibx.2013.882
Published online Aug. 29, 2013

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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				
Autoimmune disease	Natural killer p30 receptor (NKp30; NCR3; CD337)	<p>Patient studies suggest inhibiting NKp30 could help treat the autoimmune disease primary Sjögren's syndrome (pSS). In pSS, exocrine glands are destroyed by an NK-driven autoimmune reaction. In samples from patients who have pSS, the rs11575837 SNP in NKp30 was associated with lower NKp30 expression and disease risk than wild-type NKp30. In biopsies from patients who carry rs11575837, NK cells showed less NKp30-mediated interferon-γ (IFNG; IFN-γ) release than NK cells in biopsies from healthy individuals. Next steps include identifying the subtypes of NK cells present in exocrine glands and identifying alternative receptors for NKp30 ligands.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.883 Published online Aug. 29, 2013</p>	Unpatented; licensing status not applicable	<p>Rusakiewicz, S. <i>et al. Sci. Transl. Med.</i>; published online July 24, 2013; doi:10.1126/scitranslmed.3005727 Contact: Gaetane Nocturne, Institut National de la Santé et de la Recherche Médicale (INSERM), Villejuif, France e-mail: gaetanenocturne@gmail.com Contact: Xavier Mariette, same affiliation as above e-mail: xavier.mariette@bct.aphp.fr</p>
Autoimmune disease	Phosphoinositide kinase FYVE finger containing (PIKFYVE)	<p>Cell culture studies identified the molecular target of apilimod as PIKFYVE, suggesting the target could be inhibited to treat autoimmune diseases. Apilimod was previously shown to inhibit the production of IL-12 and IL-23, but its molecular target was unknown. <i>In vitro</i>, apilimod inhibited PIKFYVE kinase activity with an IC₅₀ value of 14 nM. In cell culture, small hairpin RNA-mediated knockdown of PIKFYVE decreased expression of the p40 subunit of IL-12 compared with no knockdown. Next steps could include designing and optimizing PIKFYVE inhibitors. Synta Pharmaceuticals Corp. discontinued development of apilimod in 2009 after the compound missed the primary endpoints in multiple Phase II trials. The company has an IL-12 and IL-23 inhibitor program in preclinical development for autoimmune and inflammatory disease. Novartis AG, which ran the current cell culture studies, did not disclose if it is developing inhibitors of PIKFYVE.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.884 Published online Aug. 29, 2013</p>	Unpatented; licensing status not applicable	<p>Cai, X. <i>et al. Chem. Biol.</i>; published online July 25, 2013; doi:10.1016/j.chembiol.2013.05.010 Contact: Qian Huang, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: qian.huang@novartis.com</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Breast cancer	Actin α 2 smooth aorta muscle (ACTA2; α -SMA)	<p>Mouse studies suggest a polyethylene glycol formulation of docetaxel conjugated to acetylated carboxymethylcellulose could help treat breast cancer. The conjugated docetaxel self-assembled into 120 nm-diameter nanoparticles, called Cellax. In an orthotopic mouse model of breast cancer, injection of Cellax decreased both the number of α-SMA-expressing stromal cells within the tumor and metastasis compared with injection of Abraxane nab-paclitaxel or native docetaxel. Next steps include manufacturing Cellax in preparation for Phase I trials.</p> <p>Celgene Corp. and Otsuka Pharmaceutical Co. Ltd. market Abraxane to treat breast cancer (<i>see Going stromal with docetaxel, page 6</i>).</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.885 Published online Aug. 29, 2013</p>	<p>Patent application filed; available for licensing from MaRS Innovation</p> <p>Contact: Parimal Nathwani, MaRS Innovation, Toronto, Ontario, Canada e-mail: pnathwani@marsinnovation.com</p>	<p>Murakami, M. <i>et al. Cancer Res.</i>; published online Aug. 1, 2013; doi:10.1158/0008-5472.CAN-13-0062</p> <p>Contact: Shyh-Dar Li, Ontario Institute for Cancer Research, Toronto, Ontario, Canada e-mail: sli@oicr.on.ca</p>
