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Inhibitor MEKanism

By Benjamin Boettner, Assistant Editor

Roche's Genentech Inc. unit has figured out why different MEK inhibitors exhibit varying efficacy against BRAF- or K-Ras-driven cancers, which could help in the design of next-generation inhibitors with improved therapeutic indexes.¹ Genentech already has one inhibitor for each kind of tumor in clinical trials.

Mutations in the *K-Ras* (*KRAS*) and *BRAF* genes are responsible for overactivation of the Ras-Raf-MEK-MAPK pathway in many cancers. MEK is a key component of this signaling cascade, but for unknown reasons *BRAF*-mutant tumors thus far have been more sensitive than *KRAS*-mutant tumors to MEK inhibitors.²

One hypothesis is that *BRAF* and *KRAS* interact differently with MEK. Oncogenic *BRAF* phosphorylates MEK directly, whereas *KRAS* acts upstream to activate Raf kinases and other tumorigenic effectors such as phosphoinositide 3-kinase (PI3K).

Consequently, *BRAF*-mutant cancer cells have higher basal levels of phosphorylated MEK than *KRAS*-mutant cells, rendering the former more sensitive to MEK inhibitors³ (see Figure 1, "Targeting MEK in cancer").

Genentech researchers have now taken a closer look at why three of their inhibitors—cobimetinib (GDC-0973), GDC-0623 and G-573—exhibit differential efficacy. The former is most effective in *BRAF*-mutant cancer cell lines, whereas the latter two show better results in *KRAS*-mutant cells.

GDC-0973 was discovered by Exelixis Inc. and is partnered with Genentech. The molecule is in Phase III trials for melanoma. GDC-0623 and G-573 were discovered at Genentech. GDC-0623, the more potent of the two, is in Phase I testing for solid tumors.

Using a combination of structural, biochemical and physiological data, a team led by Georgia Hatzivassiliou and Marcia Belvin showed that the compounds interacted with MEK in very different ways.

Hatzivassiliou is a scientist and Belvin is associate director of translational oncology at Genentech.

All three compounds are allosteric MEK inhibitors that do not compete with ATP for the kinase's active site but rather bind to an adjacent activation loop. The compounds do so in different ways. GDC-0973 hits a conformation of the loop that is induced by *BRAF*-mediated MEK phosphorylation. GDC-0623 and G-573 bind to unphosphorylated MEK at the Ser-212 residue and prevent MEK phosphorylation by wild-type Raf.

GDC-0973 showed more inhibition than GDC-0623 or G-573 in mouse xenografts of melanoma or colon cancer harboring a mutated *BRAF* allele. In contrast, GDC-0623 and G-573 showed better results



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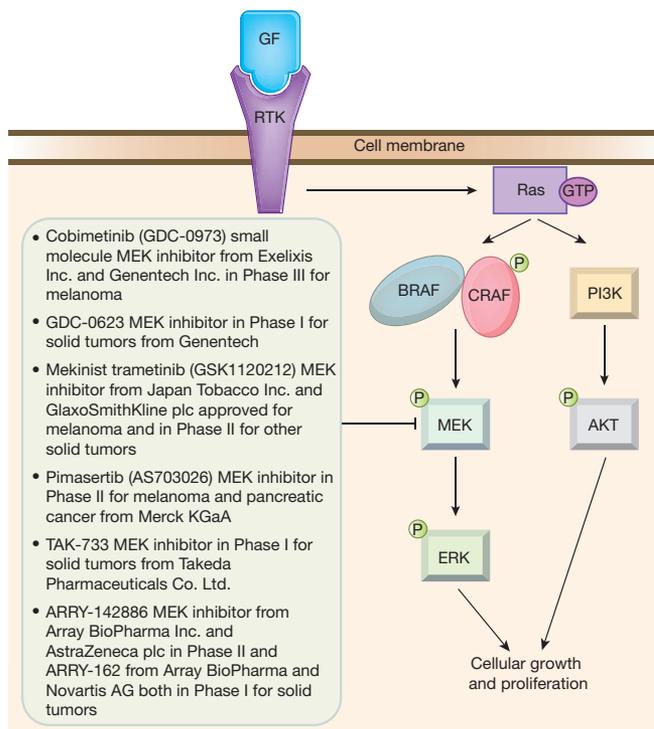


