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Two-pronged approach to T1D

By Kai-Jye Lou, Staff Writer

Researchers at the **City of Hope** have combined a method to regenerate pancreatic β cells with a strategy to induce immune tolerance and have used the dual approach to treat advanced type 1 diabetes in mice.[1] The team plans to validate the technique in other autoimmune diseases before applying it to patients with type 1 diabetes.

Type 1 diabetes (T1D) occurs when autoreactive T cells attack and destroy insulin-producing pancreatic β cells. Restoring the body's ability to produce insulin in type 1 diabetes requires regenerating insulin-producing β cells and preventing a host immune response against those new cells. The task is even harder in advanced type 1 diabetes, in which few if any functioning β cells remain.

In prior mouse studies, researchers led by Defu Zeng developed a regimen to promote tolerance and β cell regeneration. The approach involved delivering two types of murine anti-Cd3 antibodies—one that bound the Fc receptor (FcR) and one that did not—and a murine anti-Cd8a (p32; Cd8) antibody to condition the host immune system for a cell transplant. Treatment with the antibodies was then followed by transplantation of donor bone marrow and spleen cells that were depleted of $Cd4^+$ T cells.

The regimen reversed autoimmunity, eliminated islet inflammation and reversed new-onset type 1 diabetes but was unable to augment the generation of β cells in advanced type 1 diabetes.[2,3]

Now, Zeng's team has combined the immune-tolerance regimen with a cocktail of two growth factors—gastrin and epidermal growth factor (EGF)—that are known to increase β cell regeneration in mouse models and human cell culture.[4,5]

Zeng is an associate professor of diabetes, endocrinology and metabolism and of hematology and hematopoietic cell transplantation at the **Beckman Research Institute at City of Hope**.

In a mouse model of advanced type 1 diabetes, the immune tolerance regimen plus the growth factor cocktail augmented β cell regeneration and restored normal glycemia in 7 of 12 animals for up to 150 days after cessation of growth factor therapy, whereas either treatment alone failed to restore glycemic control in any animal. Mice received daily injections of the growth factor cocktail for up to 60 days.

The immune tolerance regimen eliminated islet inflammation and promoted the survival of newly generated β cells. The growth factor cocktail augmented both the generation of β cells from progenitors and β cell replication.

Results were published in *Science Translational Medicine*.

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OFFICES
BioCentury Publications, Inc.
San Francisco
PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333

Chadds Ford
223 Wilmington-West Chester Pike
Chadds Ford, PA 19317
T: +1 610 558 1873

Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798

Oxford
287 Banbury Road
Oxford OX4 7JA
United Kingdom
T: +44 (0)18 6551 2184

Washington, DC
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Washington, DC 20009
T: +1 202 462 9582

Nature Publishing Group
New York
75 Varick Street, 9th Floor
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London
The Macmillan Building
4 Crinan Street
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United Kingdom
T: +44 (0)20 7833 4000

Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
Shinjuku-ku, Tokyo 162-0843
Japan
T: +81 3 3267 8751

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"This is a really nice piece of science, well conducted, that combines an approach to promote tolerance toward β cells with the regeneration of β cells using growth factors," said James Shapiro, director of the Clinical Islet Transplant Program at the **University of Alberta**. "If such an approach were fully transplated to the clinic, it could have major impact in treatments for type 1 diabetes."

"The exciting part of this study is that the authors are able to show that they could reverse late-stage diabetes in the mouse model," said Ezio Bonvini, SVP of research at immunotherapy company **MacroGenics Inc.**

Beta testing

Zeng thinks the combination therapy has potential as both an alternative and a complement to islet transplantation due to its tolerance- and regeneration-promoting properties.

> **"Our combination approach could provide immune tolerance towards donor islets and improve their function and thus ensure the long-term survival of the graft."**
> ***—Defu Zeng, Beckman Researh Institute at City of Hope***

Shapiro was less sanguine about the approach's translational potential.

He thinks the growth factor therapy could be difficult to apply in the clinical setting because gastrin has a short half-life and the regenerative potential of β cells in adults with type 1 diabetes is likely to be lower than that seen in the mouse model.

"If you are an adult and have had type 1 diabetes for 30–40 years, your cells probably won't have the same regenerative potential as cells that are only around 18 weeks old, as seen in the late-stage mouse model," Shapiro said.

However, Zeng noted that even if the combination therapy fails to regenerate a patient's own β cells and restore glycemic control, it could still promote tolerance toward transplanted islets.

"Our combination approach could provide immune tolerance towards donor islets and improve their function and thus ensure the long-term survival of the graft," he told *SciBX*.

MacroGenics president and CEO Scott Koenig said it will be important to replicate the findings in model systems that use human cells. "At this time, we can't necessarily conclude that the regenerative component that they've included in their protocol would reconstitute human β cell function," he told *SciBX*.

Shapiro also wanted to see additional safety data on the antibodies used in the tolerance-inducing regimen. He noted that the FcR-binding property of anti-CD3 mAbs such as Orthoclone OKT3 muromonab is linked with their serious adverse effects such as cytokine release syndrome and risk of lymphoproliferative disorders. He said there may be other antibodies that could be substituted that would not carry such risk.

Johnson & Johnson marketed Orthoclone to treat glucocorticoid-resistant organ transplant rejection but discontinued manufacturing of the mAb in 2010 for competitive reasons.

Zeng said his group is considering using Orthoclone as the FcR-binding anti-CD3 antibody in the conditioning regimen but

acknowledged it could be challenging as the mAb is no longer commercially available. The group has not yet determined which anti-CD8 and non–FcR-binding anti-CD3 antibody it will use.

Zeng said the group plans to produce the antibody at a GMP facility.

Non–FcR-binding anti-CD3 mAbs that have been tested for type 1 diabetes include MacroGenics' teplizumab.[6]

> **"The exciting part of this study is that the authors are able to show that they could reverse late-stage diabetes in the mouse model."**
>
> ***—Ezio Bonvini, MacroGenics Inc.***

Teplizumab missed its primary endpoint in a Phase III trial in patients with recent-onset type 1 diabetes, although it did have a safety profile that looked better than Orthoclone's.

Teplizumab now is being evaluated in a Phase II/III trial to prevent type 1 diabetes in at-risk individuals—those who show abnormal glucose tolerance, express at least two known diabetes-associated autoantibodies and have a first-degree relative who has the disease. The **NIH**'s **National Institute of Diabetes and Digestive and Kidney Diseases** (NIDDK) is sponsoring the trial.

Translational roadmap

Zeng said his group first needs to test its tolerance-promoting regimen in disease settings that are more severe and thus have lower safety bars than type 1 diabetes.

First, the team plans to test whether the antibody-conditioning regimen can prevent graft-versus-host disease (GvHD) in patients with hematological malignancies who will be treated with a bone marrow transplant. At the same time, they plan to test the antibody regimen followed by the transplantation of bone marrow and spleen cells in nonhuman primates to confirm the protocol itself does not cause GvHD, which is a complication of bone marrow transplant.

Finally, the researchers will test the antibody regimen followed by transplantation of bone marrow and spleen cells in patients with multiple sclerosis (MS) and lupus before moving into type 1 diabetes.

For the growth factor component, Zeng said the group is looking to optimize the combination of growth factors and hormones that could augment β cell regeneration beyond what was seen with the EGF-gastrin cocktail. "We want to identify combinations that could further increase response rates and reduce treatment times," he told *SciBX*. "We would like to identify a cocktail that could reduce treatment times down to one month from two months and increase the response rate above the 60% we've seen in mouse models thus far."