Breast cancer	Mediator of cell motility 1 (MEMO1; MEMO)	<p>Mouse and cell culture studies suggest inhibiting MEMO could help treat estrogen-dependent breast cancers. In a human breast cancer cell line, small interfering RNA-mediated knockdown of MEMO decreased estrogen-driven growth compared with no knockdown. In mice injected with human breast cancer cell lines, siRNA against MEMO prevented estrogen-induced tumor formation, whereas control siRNA did not. Next steps could include screening for and evaluating pharmacological inhibitors of MEMO in models of estrogen-dependent breast cancer.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.886 Published online Aug. 29, 2013</p>	<p>Patent and licensing status unavailable</p>	<p>Jiang, K. <i>et al. J. Biol. Chem.</i>; published online July 16, 2013; doi:10.1074/jbc.M113.467837</p> <p>Contact: Qinong Ye, Beijing Institute of Biotechnology, Beijing, China e-mail: yeqn66@yahoo.com</p> <p>Contact: Hao Zhang, same affiliation as above e-mail: zhanghal197@hotmail.com</p>
Breast cancer; prostate cancer	Androgen receptor; cyclin D1 (CCND1; BCL1)	<p><i>In vitro</i> and mouse studies identified acetamide analog small molecules that could help treat prostate and other cancers. In human prostate cancer cell lines, two acetamide analogs induced apoptosis and decreased both CCND1 and androgen receptor expression compared with vehicle. In mouse xenograft models of prostate cancer or breast cancer, the lead analog decreased tumor growth compared with vehicle without causing significant toxicity. Ongoing work includes testing the lead compound in human melanoma cell lines and mouse models of melanoma and other cancers.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.887 Published online Aug. 29, 2013</p>	<p>Unpatented; licensing status not applicable</p>	<p>Rico-Bautista, E. <i>et al. Oncotarget</i> 4, 1212–1229 (2013)</p> <p>Contact: Dieter A. Wolf, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: dewolf@sanfordburnham.org</p> <p>Contact: Elizabeth Rico-Bautista, same affiliation as above e-mail: erico@sanfordburnham.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Melanoma	Cyclic adenosine monophosphate (cAMP); cell division cycle 25B (CDC25B); melanocortin 1 receptor (MC1R)	Cell culture studies suggest targeting the MC1R-cAMP-CDC25B signaling pathway could help treat melanoma. In a panel of human melanoma cell lines, activators of MC1R or cAMP signaling inhibited cell cycle progression compared with vehicle. In the cell lines, MC1R- and cAMP-mediated inhibition of cell cycle progression was dependent on inhibitory phosphorylation of CDC25B. Next steps could include screening for and evaluating pharmacological inhibitors of CDC25B in melanoma models. SciBX 6(33); doi:10.1038/scibx.2013.888 Published online Aug. 29, 2013	Patent and licensing status unavailable	Lyons, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 1, 2013; doi:10.1073/pnas.1201917110 Contact: Frank McCormick, University of California, San Francisco, Calif. e-mail: mccormick@cc.ucsf.edu
Multiple myeloma (MM)	Proteasome	<i>In vitro</i> and mouse studies identified a homopiperazine proteasome inhibitor that could help treat drug-resistant MM. In cultured, bortezomib-resistant MM cell lines and in mouse xenograft models of MM, the proteasome inhibitor blocked proliferation and decreased tumor volume compared with vehicle. Next steps include testing the molecule in additional mouse models of cancer. Takeda Pharmaceutical Co. Ltd. and Johnson & Johnson market the proteasome inhibitor Velcade bortezomib to treat MM and mantle cell lymphoma (MCL). Onyx Pharmaceuticals Inc. and Ono Pharmaceutical Co. Ltd. market the proteasome inhibitor Kyprolis carfilzomib to treat MM. SciBX 6(33); doi:10.1038/scibx.2013.889 Published online Aug. 29, 2013	Patent and licensing status unavailable	Kikuchi, J. <i>et al. J. Biol. Chem.</i> ; published online July 22, 2013; doi:10.1074/jbc.M113.480574 Contact: Yusuke Furukawa, Jichi Medical University, Tochigi, Japan e-mail: furuyu@jichi.ac.jp