Figure 1. Targeting MEK in cancer. According to findings published in *Nature*, two classes of MEK inhibitors exhibit different effects in *K-Ras* (*KRAS*)- and *BRAF*-mutant backgrounds. In cancer cells, *BRAF* or *Ras* proteins often acquire activating mutations that allow them to become independent of growth factor (GF) and receptor tyrosine kinase (RTK) function and to overstimulate their downstream signaling elements. *BRAF* strongly phosphorylates and activates MEK as its primary downstream target. *KRAS* activates MEK less strongly than *BRAF* but also drives phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB; PKBA; AKT; AKT1) signaling. MEK-ERK and PI3K-AKT signaling can cooperate to promote cancer cell proliferation.

In cancer cells that develop resistance to *BRAF* inhibitors like Zelvora[®] vemurafenib, *BRAF* trans-activates wild-type *CRAF* (*RAF1*), and the *BRAF*-*CRAF* complex is further stimulated by elevated *Ras* activity. *Ras* activity can be enhanced by *de novo* mutation of *neuroblastoma Ras viral (v-Ras) oncogene (NRAS)* or hyperactive RTKs.

than GDC-0973 in *KRAS*-mutant pancreatic or lung adenocarcinoma xenografts.

The findings were published in *Nature*.

According to Hatzivassiliou, the results point to the need for assessing the impact of *BRAF* and *KRAS* mutation status on clinical efficacy of individual allosteric MEK inhibitors.

“Conclusions with one inhibitor don’t necessarily translate to conclusions about MEK as a target in general. For example, past clinical trials with MEK inhibitors that didn’t demonstrate strong clinical efficacy need to be revisited with new compounds with known mechanisms of action,” she said.

Kevin Koch, president and CSO of **Array BioPharma Inc.**, told *SciBX*

that “this is one of the nicest examples of drug discovery where chemical structure is related to target structure. At a high level there are not many examples where minor changes in drug interactions with their targets are shown to create novel biology resulting in different drug efficacies.”

Array’s MEK inhibitors for solid tumors include ARRY-142886, which is in Phase II testing and is partnered with **AstraZeneca plc**, and ARRY-162, which is in Phase I trials and is partnered with **Novartis AG**.

Levi Garraway, an associate professor at **Harvard Medical School**, an assistant professor at the **Dana-Farber Cancer Institute** and a principal investigator at the **Broad Institute of MIT and Harvard**, said that the study may open up more fine-tuned therapeutic approaches to BRAF- and KRAS-driven cancers.

“This preclinical study should definitely heighten interest in clinical trials for MEK inhibitors. There is the potential that distinctions made in the work could eventually lead to cancer drugs that offer additional treatment options to the ones available right now,” said Garraway.

Gaining traction

In addition to helping fine-tune patient selection, the study’s mechanistic insights could spur the development of MEK inhibitors with improved efficacy.

According to Garraway, “The findings reveal new binding mechanisms and may offer a new pharmacological rationale for a subset of MEK inhibitors that could provide a way to get traction in KRAS-mutant cancers. Of course, it will be crucial to find out whether so-called KRAS-selective MEK inhibitors have any activity in patients carrying KRAS-mutant tumors.”

Gary Johnson, chair of the Department of Pharmacology at **The University of North Carolina**

at **Chapel Hill School of Medicine**, told *SciBX* that “increasing the allosteric selectivity through high-affinity interactions like those described with Ser-212 in this study is predicted to ensure greater selectivity of these kinase inhibitors. Moreover, the unique contacts formed may further increase the durability of inhibitor responses by slowing the dissociation of the inhibitor compound from its target kinase.”

Koch said that it will be important to explore different MEK inhibitor categories across multiple tumor types.