As the mechanism of β cell regeneration is unclear, Zeng said the group also plans to carry out lineage-tracing experiments to determine the progenitor cell population in the pancreas that gives rise to new β cells and then develop strategies to expand such cell populations.

City of Hope has filed a patent application covering the conditioning regimen for promoting immune tolerance. The work is available for licensing.

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Beckman Research Institute at City of Hope, Duarte, Calif.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
MacroGenics Inc., Rockville, Md.
National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
University of Alberta, Edmonton, Alberta, Canada

Casting out myeloma kidney

By Lev Osherovich, Senior Writer

A team from **The University of Alabama at Birmingham** has proposed a new strategy to treat cast nephropathy, a common renal complication of multiple myeloma.[1] The approach involves using a cyclic peptide therapeutic to block the interaction between tumor-derived immunoglobulin light chain proteins and an abundant urine protein called uromodulin. The team now needs to optimize the peptide's oral bioavailability.

Cast nephropathy, also known as myeloma kidney, causes acute kidney injury and failure in patients with MM. The condition arises from the accumulation of urinary casts, which are large aggregates of immunoglobulin light chain (IgLC) bound to uromodulin (UMOD; THP).[2]

In MM, "cancer cells overproduce immunoglobulins, and these can clog up the kidney," said Paul Sanders, professor of medicine, physiology and biophysics and director of the Nephrology Research and Training Center at UAB.

There are no targeted therapeutics aimed at cast nephropathy, and clinicians instead have focused on reducing IgLC levels with aggressive chemotherapy. However, normalizing IgLC levels can take several months of chemotherapy, and the kidney remains vulnerable to injury during the course of treatment.

Prior work by Sanders and other researchers established that THP could bind a variety of IgLC isoforms,[3] but it was not clear whether blocking the interaction could prevent kidney failure.

Now, said Sanders, "we have shown that cast nephropathy arises from the binding of immunoglobulin light chain to THP in the kidney—this presents a therapeutic opportunity."

Urine trouble

Sanders' team began by pinpointing the structural features of IgLC when bound by THP. The team used a yeast-protein interaction screening technique to identify IgLC peptide fragments with maximal binding to THP and then converged on a 12-amino-acid sequence in a conserved region of the antibody.

The team next made a cyclic version of the peptide. Cyclic peptides are more stable and potent *in vitro* and *in vivo* than their linear counterparts.

In vitro, the cyclic peptide decreased binding of full-length THP to six different IgLC variants compared with no treatment.

In rats injected with large quantities of MM-associated IgLCs, the cyclic peptide prevented cast nephropathy, and decreased kidney damage and increased acute renal function compared with vehicle.

Results were published in *The Journal of Clinical Investigation*. Sanders has filed for a patent covering the cyclic peptide, and the IP is available for licensing.

Sanders hopes to move the peptide into preclinical development and is seeking an industry partner.

Role of THP

One concern is whether blocking THP's interaction with IgLC will affect renal function in the long term. The normal physiological role of THP is unknown, but the protein does bind a variety of other proteins besides IgLC and may help prevent bacterial infections in the kidney.

"There are all kinds of hypotheses about what THP does, but nothing is certain," said Sanders. Thus, he said it is hard to predict the long-term physiological effects of the cyclic peptide on renal function.

To assess the peptide's tolerability, Sanders is now conducting pharmacokinetic, pharmacodynamic and dose-ranging studies in rats. "It's a very nontoxic molecule so far," he noted.

Because THP is continually excreted in the urine, a continual block of the protein's interaction with IgLC may require frequent dosing with the antagonistic peptide.

> **"This is exactly the kind of paper we look for to decide what to work on."**
>
> ***—Doug Treco, Ra Pharmaceuticals Inc.***

As a result, Sanders thinks an oral formulation of the cyclic peptide would be ideal as an adjunct to chemotherapy. The team injected the peptide in the current study, but Sanders cited preliminary evidence from his lab showing that the cyclic peptide might be effective when given orally.

Doug Treco, president, CEO and cofounder of cyclic peptide company **Ra Pharmaceuticals Inc.**, said Sanders' study provides good proof of concept of the feasibility of targeting the THP-IgLC interaction, but the team's peptide would likely have to be heavily modified to become an orally available drug.

"They've taken a sequence and shown it can interact with the same target as the originating protein. It looks like it could be an effective approach," said Treco.

He added that unmodified cyclic peptides like the one made by Sanders usually have low oral potency and are quickly degraded by digestive proteases.

Ra has a library of cyclic peptides with backbones engineered for maximal oral availability and stability. The company's lead candidate is a cyclic peptide antagonist of kallikrein that is being developed for hereditary angioedema (HAE).

Treco said THP was not yet sufficiently well validated as a target for Ra to jump into the space. He wanted to see some proof of clinical efficacy with the injected version of the peptide before deciding whether to launch an internal screening effort.

But, he added, "this is exactly the kind of paper we look for to decide what to work on."

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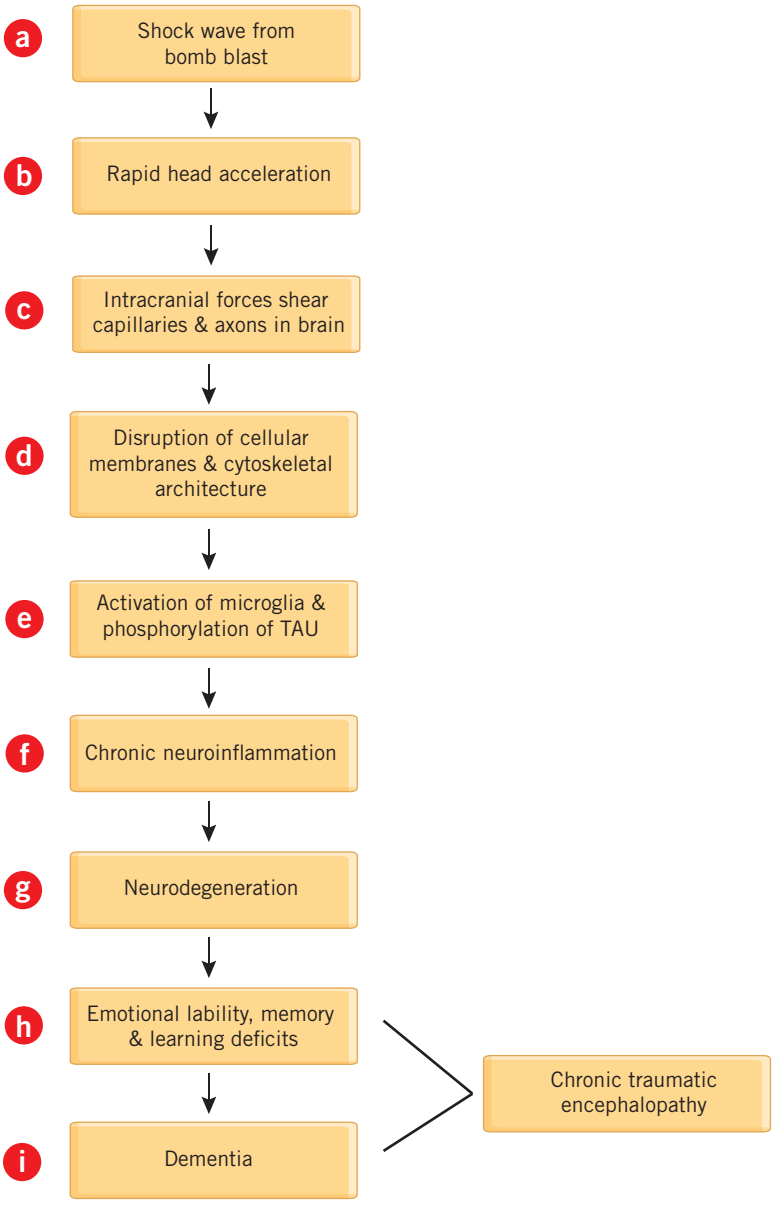
Ra Pharmaceuticals Inc., Cambridge, Mass.
The University of Alabama at Birmingham, Birmingham, Ala.