Pancreatic cancer	Regenerating islet-derived 3 β (REG3B)	Mouse studies suggest inhibiting REG3B could help treat pancreatic cancer. REG3B expression has previously been shown to be greater in primary pancreatic tumors than in healthy tissue. In a model of murine pancreatic cancer, <i>Reg3b</i> deficiency decreased tumor growth, tumor vasculature density and metastases in the liver and intestines compared with normal <i>Reg3b</i> expression. Future studies could include identifying and testing REG3B inhibitors in mice with xenograft pancreatic tumors. SciBX 6(33); doi:10.1038/scibx.2013.890 Published online Aug. 29, 2013	Patent and licensing status unavailable	Gironella, M. <i>et al. Cancer Res.</i> ; published online July 18, 2013; doi:10.1158/0008-5472.CAN-12-3057 Contact: Emma Folch-Puy, Institute of Biomedical Research of Barcelona, Spanish National Research Council, Barcelona, Spain e-mail: emma.folch@iibb.csic.es

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Hypertension	Potassium channel K2p3.1 (KCNK3); phospholipase A ₂ (PLA ₂)	<p>Studies in patient samples and cell culture suggest activating KCNK3 could help treat pulmonary arterial hypertension (PAH). Predicted loss-of-function mutations in <i>KCNK3</i> were identified in 3 of 230 patients with idiopathic PAH and 3 of 93 patients with familial PAH. In cell culture, expression of mutant alleles of <i>KCNK3</i> confirmed the disruption of protein activity. In these cells, a PLA₂ inhibitor known to activate wild-type <i>KCNK3</i> increased the activity of <i>KCNK3</i> mutants compared with vehicle. Next steps include testing additional <i>KCNK3</i>-activating compounds <i>in vitro</i> and in animal models.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.891 Published online Aug. 29, 2013</p>	Patent and licensing status unavailable	<p>Ma, L. <i>et al. N. Engl. J. Med.</i>; published online July 25, 2013; doi:10.1056/NEJMoa1211097 Contact: Wendy K. Chung, Columbia University Medical Center, New York, N.Y. e-mail: wkc15@columbia.edu</p>
Endocrine/metabolic disease				
Diabetes	IL-15; IL-15 receptor α -chain (IL-15RA)	<p>Studies in mice and human samples suggest inhibiting IL-15 or IL-15RA could help treat type 1 diabetes. Mice expressing IL-15 and IL-15ra in pancreatic β cells developed markers of type 1 diabetes, including hyperglycemia and β cell destruction, and had higher serum levels of anti-insulin antibodies than wild-type controls. In this model and a second mouse model of type 1 diabetes, blocking IL-15 signaling delayed diabetes onset. Patient pancreatic tissue samples showed higher IL-15 and IL-15RA expression than samples from healthy controls. Next steps could include determining inducers of IL-15 and IL-15RA expression in human islets and identifying the immune cells that are activated in response to IL-15 production in islets.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.892 Published online Aug. 29, 2013</p>	Patent and licensing status unavailable	<p>Chen, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 31, 2013; doi:10.1073/pnas.1312911110 Contact: Thomas A. Waldmann, National Human Genome Research Institute, Rockville, Md. e-mail: tawald@helix.nih.gov</p>
Hematology				
Hematologic mobilization	Not applicable	<p>Mouse studies suggest the nucleotide sugar uridine diphosphate glucose (UDP-glucose) could be useful for stem cell mobilization in potential bone marrow donors. In mice, injection of UDP-glucose increased hematopoietic stem and progenitor cell mobilization from the bone marrow compared with vehicle injection. In lethally irradiated mice, donor stem cells mobilized with UDP-glucose showed better long-term engraftment and repopulation capacity than cells mobilized with G-CSF (CSF3). Next steps include studies to determine whether UDP-glucose can synergize with other stem cell mobilization compounds and whether it could be used in combination with G-CSF in a clinical trial.</p> <p>SciBX 6(33); doi:10.1038/scibx.2013.893 Published online Aug. 29, 2013</p>	Patent application filed; available for licensing from the University of Pittsburgh Contact: Alexander P. Ducruet, University of Pittsburgh, Pittsburgh, Pa. phone: 412-648-2219 e-mail: aducruet@otm.tt.pitt.edu	<p>Kook, S. <i>et al. J. Clin. Invest.</i>; published online July 25, 2013; doi:10.1172/JCI64060 Contact: Byeong-Chel Lee, University of Pittsburgh Cancer Institute, Pittsburgh, Pa. e-mail: leeb4@upmc.