Another important question is whether inhibitors with efficacy in KRAS-mutant cancers can interfere with the growth of BRAF-mutant tumors resistant to Zelboraf vemurafenib, an oral small molecule inhibitor of the oncogenic BRAF V600E. BRAF-mutant cancers that are resistant to BRAF inhibitors could be targeted by MEK inhibitors that are particularly active in a KRAS-mutant background.

For example, Zelboraf resistance arises when mutant BRAF forms a complex with wild-type CRAF (RAF1). CRAF’s kinase activity is triggered by Ras overactivity, which originates with *de novo* mutations

of the KRAS homolog *neuroblastoma Ras viral (v-Ras) oncogene (NRAS)* or elevated receptor tyrosine kinase (RTK) activity⁴ (see **Figure 1**, “**Targeting MEK in cancer**”).

Roche has rights to Zelboraf from Plexxikon Inc., which **Daiichi Sankyo Co. Ltd.** acquired in 2011.

Lee Graves told *SciBX*, “It would make sense to test KRAS-specific MEK inhibitors against BRAF inhibitor-resistant melanomas since they appear to depend on high Ras activity. My prediction is that these may be superior to the MEK inhibitors exhibiting comparatively higher activities in BRAF-mutant backgrounds.”

Graves is an associate professor in the Department of Pharmacology at the UNC at Chapel Hill School of Medicine.

Garraway agreed. “The addition of MEK inhibitors with elevated potential in NRAS-mutant conditions may conceivably help prevent escape from mutant BRAF inhibition and the development of resistance,” he said.

The authors did not disclose patent and licensing status of the findings described in the *Nature* paper.

The most advanced MEK inhibitor is Mekinist trametinib (GSK1120212) from **GlaxoSmithKline plc**. The drug, which GSK in-licensed from **Japan Tobacco Inc.**, is approved for melanoma and is in Phase II testing for other tumor types.

Other MEK inhibitors include **Merck KGaA**’s pimasertib (AS703026), which is in Phase II testing for melanoma and pancreatic cancer, and **Takeda Pharmaceutical Co. Ltd.**’s TAK-733, which is in Phase I trials for solid tumor indications.

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REFERENCES

- Hatzivassiliou, G. *et al. Nature*; published online Aug. 11, 2013; doi:10.1038/nature12441
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- Solit, D.B. *et al. Nature* 439, 358–362 (2006)
- Pratilas, C.A. *et al. Proc. Natl. Acad. Sci. USA* 106, 4519–4524 (2009)
- Poulidakos, P.I. & Rosen, N. *Cancer Cell* 19, 11–15 (2011)

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—Kevin Koch,
Array BioPharma Inc.

Bacteria's painful truth

By C. Simone Fishburn, Senior Editor

In a surprise finding likely to alter how neurologists, immunologists and microbiologists view infection-associated pain, a group at **Boston Children's Hospital** has shown that bacteria can directly trigger action potentials in pain fibers, leading to the release of neuropeptides that suppress the inflammatory response.¹ The findings point to a role for sensory neurons as immune modulators and could provide new bacterial targets for pain.

Until now, the immune system has been considered the primary instigator of pain from bacterial infections. Activation of immune cells triggers the release of inflammatory mediators such as cytokines, growth factors and prostaglandins, which are thought to cause pain by activating receptors on nerve terminals.

More recently, the recognition of bacterial patterns by toll-like receptors (TLRs) on sensory neurons has been pegged as an additional contributing mechanism, although the full picture remains unclear.²

Clifford Woolf and colleagues set out to shed some light on the mechanism by identifying specific inflammatory mediators responsible for acute bacterial pain. Unexpectedly, the team discovered that the pain and inflammatory responses were not coordinated and that the traditional model might not be accurate.

Woolf is director of the F.M. Kirby Neurobiology Center at Boston Children's Hospital and a professor of neurology and neurobiology at **Harvard Medical School**.

"The first major clue something interesting was going on was that the pain occurred out of sync with the immune response," Woolf told *SciBX*.

To identify pain-promoting cytokines active in the acute stage of bacterial infection, the group injected mice with a community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strain linked to wound infections. The group then tracked the timing of pain response, mobilization of inflammatory markers and bacterial load.