Blasted brain

By Tim Fulmer, Senior Writer

U.S. researchers have designed a mouse model of blast-induced brain injury and shown that the animal develops chronic traumatic encephalopathy, a condition associated with concussive injuries in athletes.[1] The team plans to use the model to identify biomarkers and therapies for the condition.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by plaques and tangles of microtubule-associated protein-τ (MAPT; TAU; FTDP-17) throughout the brain, as well as widespread axonal and microvascular damage. Initial symptoms include depression, irritability and impulsivity. These primarily psychological symptoms are followed by cognitive impairment and memory loss and eventually by full dementia with speech and gait dysfunction (*see* **Figure 1, "Brain on the battlefield"**).



Over the past decade, CTE has been consistently linked to two groups of people who experience repeated concussive trauma to the head: military personnel exposed to close-range blasts on the battlefield[2,3] and professional athletes in contact sports such as American football.[4,5]

It is still unclear whether repeated concussive injury is the primary cause of CTE. The condition can only be diagnosed with a postmortem autopsy, and the varied medical histories of affected soldiers and athletes means a range of biological factors may underlie the disease.

Thus, a research team led by Lee Goldstein and Ann McKee set out to show that repeated concussions are necessary for the development of CTE. To do so, the group designed and characterized a mouse model of blast injury that mimicked the experience of a soldier subjected to a close-range bomb blast.

Goldstein is associate professor of psychiatry, neurology, pathology and laboratory medicine at the **Boston University of School of Medicine**. McKee is professor of neurology and pathology and co-director of the Center for the Study of Traumatic Encephalopathy at BU.

The group placed anesthetized wild-type mice inside a cylindrical enclosure and exposed the animals to a single high-pressure air blast, which was comparable to detonation of 5.8 kg of trinitrotoluene (TNT) at a distance of 5.5 meters and within the reported range of conditions associated with common blast injuries in the Iraq war.[6]

The blast did not kill or cause blunt force trauma to the mice. Nor did brains isolated from mice two weeks after the blast show any macroscopic signs of contusion, hemorrhage, hematoma or focal tissue damage.

However, immunohistological analysis of the brains showed much greater neuropathology than brains from sham-blast control mice, including increased proliferation of proinflammatory astrocytes in response to neuronal damage throughout the cerebral cortex, hippocampus and brain stem.

Mice undergoing the blast had higher levels of phosphorylated Tau in the outer layers of the cerebral cortex than the sham-blasted mice. Electron micrographs of neurons, axons and capillaries in the hippocampus of these mice also revealed cytoskeletal and structural abnormalities, whereas the hippocampus of control mice did not.

Figure 1. Brain on the battlefield. Research published in *Science Translational Medicine* by scientists at the **Boston University School of Medicine** has shown that a single concussive air blast is sufficient to generate signs of chronic traumatic encephalopathy (CTE) in mice.

The model was designed to mimic the situation of a soldier experiencing a shock wave from a nearby bomb blast on a battlefield.

Although the blast did not kill the mouse [**a**], it generated enough force to accelerate the mouse's head [**b**] and cause phosphorylation of microtubule-associated protein-τ (MAPT; TAU; FTDP-17) as well as damage at the cellular level [**c–e**], including neuroinflammation and neurodegeneration [**f,g**]. That damage was associated with significant cognitive impairment [**h,i**], a hallmark of CTE.

Importantly, the tissue pathology was associated with functional impairments.

Axonal conduction velocity in the hippocampus was significantly slower than that in control mice two weeks after blast exposure ($p<0.05$), and memory-associated synaptic transmission was impaired in brain slices from blast-exposed mice ($p<0.05$). Also, based on the animals' behavior in a maze, hippocampal-dependent spatial learning and memory were significantly poorer in blast-exposed mice than in controls ($p<0.05$).

The final step was confirming that the cognitive abnormalities were the direct result of the pressure wave accelerating the mouse's head and causing a concussion. To do so, the researchers constrained the mouse's head in the blast chamber before delivering the blast to see whether they could prevent the development of cognitive impairment.

Indeed, head immobilization during blast exposure was sufficient to eliminate blast-related learning impairments and memory deficits.

In conclusion, the researchers wrote that their mouse model "is expected to open new avenues for investigation of mechanisms, biomarkers, and risk factors relevant to blast-related injury" and could facilitate the development of "diagnostics, therapeutics, and prophylactic measures for blast neurotrauma and its aftermath"

Data were published in *Science Translational Medicine*. Other principal investigators on the paper were Patric Stanton, professor of cell biology and anatomy at the **New York Medical College**, and Rudolph Tanzi, professor of child neurology and mental retardation at the **Harvard Medical School** and a researcher in the Genetics and Aging Research Unit at **Massachusetts General Hospital**.

"[The mouse model] nicely creates a link between blast injury and the neuropathology that is seen in CTE. Human pathological studies have not been able to do this directly."

—Christopher Giza, University of California, Los Angeles School of Medicine

Making use of the model

The mouse model "nicely creates a link between blast injury and the neuropathology that is seen in CTE," said Christopher Giza, associate professor of pediatric neurology and neurosurgery at the **University of California, Los Angeles David Geffen School of Medicine**. "Human pathological studies have not been able to do this directly."

He added that therapies designed to block TAU deposition and other chronic sequelae of blast injury can now be tested and the long-term outcomes studied much more readily in the rodent model.

Giza and colleagues previously have shown that cerebral concussions and mild traumatic brain injury are sufficient to increase fear-based learning and impair brain responsiveness and neuroplasticity in rats.[7,8]

He said the new model also could be used to look at the consequences of repeated blasts and "to look for imaging correlates of the blast injury in the mice and see how it translates to any human blast imaging studies that have been published."

Corresponding author Goldstein told *SciBX* a top priority moving forward is using the model "to study the effects of potential preventive strategies and therapies, including anti-inflammatory agents and anti-TAU compounds."

At least two companies have disclosed TAU-targeting compounds in development. Rember, a TAU aggregation inhibitor from **TauRx Pharmaceuticals Ltd.**, is in Phase II testing to treat Alzheimer's disease (AD). ReS19-T, a small molecule that prevents neurotoxicity associated with TAU from **reMYND N.V.**, is in preclinical testing for AD. Neither company responded to requests for comment. ReS19-T is being developed in partnership with **Roche**.

Corresponding author McKee added that the model could be useful for designing a diagnostic for CTE that includes neuroimaging readouts as well as levels of circulating TAU protein in the cerebrospinal fluid.