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Bacterial infection	Not applicable	Rat studies suggest decreasing mitochondrial reactive oxygen species could help prevent kidney damage in acute infectious pyelonephritis. In a rat model of acute pyelonephritis, a mitochondria-targeted plastoquinone antioxidant called SkQR1 decreased kidney pathology and increased survival compared with no treatment. In this model, SkQR1 pretreatment prevented an increase in leukocyte numbers and leukocyte-produced reactive oxygen species. Next steps include additional preclinical studies to evaluate the plastoquinone antioxidant in additional nephrological and urological pathologies. Mitotech LLC has mitochondria-targeted antioxidants, including SkQR1, in preclinical development.	SkQR1 and related molecules covered by issued and filed patents; licensing details available from Mitotech Contact: Maxim Skulachev, Mitotech LLC, Moscow, Russia e-mail: max@mitotech.ru	Plotnikov, E.Y. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 29, 2013; doi:10.1073/pnas.1307096110 Contact: Dmitry B. Zorov, Lomonosov Moscow State University, Moscow, Russia e-mail: zorov@genebee.msu.su
SciBX 6(33); doi:10.1038/scibx.2013.894 Published online Aug. 29, 2013				
Inflammation				
Allergy	Transforming growth factor- β 1 (TGFB1); transforming growth factor- β receptor 1 (TGFBRI; ALK5); TGFB2 (TGFB-RII)	Studies in human samples suggest inhibiting TGFBRI or TGFB2 could help treat allergy-related conditions. In 58 patients with Loeys-Dietz syndrome (LDS), a monogenic condition associated with mutations in the genes encoding TGFB1 or the TGFBRI and TGFB2 receptors, incidences of allergy-related conditions including asthma, food allergy, rhinitis, eczema and functional gastrointestinal disorders were increased compared with those in the general population. In patient samples, TGFBRI and TGFB2 signaling activity and markers of allergies were greater than those in healthy controls. Next steps could include testing TGFB1 inhibitors in allergy models. Eli Lilly and Co.'s LY2157299, an inhibitor of TGFBRI and TGFB2, is in Phase II testing to treat various cancers.	Patent and licensing status unavailable	Frishmeyer-Guerrero, P.A. <i>et al. Sci. Transl. Med.</i> ; published online July 24, 2013; doi:10.1126/scitranslmed.3006448 Contact: Harry C. Dietz, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: hdietz@jhmi.edu
SciBX 6(33); doi:10.1038/scibx.2013.895 Published online Aug. 29, 2013				
Inflammatory disease	Heparan sulfate glycosaminoglycan (HSGAG)	<i>In vitro</i> studies identified heparan sulfate mimetics that could help treat inflammatory diseases. Sulfated HSGAGs regulate proinflammatory chemokines, but such compounds can have unwanted inhibitory effects on coagulation. HSGAG mimetics were designed from a disaccharide precursor core with tunable binding properties based on variable sulfation sequences. <i>In vitro</i> , a trisulfated mimetic antagonized heparin binding to the proinflammatory chemokine CC motif ligand 5 (RANTES; CCL5) without altering the coagulation cascade. Next steps could include testing the lead mimetics in animal models of inflammation.	Patent and licensing status unavailable	Sheng, G.J. <i>et al. J. Am. Chem. Soc.</i> ; published online July 23, 2013; doi:10.1021/ja4027727 Contact: Linda C. Hsieh-Wilson, California Institute of Technology and the Howard Hughes Medical Institute, Pasadena, Calif. e-mail: lhw@caltech.edu
SciBX 6(33); doi:10.1038/scibx.2013.896 Published online Aug. 29, 2013				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	β -Amyloid (A β)	<i>In silico</i> and <i>in vitro</i> studies identified A β fiber-binding compounds that could help treat AD. In a structure-based computational screen of 18,000 compounds for A β fiber binding, the 25 top-ranked hits were selected for experimental validation. In binding assays and human cell lines, eight hits bound A β fibers and decreased A β -associated cytotoxicity compared with no treatment. Next steps include evaluating the lead compounds in additional cellular and animal models of AD. SciBX 6(33); doi:10.1038/scibx.2013.897 Published online Aug. 29, 2013	Patent application filed; licensed	Jiang, L. <i>et al. eLife</i> ; published online July 16, 2013; doi:10.7554/eLife.00857 Contact: David S. Eisenberg, University of California, Los Angeles, Calif. e-mail: david@mbi.ucla.edu