The pain response peaked at six hours postinfection, but the mobilization of immune markers such as neutrophils and inflammatory cytokines only started to occur at that time point and reached maximal levels 24–72 hours after infection.

Bacterial concentrations were the sole marker whose time course corresponded with pain, suggesting the organisms themselves may play a role in generating the hypersensitivity response.

To test this, the team applied live or heat-inactivated bacteria directly to dorsal root ganglia neurons, looking for differences that might reveal elements in live bacterial infections that cause pain.

In both cases the researchers detected increases in calcium flux and nerve firing, confirming that bacteria can directly activate sensory nerve fibers (nociceptors).

However, the live and heat-treated bacteria activated different subpopulations of nociceptors, suggesting that distinct heat-stable and heat-sensitive factors might be involved.

Several bacterial strains reproduced the results of CA-MRSA following heat inactivation, including *Streptococcus pneumoniae*, *Helicobacter pylori* and *Pseudomonas aeruginosa*, providing a clue that the heat-stable component might be a common secreted bacterial factor.

The team focused on bacterial N-formylated peptides because they are heat-stable compounds that were recently associated with olfactory sensation.³ The group determined that N-formyl-methionyl-isoleucyl-phenylalanine-leucine (FMIFL) was the heat-resistant factor from *S. aureus* and established that FMIFL interacts with formyl peptide receptor 1 (FPR1) on mechanical nociceptors.

In live dorsal root ganglion cultures, the heat-sensitive bacterial factor that triggered bacterial pain was identified as the pore-forming toxin α -hemolysin (α HL). Although pore-forming toxins have been widely studied as bacterial virulence factors, the new findings are the first demonstration of a role in sensory pain.

The team showed that α HL binds to nerve fibers via the membrane anchor ADAM10, creating pores in the neuronal membrane that cause an influx of calcium and trigger action potential firing.

These action potentials travel along the nerve both toward and away from the spinal cord. Signals that travel toward the spinal cord enter the CNS and send pain messages to the brain, whereas those traveling in the opposite (antidromal) direction stimulate the release of neuropeptides at peripheral nerve terminals (see **Figure 1**, "A dual role for nociceptors").

To determine the role of these neuropeptides, Woolf's team created knockout mice lacking the NaV1.8 (PN3; SCN10A)-lineage

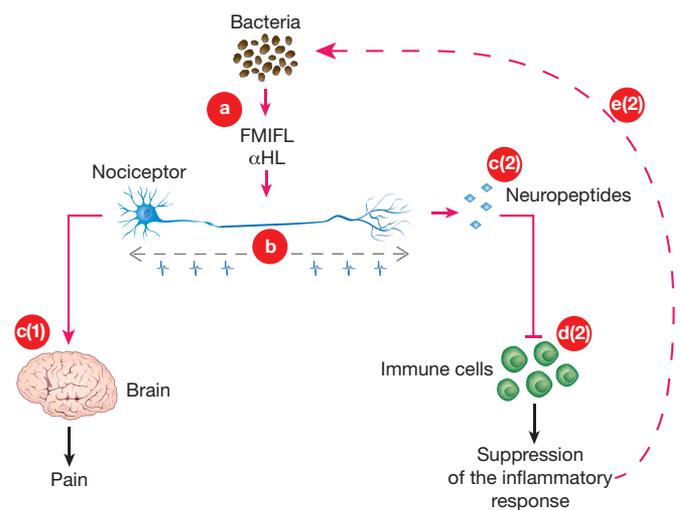


Figure 1. A dual role for nociceptors. Bacteria release factors, such as N-formyl-methionyl-isoleucyl-phenylalanine-leucine (FMIFL) and α -hemolysin (α HL), that directly stimulate nerve fibers [a] and produce action potentials in two directions [b]. In one direction, action potentials travel toward the spinal cord and send pain messages to the brain [c(1)]. In the other direction, they travel toward the periphery, causing the release of neuropeptides [c(2)]. The neuropeptides inhibit the activation of immune cells [d(2)], decreasing their ability to clear the bacteria [e(2)] and showing an immune-suppressive role for nociceptors that accompanies their role in pain transmission.

nociceptors, the main neurons involved in the bacterial pain response. Unexpectedly, this resulted in lymph node enlargement and an increase in tissue swelling and greater numbers of neutrophils and monocytes at the sites of infection compared with no knockout.