The mouse model is not covered by patents, McKee said.

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   Contact: Ann C. McKee, same affiliation as above
   e-mail: amckee@bu.edu
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Boston University School of Medicine, Boston, Mass.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Charlestown, Mass.
New York Medical College, Valhalla, N.Y.
reMYND N.V., Leuven, Belgium
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
TauRx Pharmaceuticals Ltd., Singapore
University of California, Los Angeles David Geffen School of Medicine, Los Angeles, Calif.

HLA in sequence

By Lauren Martz, Staff Writer

A group of Australian researchers and an **FDA**-led team have independently identified a mechanism behind human leukocyte antigen allele–mediated autoimmune reactions to certain drugs.[1,2] The findings could expand the use of human leukocyte antigen genotyping in clinical trials, patient care and drug design to improve therapeutic outcomes and safety.

Meanwhile, a team from **Stanford University** has published a new technology that could improve the accuracy and reduce the cost of human leukocyte antigen (HLA) genotyping.[3] Improved HLA genotyping technology could help facilitate patient screening for known drug-HLA interactions and could help identify new interactions (*see* **Box 1, "Human leukocyte antigen genotyping"**).

HLAs are proteins that present pathological antigens to T cells to induce an adaptive immune response. The *HLA* genes that encode the proteins are highly polymorphic, with most of the diversity originating at the cleft where HLA interacts with and binds antigens. The binding region controls the selection of pathological or self antigens that the HLA molecules present to T lymphocytes.

Autoimmune adverse drug reactions—such as abacavir hypersensitivity syndrome in patients expressing the major histocompatibility complex class I B 5701 (HLA-B 5701) allele and Stevens-Johnson syndrome in carbamazepine-treated patients expressing HLA-B 1502—have been associated with the expression of specific *HLA* alleles, although the underlying mechanisms were murky.

GlaxoSmithKline plc markets Ziagen abacavir to treat HIV/AIDS. **Novartis AG** markets Tegretol carbamazepine to treat epilepsy.

In a paper published in *Nature*, an Australian team led by Anthony Purcell, Jamie Rossjohn and James McCluskey showed that the two drugs bound the antigen-binding sites of specific HLA alleles and altered the repertoire of antigen proteins that were bound. The result was the presentation of self antigens to T cells, which in turn induced an autoimmune reaction.

Purcell is associate professor and senior research fellow in the Department of Biochemistry and Molecular Biology at **The University of Melbourne**. Rossjohn is senior lecturer in the Department of Biochemistry and Molecular Biology at **Monash University**. McCluskey is deputy vice-chancellor of research at the University of Melbourne.

The paper also included researchers from the **Australian Centre for Vaccine Development at the Queensland Institute of Medical Research** and the **Cardiff University School of Medicine**.

In cultured antigen-presenting cells, abacavir altered the HLA-B 5701 binding peptide repertoire by about 25%, whereas abacavir treatment did not alter the peptide repertoire in cells expressing closely related HLA alleles.

Box 1. Human leukocyte antigen genotyping.

A **Stanford University** team has developed a new human leukocyte antigen (HLA) sequencing method that could be more cost effective and accurate than existing technologies to extend the applications of HLA genotyping, which has previously focused on matching bone marrow donors and recipients.

HLA polymorphisms are clinically relevant because specific alleles have been associated with various autoimmune diseases including multiple sclerosis (MS), celiac disease, rheumatoid arthritis (RA) and type 1 diabetes.[4–7] Additionally, matching HLA genotypes is essential for host acceptance of bone marrow transplants.[8]

Despite the clear importance of knowing a patient's HLA genotypes, the actual sequencing is expensive and time consuming. Most methods exclusively sequence the antigen-binding cleft because it is the most variable, but this can lead to undetected sequence variation in other regions of the *HLA* genes.

In a paper published in the *Proceedings of the National Academy of Sciences*, Stanford's Michael Mindrinos and colleagues developed a high throughput HLA sequencing method that maps most of the *HLA* genome to reduce or eliminate ambiguity.

The method also identified previously undetected HLA alleles that could be implicated in disease susceptibility or could further improve matching of patient and donor transplant compatibility.

Mindrinos is associate director of the **Stanford Genome Technology Center**. The paper also included researchers from the university and the **Howard Hughes Medical Institute**.

The team developed primers to sequence the *major histocompatibility complex class I A* (*HLA-A*), *HLA-B*, *HLA-C* and *major histocompatibility complex class II DR β1* (*HLA-DRB1*) genes.

Sequencing the amplified DNA matched 99% of reference DNA samples from 40 cell lines with known HLA genotypes. In 59 clinical samples, sequencing determined HLA genotype and identified 3 new HLA alleles—2 previously undetected short insertions and 1 single base pair deletion. Genotyping of a few samples can be done within five days.

Mindrinos said the benefits of his sequencing technology are "higher resolution, lower cost and higher throughput. This technology has reduced the cost of HLA typing and improved its accuracy such that it can soon be part of a standard patient profile, equivalent to a blood type." He told *SciBX* that the method is less expensive because it can analyze more than 2,000 samples per instrument run, which is over 1,000 samples more than competing high throughput sequencing technology.

According to Mindrinos, applications of the technology include matching transplantations, evaluating responses in clinical trials of therapeutics and vaccines, and conducting disease association studies. His group is now working to extend the HLA genotyping method to cover the four other *HLA* genes.

He said Stanford University is filing a patent application. The technology is unavailable for licensing. —*LM*

In isolated T cell lines from healthy HLA-B 5701 donors, culture with abacavir plus peptides that bound HLA-B 5701 only in the presence of the drug induced T cell activation, whereas abacavir alone did not activate T cells.

Crystallization studies of abacavir with the HLA alleles and self peptides showed the drug noncovalently bound and altered the shape of the peptide-binding site.

In a separate paper published in May in *AIDS*, an FDA-led team came to a similar conclusion about abacavir's mechanism of HLA-related drug autoimmunity. The group found that abacavir noncovalently bound HLA-B 5701 to alter the antigen-binding site and allow the presentation of self antigens.

"HLA genotyping technology will allow us to identify patients with certain types of HLA alleles that may be susceptible to drug interactions and will allow us to screen patient populations. This could help guide clinical trial design and patient selection for particular drugs."

—Michael Norcross, Food and Drug Administration

To determine whether the phenomenon occurred in other HLA-drug interactions, the Australian team replicated the studies with HLA-B 1502 alleles and carbamazepine. Indeed, the drug bound noncovalently to the antigen-binding cleft and altered the HLA peptide repertoire by about 15%.

Purcell told *SciBX*, "We are currently investigating other drug hypersensitivity reactions that are strongly associated with different HLA haplotypes. The potential of other small molecules to also modulate immune responses via a similar mechanism is a focus of ongoing research."

Michael Norcross, lead author on the *AIDS* paper and lead research investigator at the FDA's Center for Drug Evaluation and Research, told *SciBX* that next steps for the team include developing assays that cover all of the HLA types in the general human population and studying the impact of other drugs on those HLAs to see if any induce changes in the binding sites, the self peptides recognized and the T cell response.

Norcross cautioned that a drug's interaction with HLA molecules does not tell the entire story because not all people with HLA alleles linked to drug reactions actually have the reactions. Thus, future research is required to identify the other factors that determine whether a patient will develop an adverse reaction.