Alzheimer's disease (AD)	Liver X receptor- β (NR1H2; LXR- β)	SAR and mouse studies suggest flavonoid LXR- β agonists could be useful for treating AD. In cultured microglia, flavonoid LXR- β agonists upregulated lipid transport proteins that could counteract β -amyloid (A β) in AD without also causing lipid and triglyceride accumulation in liver cells. In a mouse model of AD, the lead compound decreased total brain A β compared with vehicle control. Next steps include further optimizing the compounds and testing their functional effects in mouse AD models. Vitae Pharmaceuticals Inc.'s LXR- β agonist, VTP-4, is in preclinical development for AD. SciBX 6(33); doi:10.1038/scibx.2013.898 Published online Aug. 29, 2013	Patent pending; available for licensing	Hu, Y. <i>et al. J. Med. Chem.</i> ; published online July 11, 2013; doi:10.1021/jm301913k Contact: Xianzhang Bu, Sun Yat-sen University, Guangzhou, China e-mail: phsboxz@mail.sysu.edu.cn
Amyotrophic lateral sclerosis (ALS)	Fusion (involved in t(12;16) in malignant liposarcoma) (FUS; TLS)	Mouse studies suggest inhibiting FUS aggregation could help treat ALS. In mice, expression of an aggregation-prone FUS mutant resulted in motor neuron damage, motor neuron loss and eventual mouse death. In the mouse model, expression of the mutant protein led to pathogenic FUS inclusions throughout the nervous system and increased neuroinflammation compared with expression of wild-type FUS. Next steps could include identifying therapeutics that inhibit FUS aggregation. SciBX 6(33); doi:10.1038/scibx.2013.899 Published online Aug. 29, 2013	Patent and licensing status unavailable	Shelkovnikova, T.A. <i>et al. J. Biol. Chem.</i> ; published online July 18, 2013; doi:10.1074/jbc.M113.492017 Contact: Natalia N. Ninkina, Cardiff University, Cardiff, U.K. e-mail: ninkinan@cf.ac.uk Contact: Vladimir L. Buchman, same affiliation as above e-mail: buchmanvl@cf.ac.uk
Epilepsy; seizures	Microtubule-associated protein- τ (MAPT; TAU; FTDP-17)	Mouse studies suggest inhibiting TAU protein could help prevent seizures. In a mouse model of severe seizures, high Tau protein levels resulted in quicker progression to severe seizures than low Tau protein levels. In mice, intracerebroventricular delivery of Tau-targeting antisense oligonucleotides (ASOs) decreased Tau protein levels and severity of pentylenetetrazole-induced seizures compared with scrambled ASOs. Next steps could include testing ASOs in epilepsy patients. SciBX 6(33); doi:10.1038/scibx.2013.900 Published online Aug. 29, 2013	Patent and licensing status unavailable	De Vos, S.L. <i>et al. J. Neurosci.</i> ; published online July 31, 2013; doi:10.1523/JNEUROSCI.2107-13.2013 Contact: Timothy M. Miller, Washington University in St. Louis, St. Louis, Mo. e-mail: millert@neuro.wustl.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Nerve damage	Low-density lipoprotein-related protein 1 α -2-macroglobulin receptor (LRP1; CD91); neurotrophic tyrosine kinase receptor 3 (NTRK3; TrkC)	Cell culture and rat studies suggest targeting LRP1 could promote neuronal regeneration. In rat dorsal root ganglion cultures, LRP1 agonists stimulated neurite outgrowth by activating TrkC signaling. In rats, intrathecal infusion of glutathione-S-transferase (GST) fusion proteins that agonize LRP1 increased TrkC pathway activity and neurite outgrowth compared with no GST infusion. In rat models of spinal cord injury, infusion of LRP1 ligands increased axonal projections and regeneration at lesion sites compared with vehicle. Next steps include testing and defining the effects of LRP1 ligands in additional injury models. Angiochem Inc.'s ANG2004, an LRP1-targeting peptide, is in preclinical development for diabetes and obesity. Raptor Pharmaceutical Corp.'s HepTide, an LRP1-targeting peptide, is in preclinical development for liver cancer.	Patent and licensing status unavailable	Yoon, C. <i>et al. J. Biol. Chem.</i> ; published online July 18, 2013; doi:10.1074/jbc.M113.478552 Contact: W. Marie Campana, University of California, San Diego, La Jolla, Calif. e-mail: wcampana@ucsd.edu
SciBX 6(33); doi:10.1038/scibx.2013.901 Published online Aug. 29, 2013				

Various