That finding led the researchers to conclude that the nociceptors themselves, via the neuropeptides, suppress immune activation.

Through a series of microarray analyses and *in vitro* experiments, the researchers identified three neuropeptides—calcitonin gene-related peptide (CGRP), galanin (GAL) and somatostatin—that are highly expressed in sensory neurons and prevent macrophages from releasing inflammatory cytokines.

Together, the data from the extensive study generated two key findings. The first is that pathogens can directly activate nociceptors. The second is that this activation causes the release of factors that modulate the immune response.

Data were published in *Nature*.

“As a body of work this is a paradigm shift in how bacteria cause pain,” said Michael Gold, a professor of anesthesiology at the **University of Pittsburgh School of Medicine**. “Traditionally, it has been all about recruitment and activation of immune cells, leading to them releasing various factors that act on nerve cells. Now they are showing the bacteria to be the main modulators.”

Victor Nizet agreed and told *SciBX* that the finding that nociceptors serve an immune function at the same time as mediating pain extends beyond neurology. “It’s almost like discovering a new immune cell, the nociceptor,” he said.

Nizet is a professor of pediatrics and pharmacy at the **University of California, San Diego** and specializes in molecular microbiology and innate immunity.

He added, “In addition to skin cells and other epithelial cells that produce molecules that control and kill bacteria, you see that the nociceptor now also participates in the immune response. Understanding this mechanism could lead the way for preventing adverse consequences.”

Painful remedies

The therapeutic targets identified by the paper are the bacterial proteins FMIFL and α HL or their points of entry, FPR1 and ADAM10. However, based on ongoing research, Woolf believes that these may represent only two of several bacterial protein mediators of pain. Thus,

he thinks hitting these targets may have only a limited analgesic effect.

Nonetheless, according to Nizet, the findings provide two new handles for attacking bacteria such as MRSA.

The first is the bacterial virulence factors, in this case α HL, which can be targeted to render the pathogen harmless. Nizet said that this approach has been exploited for antivirals but underutilized for antibacterials, which have relied heavily on traditional antibiotics that kill or inactivate the organisms.

The second handle is the nociceptor, which has immunomodulatory properties. Blocking the release of neuropeptides could remove the brake on the immune system, thus enhancing the local immune response and enabling the body to clear the bacteria, he told *SciBX*.

David Yeomans, an associate professor of anesthesiology and perioperative and pain

medicine and director of pain research at **Stanford University**, was more cautious about the translational potential of the findings.

Yeomans said that the study is mechanistically groundbreaking but creating analgesics that block pain transmission in nociceptors now appears to carry the risk that it could remove a necessary brake on the immune system and result in local inflammation.

“Until now not a whole lot of attention has been paid by the pain people or the anti-infective people to each other’s fields, but this may make them communicate more,” he told *SciBX*.

The findings have not been patented.

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REFERENCES

1. Chiu, I.M. *et al. Nature*; published online Aug. 21, 2013; doi:10.1038/nature12479
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3. Rivière, S. *et al. Nature* **459**, 574–577 (2009)

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Supersizing adoptive T cell therapies

By Tracey Baas, Senior Editor

Despite the striking efficacy of chimeric antigen receptor–based T cell therapies in small clinical trials in patients with leukemia, the ability to rapidly provide T cells to a large number of recipients is limited by the lack of readily available tumor antigen–associated human T lymphocytes. To tackle this problem, a **Memorial Sloan-Kettering Cancer Center** team has incorporated patient-derived induced pluripotent stem cells into an immunotherapy protocol to provide large-scale production of T cells endowed with enhanced antitumor properties.¹

The team was led by Michel Sadelain, director of MSKCC's Center for Cell Engineering. He also led the teams that produced second-generation CD19-specific chimeric antigen receptor (CAR)-expressing T cells that efficiently induced complete remission in five of five patients with chemotherapy-refractory acute lymphoblastic leukemia (ALL).²

In those studies, T cells were isolated from a patient, transduced with a specific tumor-associated antigen, expanded *ex vivo* and reinfused into the same patient.