"HLA genotyping technology will allow us to identify patients with certain types of HLA alleles that may be susceptible to drug interactions and will allow us to screen patient populations. This could help guide clinical trial design and patient selection for particular drugs," said Norcross. AIDS patients are currently screened for HLA-B 5701 prior to treatment.

He added, "If we see drugs in development or even approved that change an HLA molecule's structural characteristics, we should further characterize the HLA interactions as a first step. What we do with the known risk of reaction will depend on the frequency and severity of the reactions that occur."

The good news, he said, is it should be possible to identify potential drug-HLA interactions very early in the drug development process. "All that we need to do is look at these molecules in assays to see whether they interact with any forms of HLA," he said. "It would also be very valuable to look for interactions between drug metabolites and HLA molecules."

Purcell said it may be possible to modify existing drugs that carry a risk of severe autoimmune reactions to prevent their binding to HLA molecules.

"The interaction of abacavir with HLA-B 5701 is very specific, and we predict even small changes to the drug may prevent binding to and shifts in the peptide repertoire of this HLA molecule," he said.

The findings by Purcell's team have not been patented and are not available for licensing. Patent and licensing status for the FDA's study is undisclosed.

Martz, L. *SciBX* 5(23); doi:10.1038/scibx.2012.591
Published online June 7, 2012

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   e-mail: michael.norcross@fda.hha.gov
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   Contact: Jamie Rossjohn, Monash University, Clayton, Victoria, Australia
   e-mail: jamie.rossjohn@monash.edu
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   Contact: Michael Mindrinos, Stanford University, Palo Alto, Calif.
   e-mail: mindrinos@stanford.edu
   Contact: Mark M. Davis, same affiliation as above
   e-mail: mmdavis@stanford.edu
   Contact: Ronald W. Davis, same affiliation as above
   e-mail: dbowe@stanford.edu
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COMPANIES AND INSTITUTIONS MENTIONED

Australian Centre for Vaccine Development at the Queensland Institute of Medical Research, Brisbane, Queensland, Australia
Cardiff University School of Medicine, Heath Park, U.K.
Food and Drug Administration, Silver Spring, Md.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Howard Hughes Medical Institute, Chevy Chase, Md.
Monash University, Clayton, Victoria, Australia
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Stanford Genome Technology Center, Stanford, Calif.
Stanford University, Stanford, Calif.
The University of Melbourne, Parkville, Victoria, Australia