Autoimmune disease; cachexia	Tumor necrosis factor- α (TNF- α)	Biochemical and cell culture studies identified a bicyclic peptide inhibitor of TNF- α that could help treat cachexia and autoimmune disease. TNF- α is upregulated in cachexia and multiple autoimmune diseases. A screen of a library of bicyclic peptides yielded a candidate that selectively bound TNF- α with a K_d value of 0.45 μ M. In an ELISA, the peptide inhibited the interaction between TNF- α and TNF receptor 1 (TNFRSF1A; TNFR1; CD120a). In cultured fibroblasts, the bicyclic peptide decreased TNF- α -induced cell death compared with monocyclic and linear peptides. Next steps include optimizing the potency and pharmacological properties of the inhibitor.	Patent application filed; available for licensing	Lian, W. <i>et al. J. Am. Chem. Soc.</i> ; published online July 18, 2013; doi:10.1021/ja405106u Contact: Dehua Pei, The Ohio State University, Columbus, Ohio e-mail: pei.3@osu.edu
SciBX 6(33); doi:10.1038/scibx.2013.902 Published online Aug. 29, 2013				

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
Assays & screens			
Nanometer-scale thermometry in living cells	Nanometer-scale thermometry in living cells could be useful for monitoring cellular activity in response to stimuli and could aid the development of temperature-sensitive therapeutics. The thermometry approach uses diamond nanocrystals that act as temperature sensors and gold nanoparticles that act as light-sensitive local heating sources. In a single human fibroblast injected with the diamond nanocrystals and gold nanoparticles, laser-mediated heating of the gold nanoparticles generated controlled and localized temperature differences of up to 5 K over distances of about 7 μ M within the cell. Next steps include improving the accuracy of the temperature measurements and developing a system to deliver the diamond nanocrystals to targeted organs.	Provisional patent application filed; available for licensing	Kucsko, G. <i>et al. Nature</i> ; published online July 31, 2013; doi:10.1038/nature12373 Contact: Mikhail D. Lukin, Harvard University, Cambridge, Mass. e-mail: lukin@physics.harvard.edu
	SciBX 6(33); doi:10.1038/scibx.2013.903 Published online Aug. 29, 2013		
Phenotypic neuronal assays to screen for small molecules that decrease β -amyloid (A β)	Phenotypic screening of embryonic stem cell (ESC)-derived neurons could help identify small molecules that decrease A β to treat Alzheimer's disease (AD). The assays used ESC-derived neurons generated from the Tg2576 mouse model of AD and allowed the monitoring of the synthesis and synaptic activity of A β . The assay was used to screen a library of 446 small molecules and yielded 4 hits that inhibited A β synthesis with single-digit micromolar and submicromolar IC ₅₀ values. Next steps include integrating the assay into an automated high throughput screening platform that operates in a 384-well format.	Patent application filed; available for licensing from Columbia Technology Ventures	McIntire, L.B.J. <i>et al. Chem. Biol.</i> ; published online July 25, 2013; doi:10.1016/j.chembiol.2013.06.005 Contact: Tae-Wan Kim, Columbia University Medical Center, New York, N.Y. e-mail: twk16@columbia.edu
	SciBX 6(33); doi:10.1038/scibx.2013.904 Published online Aug. 29, 2013		
Strategy to decrease off-target peptide recognition by affinity-enhanced, T cell receptor (TCR)-based T cell therapies	Amino acid scanning and cell culture screens could be used to decrease the risk of off-target toxicity from TCR-based T cell therapies to treat cancer. Clinical use of T cells engineered to express affinity-enhanced TCRs targeting melanoma-associated antigen A3 (MAGEA3) led to two patients dying of cardiac failure. An <i>in silico</i> scan of non-MAGEA3 protein sequences identified three proteins containing a peptide motif that could be recognized by the TCRs targeting MAGEA3. In cell lines individually pulsed with each of the three non-MAGEA3 peptides, only the cells pulsed with a peptide derived from the muscle protein titin (TTN) induced activation of MAGEA3-targeting T cells. In 3D beating cultures of iCell cardiomyocytes and in five independent human cardiac tissue samples, titin expression was confirmed, suggesting the off-target clinical toxicity was a result of the T cells targeting titin. Next steps include using the strategy to avoid future off-target toxicities. iCells are marketed by Cellular Dynamics International Inc. (See <i>Sleuthing for toxicity</i> , page 1.)	Unpatented; licensing status not applicable	Cameron, B.J. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 7, 2013; doi:10.1126/scitranslmed.3006034 Contact: Bent K. Jakobsen, Immunocore Ltd., Abingdon, U.K. e-mail: bent.jakobsen@immunocore.com