The problem is that a personalized immunotherapy–based protocol may not be possible when collection or expansion of T cells

is problematic, such as in individuals with small numbers of T cells because of immunosuppression or previous cancer treatment.

Thus, Sadelain's team wanted to design a protocol conducive to producing large quantities of either autologous or allogeneic T cells. Large batches of autologous T cells would allow multiple dosings to one patient. Large batches of allogeneic T cells generated from one donor would allow multiple recipients to be dosed. Both approaches would be more practical than current CAR protocols (*see Figure 1, "CAR-expressing T cell production to develop immunotherapeutics"*).

The solution, the group hypothesized, was induced pluripotent stem (iPS) cells. The goal would be to engineer patient-derived iPS cells to produce antigen-specific CAR-based T cells capable of large-scale expansion.

First, the researchers obtained peripheral blood T lymphocytes from a healthy volunteer and transduced the cells with two retroviral vectors that encoded the reprogramming factors *Klf4*, *Sox2*, *Oct4* and *c-Myc* (*MYC*). Resulting pluripotent cells then were transduced with a lentiviral vector encoding MSKCC's second-generation CD19-specific CAR.

Using a 3-step, 30-day protocol, the team differentiated the CAR-expressing iPS cells into CAR-expressing T cells by taking them through phases of embryoid body formation, hematopoietic precursor specification and finally T lymphoid commitment.

When the differentiated T cells were added to cultured CD19⁺ cells, they expressed the T cell activation markers *IL-2 receptor α -chain* (*CD25*)