This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Cancer	BMX non-receptor tyrosine kinase (BMX; ETK)	Mouse studies suggest inhibiting BMX could help treat cancer. In mouse models of melanoma, lung cancer and colon cancer, Bmx deficiency led to lower tumor growth than normal Bmx expression. In a mouse model of lung cancer, the Bmx deficiency decreased tumor angiogenesis. Next steps could include screening for BMX-specific inhibitors and evaluating them in mouse models of cancer. ***SciBX* 5(23); doi:10.1038/scibx.2012.592** **Published online June 7, 2012**	Patent and licensing status unavailable	Holopainen, T. *et al. Cancer Res.*; published online May 16, 2012; doi:10.1158/0008-5472.CAN-11-1070 **Contact:** Kari Alitalo, University of Helsinki, Helsinki, Finland e-mail: kari.alitalo@helsinki.fi
Cancer	Indoleamine 2,3-dioxygenase 1 (IDO1)	*In vitro* studies identified an IDO1 inhibitor that could help treat cancer. In SAR studies and in IDO1-expressing human and murine cells, a lead phenyltriazole analog was identified as a selective, nanomolar inhibitor of IDO1. Planned studies include testing the compound in mice with murine mast cell tumors. iTeos Therapeutics S.A. has undisclosed IDO (INDO) inhibitors in preclinical development for cancer. 1-Methyl-D-tryptophan (D-1MT), an IDO inhibitor from NewLink Genetics Corp., is in Phase Ib/II testing to treat solid tumors. INCB24360, an IDO inhibitor from Incyte Corp., is in Phase I testing to treat solid tumors. ***SciBX* 5(23); doi:10.1038/scibx.2012.593** **Published online June 7, 2012**	Patented by the Ludwig Institute for Cancer Research and the Swiss Institute of Bioinformatics; licensed to iTeos	Röhrig, U.F. *et al. J. Med. Chem.*; published online May 22, 2012; doi:10.1021/jm300260v **Contact:** Olivier Michielin, Swiss Institute of Bioinformatics, Lausanne, Switzerland e-mail: olivier.michielin@isb-sib.ch **Contact:** Vincent Zoete, same affiliation as above e-mail: vincent.zoete@isb-sib.ch
Cancer	Silver homolog (SILV; PMEL17; GP100)	*In vitro* and mouse studies suggest PMEL17 could be a target for melanoma antibody-drug conjugate (ADC) therapy. In melanoma cell lines, a PMEL17-targeting antibody conjugated to the antimitotic reagent monomethyl auristatin E led to cell death, with increased potency correlating with higher levels of PMEL17 expression on the melanoma cells. In mice with human PMEL17-expressing melanoma xenografts, the ADC therapy decreased tumor growth compared with a control ADC therapy or vehicle. Next steps include safety studies in two animal species. ***SciBX* 5(23); doi:10.1038/scibx.2012.594** **Published online June 7, 2012**	Patent application filed; unavailable for licensing	Chen, Y. *et al. J. Biol. Chem.*; published online May 21, 2012; doi:10.1074/jbc.M112.361485 **Contact:** Paul Polakis, Genentech Inc., South San Francisco, Calif. e-mail: ppolakis@gene.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Multiple myeloma (MM)	CC chemokine receptor 1 (CCR1; CD191)	Mouse studies identified a CCR1 antagonist that could help treat MM and associated osteolytic bone disease. In a mouse model of MM, prophylactic or therapeutic administration of the CCR1 antagonist CCX721 decreased both tumor burden and osteolytic bone damage compared with vehicle control and had an effect comparable to that of Aclasta zoledronic acid. ChemoCentryx Inc. did not disclose next steps, which could include testing CCX721 in additional animal cancer models. ChemoCentryx and GlaxoSmithKline plc's CCX345, a CCR1 antagonist that is an analog of CCX721, is in Phase II testing to treat rheumatoid arthritis (RA). Novartis AG markets Aclasta zoledronic acid for multiple indications including osteoporosis and bone cancer. ***SciBX*** **5(23); doi:10.1038/scibx.2012.595** **Published online June 7, 2012**	Patent applications filed; licensed by GlaxoSmithKline	Dairaghi, D.J. *et al. Blood*; published online May 22, 2012; doi:10.1182/blood-2011-10-384784 **Contact:** Daniel J. Dairaghi, ChemoCentryx Inc., Mountain View, Calif. e-mail: ddairaghi@chemocentryx.com
Non–small cell lung cancer (NSCLC)	Epidermal growth factor receptor (EGFR); c-Met proto-oncogene (MET; HGFR)	Mouse studies suggest combining EGFR and MET inhibitors could help treat drug-resistant NSCLC. Mutations in EGFR and amplifications in MET are associated with resistance to EGFR inhibitors. In mice with lung tumors caused by lung-specific genetic amplification of *Met* and mutated *Egfr*, an EGFR inhibitor plus a MET inhibitor increased tumor regression compared with either treatment alone. Next steps could include testing the combination therapy in additional animal models. At least 24 companies have EGFR inhibitors in development stages ranging from preclinical to marketed to treat cancer. At least four companies have MET inhibitors in clinical and preclinical testing to treat cancer. ***SciBX*** **5(23); doi:10.1038/scibx.2012.596** **Published online June 7, 2012**	Patent and licensing status unavailable	Xu, L. *et al. Cancer Res.*; published online May 2, 2012; doi:10.1158/0008-5472.CAN-11-3720 **Contact:** Kwok-Kin Wong, Dana-Farber Cancer Institute, Boston, Mass. e-mail: kwong1@partners.org
Prostate cancer	Myeloid/lymphoid or mixed-lineage leukemia 2 (MLL2)	Patient sample and cell culture studies suggest inhibiting MLL2 could help treat prostate cancer. Exome sequencing of tumor tissue from patients with castration-resistant prostate cancer identified recurrent mutations in *MLL2*. In a human prostate cancer cell line, MLL2 and other MLL (HRX)-complex members interacted directly with the androgen receptor, which is a known disease target. In the cells, small interfering RNA against MLL2 decreased androgen receptor signaling compared with control siRNA. Next steps include testing compounds that target the MLL complex in preclinical models of prostate cancer. At least 11 companies have androgen receptor antagonists in development stages from preclinical to marketed for prostate cancer. ***SciBX*** **5(23); doi:10.1038/scibx.2012.597** **Published online June 7, 2012**	Patent application filed covering diagnostic applications; available for licensing	Grasso, C.S. *et al. Nature*; published online May 20, 2012; doi:10.1038/nature11125 **Contact:** Arul M. Chinnaiyan, University of Michigan, Ann Arbor, Mich. e-mail: arul@umich.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	Speckle-type POZ protein (SPOP)	Patient sample and cell culture studies suggest *SPOP* could be useful as a marker for patient stratification and a therapeutic target in prostate cancer. SPOP encodes a subunit of a cullin-based E3 ubiquitin ligase. Sequencing of patient primary prostate tumor samples identified *SPOP* mutations in 13% of the tumors. In cultured human prostate cancer cells, expression of the most frequently identified *SPOP* mutant or SPOP-targeted siRNA led to greater invasiveness than expression of wild-type *SPOP* or nontargeted siRNA. Next steps could include identifying compounds that modulate mutant *SPOP* activity or show efficacy against *SPOP* mutant prostate cancer. ***SciBX* 5(23); doi:10.1038/scibx.2012.598** **Published online June 7, 2012**	Patent and licensing status unavailable	Barbieri, C.E. *et al. Nat. Genet.*; published online May 20, 2012; doi:10.1038/ng.2279 **Contact:** Levi A. Garraway, Dana-Farber Cancer Institute, Boston, Mass. e-mail: levi_garraway@dfci.harvard.edu
Renal cancer	DnaJ (Hsp40) homolog subfamily B member 8 (DNAJB8)	*In vitro* and mouse studies suggest blocking DNAJB8 on cancer stem cells could help treat renal cell carcinoma. In renal carcinoma cell lines, anti-DNAJB8 small interfering RNA eliminated the cancer stem cell population and decreased tumor-initiating ability compared with siRNA controls. In mice, immunization with Dnajb8 led to a greater antitumor effect against renal cell carcinomas than immunization with survivin (BIRC5), a tumor antigen expressed on both cancer stem cells and noncancer stem cells. Next steps could include testing the vaccination strategy in additional animal models. ***SciBX* 5(23); doi:10.1038/scibx.2012.599** **Published online June 7, 2012**	Patent and licensing status unavailable	Nishizawa, S. *et al. Cancer Res.*; published online May 2, 2012; doi:10.1158/0008-5472.CAN-11-3062 **Contact:** Yoshihiko Hirohashi, Sapporo Medical University, Sapporo, Japan e-mail: hirohash@sapmed.ac.jp
Skin cancer	Not applicable	Mouse studies suggest fat removal surgery could help treat and prevent skin cancer in obese subjects. High-fat diets and a high BMI are associated with increased risk of skin cancer. In mice fed a high-fat diet, removal of parametrial fat pads decreased the size and number of UVB-induced skin tumors compared with no fat pad removal. In the same mice, removal of parametrial fat pads led to lower proliferation and greater apoptosis in skin tumors than what was seen in sham-operated controls. Next steps include determining whether obese individuals that have received fat removal surgery have reduced risk of developing skin cancers. ***SciBX* 5(23); doi:10.1038/scibx.2012.600** **Published online June 7, 2012**	Unpatented; available for licensing	Lu, Y.-P. *et al. Proc. Natl. Acad. Sci. USA*; published online May 21, 2012; doi:10.1073/pnas.1205810109 **Contact:** Allan H. Conney, Rutgers University, Piscataway, N.J. e-mail: aconney@pharmacy.rutgers.edu **Contact:** Yao-Ping Lu, same affiliation as above e-mail: sago@pharmacy.rutgers.edu