	SciBX 6(33); doi:10.1038/scibx.2013.905 Published online Aug. 29, 2013		

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Mouse model of fibroblast growth factor 9 (Fgf9; Gaf)-driven lung cancer	Transgenic mice with inducible expression of Fgf9 in lung epithelium could be useful as a model to help identify new treatments for lung cancer. In the mouse model, doxycycline-induced expression of <i>Fgf9</i> resulted in the formation of papillary adenocarcinomas in the lung within eight days of induction. In this model, knocking out fibroblast growth factor receptor 3 (Fgfr3; Cd333) prevented the formation of lung adenocarcinomas. Next steps include using the model to study signaling pathways activated by FGFR signaling and further define the events involved in lung cancer oncogenesis and metastasis.	Model unpatented; available for licensing	Yin, Y. <i>et al. Cancer Res.</i> ; published online July 18, 2013; doi:10.1158/0008-5472.CAN-13-0495 Contact: David M. Ornitz, Washington University in St. Louis, St. Louis, Mo. e-mail: dornitz@wustl.edu
	SciBX 6(33); doi:10.1038/scibx.2013.906 Published online Aug. 29, 2013		
Mouse model of methylmalonic acidemia-associated renal pathology	A mouse model of methylmalonic acidemia-associated renal pathology could help identify new treatments for the condition, which is a metabolic disorder caused primarily by mutations in methylmalonyl CoA mutase (MUT). In this model, <i>Mut</i> knockout mice were engineered to express a liver-specific <i>Mut</i> transgene. The mice showed severe proximal tubular mitochondrial changes that recapitulate the renal pathology of methylmalonic acidemia seen in patient biopsy samples. In the mouse model, dietary supplementation with the antioxidants ubiquinone and vitamin E decreased weight loss compared with no supplementation and improved markers of renal function. Next steps include evaluating additional antioxidant compounds in the mice and then conducting a clinical trial in patients who have methylmalonic acidemia to evaluate the most effective compound.	Model unpatented; available for licensing from the NIH Contact: Tara Kirby, National Institutes of Health, Bethesda, Md. e-mail: kirbyt@mail.nih.gov	Manoli, I. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 29, 2013; doi:10.1073/pnas.1302764110 Contact: Charles P. Venditti, National Institutes of Health, Bethesda, Md. e-mail: venditti@mail.nih.gov
	SciBX 6(33); doi:10.1038/scibx.2013.907 Published online Aug. 29, 2013		
Mouse models of idiopathic basal ganglia calcification (IBGC)	Mouse models of IBGC could be useful for studying associations between brain lesions and cognitive, motor and psychiatric symptoms. In human samples, exome sequencing revealed that <i>platelet derived growth factor B</i> (<i>PDGFB</i> ; <i>PDGF2</i>) mutations co-segregated with IBGC. In three different mouse models with reduced expression of <i>Pdgfb</i> , which have known defects in the blood brain barrier (BBB), calcified lesions similar to those in humans were detected and brain calcification was shown to progress with age. Next steps include performing behavioral tests on these mice and evaluating the BBB in humans who have <i>PDGFB</i> mutations.	Unpatented; unlicensed	Keller, A. <i>et al. Nat. Genet.</i> ; published online Aug. 4, 2013; doi:10.1038/ng.2723 Contact: Christine Klein, University of Luebeck, Luebeck, Germany e-mail: christine.klein@neuro.uni-luebeck.de Contact: Christer Betsholtz, Uppsala University, Uppsala, Sweden e-mail: christer.betsholtz@ki.se Contact: Maria J. Sobrido, Clinical University Hospital, Santiago de Compostela, Spain e-mail: ssobrido@telefonica.net Contact: Annika Keller, University Hospital Zurich, Zurich, Switzerland e-mail: annika.keller@usz.ch