Cardiovascular disease				
Cardiovascular disease	Cardiolipin synthase 1 (CRLS1; CLS)	Mouse studies suggest increasing CLS activity could help prevent diabetes-associated heart failure. In a mouse model of streptozotocin-induced diabetes, transgenic Cls expression decreased diabetes-associated maladaptive myocardial remodeling and dysfunction of cardiac mitochondria compared with wild-type Cls expression. Next steps could include screening for compounds that increase CLS activity. ***SciBX* 5(23); doi:10.1038/scibx.2012.601** **Published online June 7, 2012**	Patent and licensing status unavailable	Kiebish, M.A. *et al. J. Biol. Chem.*; published online May 14, 2012; doi:10.1074/jbc.M112.340521 **Contact:** Richard W. Gross, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: rgross@wustl.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Dermatology				
Itch	Toll-like receptor 3 (TLR3)	Studies in mice suggest antagonizing TLR3 could help treat itching. In a mouse model of chemically induced pruritus, global *Tlr3* knockout or *Tlr3* knockout only in the dorsal root ganglia led to lower levels of itch than no knockout. Next steps include testing the effects of TLR3 antagonists in mice. ***SciBX* 5(23); doi:10.1038/scibx.2012.602** **Published online June 7, 2012**	Patent pending; available for licensing from Brigham and Women's Hospital **Contact:** Arlene Parquette, Brigham and Women's Hospital, Boston, Mass. e-mail: aparquette@partners.org	Liu, T. *et al. J. Clin. Invest.*; published online May 8, 2012; doi:10.1172/JCI45414 **Contact:** Ru-Rong Ji, Duke University School of Medicine, Durham, N.C. e-mail: ru-rong.ji@duke.edu
Endocrine/metabolic disease				
Diabetes	MAP kinase kinase kinase 14 (MAP3K14; NIK)	Mouse studies suggest inhibiting NIK in the liver could help treat type 2 diabetes. In mouse models of high-fat diet–induced and leptin deficiency–induced obesity, Nik activity in the liver was greater than that in mice with normal diets and in nondeficient mice. Next steps include identifying small molecules that target NIK in the liver. ***SciBX* 5(23); doi:10.1038/scibx.2012.603** **Published online June 7, 2012**	Unpatented; unavailable for licensing	Sheng, L. *et al. Nat. Med.*; published online May 13, 2012; doi:10.1038/nm.2756 **Contact:** Liangyou Rui, University of Michigan Medical School, Ann Arbor, Mich. e-mail: ruily@umich.edu
Infectious disease				
Amebiasis	Not applicable	*In vitro*, mouse and hamster studies suggest auranofin could be repurposed to treat amebiasis, a disease caused by infection with the protozoa *Entamoeba histolytica*. A high throughput screen for compounds that inhibit *E. histolytica* identified the rheumatoid arthritis (RA) drug auranofin. *In vitro* assays showed auranofin was 10 times more potent against *E. histolytica* than the current standard therapy metronidazole. In a mouse model of amebic colitis and a hamster model of amebic liver abscess, oral auranofin decreased parasite burden, inflammatory response and liver damage compared with oral metronidazole or saline control. Next steps include clinical testing. Prometheus Laboratories Inc. markets Ridaura auranofin to treat RA. Pfizer Inc. markets Flagyl metronidazole to treat giardiasis, *Clostridium difficile*–associated diarrhea (CDAD) and other bacterial and parasitic infections. ***SciBX* 5(23); doi:10.1038/scibx.2012.604** **Published online June 7, 2012**	Patent application filed; available for licensing	Debnath, A. *et al. Nat. Med.*; published online May 20, 2012; doi:10.1038/nm.2758 **Contact:** Anjan Debnath, University of California, San Francisco, Calif. e-mail: anjan.debnath@ucsf.edu
Malaria	*Plasmodium falciparum* calcium-dependent protein kinase 4 (PfCDPK4; PF07_0072)	Studies in cell culture, mosquitoes and mice suggest antagonizing PfCDPK4 could be useful for preventing transmission of malaria to mosquitoes. In a mouse model of malaria, a small molecule inhibitor of PfCDPK4 decreased *P. falciparum* gamete formation and infection of mosquitoes compared with vehicle. Next steps include toxicological testing of the lead compound in large animal models of malaria. ***SciBX* 5(23); doi:10.1038/scibx.2012.605** **Published online June 7, 2012**	Patent pending; available for licensing	Ojo, K.K. *et al. J. Clin. Invest.*; published online May 8, 2012; doi:10.1172/JCI61822 **Contact:** Kayode K. Ojo, University of Washington, Seattle, Wash. e-mail: ojo67kk@u.washington.edu **Contact:** Wesley C. Van Voorhis, same affiliation as above e-mail: wvanvoorhis@medicine.washington.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Inflammation	MicroRNA-181b (miR-181b)	Patient sample and mouse studies suggest agonizing miR-181b could help treat inflammation. In a mouse model of endotoxic shock, miR-181b mimics decreased NF-κB–mediated vascular inflammation and lung injury and increased survival compared with control miRNA. In plasma samples from patients with sepsis, miR-181b levels were lower than those in samples from patients without sepsis. Next steps include testing miR-181b mimics in mouse models of chronic inflammation. ***SciBX* 5(23); doi:10.1038/scibx.2012.606** **Published online June 7, 2012**	U.S. and international patent applications pending covering use of miR-181b mimics in acute and chronic inflammation; available for licensing	Sun, X. *et al. J. Clin. Invest.*; published online May 24, 2012; doi:10.1172/JCI61495 **Contact:** Mark W. Feinberg, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. e-mail: mfeinberg@rics.bwh.harvard.edu
Inflammation	p38 Mitogen-activated protein kinase (p38 MAPK; MAPK14)	Mouse studies suggest inhibiting p38 MAPK in dendritic cells (DCs) could help treat inflammation. p38 MAPK inhibition has known anti-inflammatory effects but also has proinflammatory side effects such as allergic skin disease. In a mouse model of allergic skin disease, knockout of *p38 Mapk* in keratinocytes or myeloid cells led to increased allergic skin reactions compared with normal *p38 Mapk* expression, whereas knockout in DCs led to decreased allergic skin reactions. Next steps include developing a DC-selective drug delivery vehicle for p38 MAPK inhibitors. At least nine companies have p38 MAPK inhibitors in clinical and preclinical testing for multiple indications. ***SciBX* 5(23); doi:10.1038/scibx.2012.607** **Published online June 7, 2012**	Findings unpatented; available for licensing	Ritprajak, P. *et al. Proc. Natl. Acad. Sci. USA*; published online May 21, 2012; doi:10.1073/pnas.1202984109 **Contact:** Jin Mo Park, Massachusetts General Hospital and Harvard Medical School, Charlestown, Mass. e-mail: jmpark@cbrc2.mgh.harvard.edu
Musculoskeletal disease				
Musculoskeletal disease	Adenosine A_{2A} receptor ($ADORA_{2A}$)	Mouse and cell culture studies suggest activating $ADORA_{2A}$ could help prevent joint implant failure. Inflammation- and osteoblast-mediated bone resorption cause prostheses loosening, which leads to implant failure. In mice, an $ADORA_{2A}$ agonist decreased particle-induced bone loss, inflammation and osteoclast numbers compared with saline. In human bone marrow samples, the agonist inhibited osteoclast differentiation. Next steps include incorporating $ADORA_{2A}$ agonists into joint implants. Lexiscan, a short-acting $ADORA_{2A}$ agonist from Gilead Sciences Inc. and Astellas Pharma Inc., is marketed as a cardiovascular imaging agent. CorVue binodenoson for injection, a selective $ADORA_{2A}$ agonist from Pfizer Inc., is under review as a cardiovascular imaging agent. At least seven other companies have $ADORA_{2A}$ agonists in Phase III testing or earlier to treat various indications. ***SciBX* 5(23); doi:10.1038/scibx.2012.608** **Published online June 7, 2012**	Patented; available for licensing	Mediero, A. *et al. Sci. Transl. Med.*; published online May 23, 2012; doi:10.1126/scitranslmed.3003393 **Contact:** Bruce N. Cronstein, New York University School of Medicine, New York, N.Y. e-mail: bruce.cronstein@nyumc.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Epilepsy; seizures	BCL2-associated agonist of cell death (BAD)	Mouse studies suggest inhibiting BAD-mediated glucose metabolism could help prevent seizures. In mice, Bad knockout or expression of a mutant Bad protein with impaired ability to mediate glucose metabolism led to less sensitivity to seizure-inducing agents and lower seizure severity compared with those seen in wild-type mice. Next steps include studies to determine if acute BAD modulation in the brain can modify seizure responses. *SciBX* 5(23); doi:10.1038/scibx.2012.609 Published online June 7, 2012	Unpatented; licensing status not applicable	Giménez-Cassina, A. *et al. Neuron*; published online May 24, 2012; doi:10.1016/j.neuron.2012.03.032 **Contact:** Nika N. Danial, Harvard Medical School, Boston, Mass. e-mail: nika_danial@dfci.harvard.edu **Contact:** Gary Yellen, same affiliation as above e-mail: gary_yellen@hms.harvard.edu