	SciBX 6(33); doi:10.1038/scibx.2013.908 Published online Aug. 29, 2013		

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Rat model of Roux-en-Y gastric bypass	Roux-en-Y gastric bypass-treated rats could be used to study the mechanisms underlying the efficacy of the procedure and could help develop new treatments for metabolic diseases. In diet-induced obese rats and two nonobese, diabetic rat models, the bypass procedure was shown to reprogram intestinal glucose metabolism after exposure to undigested nutrients. In rats that received the bypass procedure, reprogramming of intestinal glucose metabolism resulted in increased glycemic control and whole-body glucose disposal compared with what was seen in sham-operated controls. Next steps could include studies to determine whether the observed reprogramming of intestinal activity also occurs in humans.	Patent and licensing status unavailable	Saeidi, N. <i>et al. Science</i> ; published online July 26, 2013; doi:10.1126/science.1235103 Contact: Nicholas Stylopoulos, Boston Children's Hospital, Boston, Mass. e-mail: nicholas.stylopoulos@childrens.harvard.edu
Drug delivery			
Lentiviral vectors targeting endoglin (CD105; ENG) for endothelial cell-targeted therapy	<i>In vitro</i> and mouse studies suggest lentiviral vectors targeting CD105 could be used for endothelium-targeted gene delivery. In mice, lentiviruses that encoded GFP and targeted the endothelial cell surface protein CD105 accumulated in the liver and specifically transduced liver sinusoidal endothelial cells over other liver cells. In the mice, CD105-targeting lentiviruses encoding erythropoietin increased erythropoietin and hematocrit levels compared with vehicle. In mice transplanted with human liver endothelial cells or in a human artery section, lentiviruses targeting human CD105 specifically transduced the human endothelial cells. Next steps could include testing the vectors in disease models.	Patent and licensing status unavailable	Abel, T. <i>et al. Blood</i> ; published online July 24, 2013; doi:10.1182/blood-2012-11-468579 Contact: Christian J. Buchholz, Paul Ehrlich Institute, Langen, Germany e-mail: christian.buchholz@pei.de
Drug platforms			
Crystal structure of glucagon receptor (GCGR)	A crystal structure of GCGR could help drug discovery efforts targeting class B GPCRs. Researchers solved the structure of the 7-transmembrane helical domain of GCGR at 3.4 Å resolution. The structure showed that a stalk extends from the N terminus of helix I that may be involved in glucagon (GCG) binding. Compared with class A GPCR structures, GCGR has a large ligand-binding pocket. Next steps could include building models of interactions between peptide ligands and other class B GPCRs.	Patent and licensing status unavailable	Siu, F.Y. <i>et al. Nature</i> ; published online July 17, 2013; doi:10.1038/nature12393 Contact: Raymond C. Stevens, The Scripps Research Institute, La Jolla, Calif. e-mail: stevens@scripps.edu Contact: Ming-Wei Wang, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China e-mail: wangmw@mail.shcnc.ac.cn
Photoreceptor replacement therapy for degenerative retinal disease	Embryonic stem cell (ESC)-derived photoreceptors could help treat degenerative retinal diseases. In an adapted 3D culture system, mouse ESCs differentiated into photoreceptor-expressing rod precursor cells. In three mouse models of retinal degeneration, subretinal injection of 200,000 rod precursors resulted in the integration of approximately 25,000 morphologically normal rod photoreceptors that responded to metabotropic glutamate receptor subtype 8 (mGluR8; GRM8) agonists and antagonists in a manner comparable to that of wild-type photoreceptors. This number of integrated photoreceptors was insufficient to yield electroretinographic responses. Next steps could include improving the efficiency of integration.	Patent and licensing status unavailable	Gonzalez-Cordero, A. <i>et al. Nat. Biotechnol.</i> ; published online July 21, 2013; doi:10.1038/nbt.2643 Contact: Robin R. Ali, Institute of Ophthalmology, University College London, London, U.K. e-mail: r.ali@ucl.ac.uk

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