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Chemistry			
A two-step process for generating bispecific antibodies using unnatural amino acids	A two-step process for generating bispecific antibodies with unnatural amino acids could help optimize production. Two distinct Fab fragments were each engineered to incorporate single unnatural p-acetylphenylalanine residues, which were then coupled to linkers and conjugated to form a bispecific antibody. The two-step approach was used to generate an antibody that targets HER2 (EGFR2; ERBB2; neu) and CD3, an epitope expressed on cytotoxic T lymphocytes. In cocultures of human peripheral blood mononuclear cells with HER2-positive and HER2-negative human breast cancer cell lines, the bispecific antibody led to selective lysis of $HER2^{+}$ cells at picomolar concentrations. Next steps include using the approach to generate other bispecific antibodies. Amgen Inc.'s Blinatumomab, a bispecific T cell engager (BiTE) that binds CD19 and CD3, is in Phase II testing for relapsed or refractory acute lymphoblastic leukemia ALL. *SciBX* 5(23); doi:10.1038/scibx.2012.610 Published online June 7, 2012	Patent and licensing status undisclosed	Kim, C.H. *et al. J. Am. Chem. Soc.*; published online May 26, 2012; doi:10.1021/ja303904e **Contact:** Peter G. Schultz, The Scripps Research Institute, La Jolla, Calif. e-mail: schultz@scripps.edu **Contact:** Vaughn V. Smider, same affiliation as above e-mail: vvsmider@scripps.edu
Computational models			
Method for quantifying somatic DNA alterations in tumors to guide treatment decisions	A computational method for quantifying DNA alterations in tumors may help determine whether a mutation occurs in all or only a subset of cancer cells, which could guide treatment decisions. The computational model collects genomic information from a mixture of cancerous and noncancerous cells, as occurs during a biopsy, and determines the fraction of cancer cells containing a given mutation. In more than 2,000 tumor biopsies across multiple cancer types, the method determined the tumor cell purity and detected point mutations. Next steps include longitudinal studies to look at patient response to targeted therapies against particular mutations. *SciBX* 5(23); doi:10.1038/scibx.2012.611 Published online June 7, 2012	Patent and licensing status unavailable	Carter, S.L. *et al. Nat. Biotechnol.*; published online April 29, 2012; doi:10.1038/nbt.2203 **Contact:** Gad Getz, The Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: gadgetz@broadinstitute.org **Contact:** Scott L. Carter, same affiliation as above e-mail: scarter@broadinstitute.org
Disease models			
Mouse model of blast-induced neurotrauma	A mouse model that mimics bomb blasts experienced by soldiers could be useful for identifying and testing compounds to treat chronic traumatic encephalopathy (CTE), a neurodegenerative disease associated with repeated concussions. In the model, wild-type mice were subjected to a single high-pressure blast of air that caused brief, rapid head accelerations without killing the mice or causing overt tissue damage. Immunohistological and microscopic studies of mouse brain tissue showed significant neuropathological damage following the single blast, including phosphorylated microtubule-associated protein-τ (MAPT; TAU; FTDP-17) aggregates. The pathology also was associated with CTE-like learning and memory deficits in the mice. Next steps include using the model to identify therapies for CTE (*see* **Blasted brain, page 5**). *SciBX* 5(23); doi:10.1038/scibx.2012.612 Published online June 7, 2012	Unpatented; licensing status not applicable	Goldstein, L.E. *et al. Sci. Transl. Med.*; published online May 16, 2012; doi:10.1126/scitranslmed.3003716 **Contact:** Lee E. Goldstein, Boston University School of Medicine, Boston, Mass. e-mail: lgold@bu.edu **Contact:** Ann C. McKee, same affiliation as above e-mail: amckee@bu.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Hydrogen peroxide–inactivated viral vaccines	*In vitro* and mouse studies suggest hydrogen peroxide–inactivated viral vaccines could be used to prevent viral infections. Antibodies from mice inoculated with hydrogen peroxide–inactivated yellow fever virus showed greater antigenicity than those obtained from mice inoculated with formaldehyde- or β-propiolactone–inactivated virus. In mice, inoculation with hydrogen peroxide–inactivated vaccinia virus or West Nile virus increased neutralizing antibody titers and survival after viral challenge compared with inoculation using formaldehyde- or UV-inactivated viruses. Ongoing work includes developing improved flavivirus vaccines and cGMP manufacturing of hydrogen peroxide–inactivated vaccines against yellow fever virus, West Nile virus and dengue virus. ***SciBX*** **5(23); doi:10.1038/scibx.2012.613** **Published online June 7, 2012**	Patented; licensed to Najit Technologies Inc.; available for partnering and licensing from Najit	Amanna, I.J. *et al. Nat. Med.*; published online May 27, 2012; doi:10.1038/nm.2763 **Contact:** Mark K. Slifka, Oregon Health & Science University, Portland, Ore. e-mail: slifkam@ohsu.edu
Protocol for generating functional cardiomyocytes from human pluripotent stem cells	A protocol to generate cardiomyocytes from human pluripotent stem cells could be useful for producing cell replacement therapies. The cardiomyocyte-generating protocol involves treating human pluripotent stem cells with small molecule inhibitors of glycogen synthase kinase 3β (GSK3B) prior to differentiation and small molecule inhibitors of wingless-type MMTV integration site (WNT) signaling during differentiation. The protocol generated functional cardiomyocytes at yields of up to 98%. Next steps include optimizing the protocol to generate cardiomyocytes with mature, adult-like phenotypes and scaling up the approach. ***SciBX*** **5(23); doi:10.1038/scibx.2012.614** **Published online June 7, 2012**	Patent application filed; available for licensing	Lian, X. *et al. Proc. Natl. Acad. Sci. USA*; published online May 28, 2012; doi:10.1073/pnas.1200250109 **Contact:** Sean Palecek, University of Wisconsin–Madison, Madison, Wis. e-mail: palecek@engr.wisc.edu
Specific and noncovalent binding of small molecule therapeutics to human leukocyte antigen (HLA) polymorphisms alters peptide antigen presentation	*In vitro* studies identified a mechanism for drug-related autoimmune reactions that could aid the design of safer therapeutics. In cells expressing the HLA-B 5701 polymorphism, which has been linked to abacavir hypersensitivity syndrome, the drug bound to the HLA antigen-binding site, prevented binding of normal antigens and induced binding of self antigens. This led to generation of T cells that targeted the self antigens. In cells expressing the HLA-B 1502 polymorphism, which has been linked to the drug reaction–associated condition Stevens-Johnson syndrome, the HLA-drug interaction and altered peptide binding also were observed. Next steps include studying other drug hypersensitivity reactions associated with HLA haplotypes (*see* **HLA in sequence, page 7**). ***SciBX*** **5(23); doi:10.1038/scibx.2012.615** **Published online June 7, 2012**	Findings unpatented; unavailable for licensing	Illing, P.T. *et al. Nature*; published online May 23, 2012; doi:10.1038/nature11147 **Contact:** Jamie Rossjohn, Monash University, Clayton, Victoria, Australia e-mail: jamie.rossjohn@monash.edu
Markers			
Catalog of rare genetic variants	A human genetic study has identified a catalog of rare genetic variants that could influence disease. In 2,440 European and African individuals, 15,585 protein-coding genes were sequenced. Analysis of the sequencing data showed that each subject had an average of 150 function-altering gene variants compared with a reference human genome sequence. In the cohort, 82% of the variants were unique to the individual in which they were found. Next steps include determining how rare variants in known disease genes affect disease susceptibility. ***SciBX*** **5(23); doi:10.1038/scibx.2012.616** **Published online June 7, 2012**	Unpatented; licensing status not applicable	Tennessen, J.A. *et al. Science*; published online May 17, 2012; doi:10.1126/science.1219240 **Contact:** Joshua M. Akey, University of Washington, Seattle, Wash. e-mail: akeyj@uw.edu **Contact:** Michael J. Bamshad, same affiliation as above e-mail: mbamshad@u.washington.edu

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