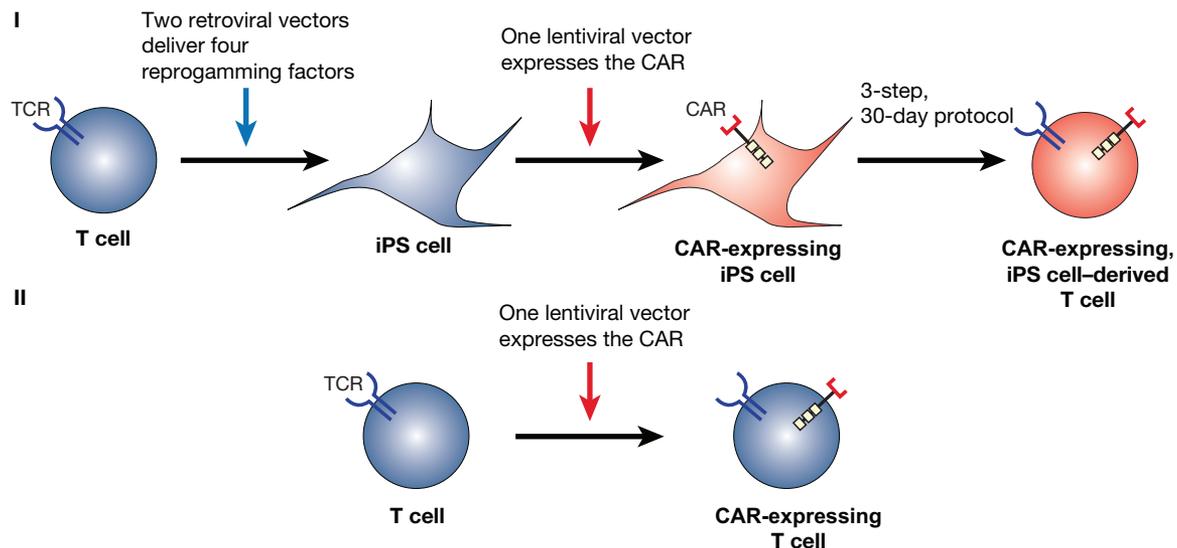


Figure 1. CAR-expressing T cell production to develop immunotherapeutics. (I) Themeli *et al.* transduced a healthy volunteer's T cells with two retroviral vectors encoding four transcription factors that reprogram the T cells into induced pluripotent stem (iPS) cells. The iPS cells then were transduced with a lentiviral vector encoding a chimeric antigen receptor (CAR) to provide CAR-expressing iPS cells. The team next differentiated the CAR-expressing iPS cells into T cells using a 3-step, 30-day protocol that takes the cells through phases of embryoid body formation, hematopoietic precursor specification and finally T cell commitment.

The resulting T cells expressed both the CAR and an endogenous T cell receptor (TCR) that matched the original TCR of the patient-obtained T cell. Methods to expand the CAR-expressing, iPS cell–derived T cells resulted in a 1,000-fold increase in numbers.

(II) CAR-expressing T cells also can be directly engineered from patient-obtained T cells using the lentiviral vector encoding CAR. Methods to expand the CAR-expressing T cells are not as proficient as those to expand CAR-expressing, iPS cell–derived T cells.

and CD69, secreted type I cytokines and ultimately eliminated the CD19⁺ cells. Those results suggested the CD19-specific, iPS cell-derived T cells were functional.

This same process did not happen when the differentiated T cells were added to cultured CD19⁻ cells, thus demonstrating the antigenic specificity of the engineered T cells.

With proof of concept established, the next step was to modify the protocol to enable the production of larger batches.

Coculturing with CD19⁺, artificial antigen-presenting cells, IL-7 and IL-15 stimulated and expanded CD19-specific iPS cell-derived T cells. After three weekly stimulations, the CD19-specific iPS cell-derived T cell population increased by up to 1,000-fold.

In mice with CD19⁺ lymphoma cells, the expanded T cells delayed tumor progression and initiated tumor regression, and they increased survival compared with no treatment. The results for the expanded cells were similar to those for endogenous T cells that were isolated from the same healthy volunteer and engineered to express MSKCC's second-generation CD19-specific CAR.

The findings suggest large-batch engineering of CAR-based T cells using iPS cells can be performed without sacrificing functionality.

Results were published in *Nature Biotechnology*.

The safety scale

Jianxun Song, assistant professor of microbiology and immunology at **Pennsylvania State University Hershey College of Medicine**, said that key next steps would be to show safety and simplify the approach, regardless of whether iPS cells are used to generate allogeneic or autologous T cells.

“Adoptive transfer of iPS cell-derived T cells has the potential to trigger cross-reactivity or development of autoimmunity once the T cells are fully activated. Incorporating a suicide gene would be a good option,” he said. “This allows the removal of the transferred T cells by the injection of a drug to induce the suicide gene and shut off the system.”

In 2011, Song's group used antigen-specific T cell receptor (TCR)-expressing iPS cells in xenograft mice to show that the iPS cells differentiated into antigen-specific cytotoxic T cells and prevented tumor growth.³

Aya Jakobovits, president and CEO of cancer immunotherapy company **Kite Pharma Inc.**, said that the best use of the method could be instances in which very low levels of T cells are a problem.

“As more data become available, especially from multicenter trials using CAR- or TCR-engineered T cells, banking T cells upon diagnosis—before therapies begin—could become an attractive and affordable option,” she said. “If at the time of diagnosis the patient already presents with an extremely low T cell number, then the iPS T cell approach can be beneficial.”

However, Song said that the MSKCC group's 30-day protocol may not be worth the time. “iPS cell-derived T cells take a substantial time to generate, grow to large numbers, transduce with CARs or TCRs and expand to large numbers,” he noted. This strategy might be worthwhile for creating T cells that can be banked for future use, but patients who need to start treatment may not be able to wait that long, he said.

Sadelain countered that the approach “does incorporate more time up front but opens up opportunities to stockpile large numbers of

antigen-specific T cells, even before they are needed. This ultimately saves time when patients need to start treatment.”

“Our approach also makes the first step toward off-the-shelf immunotherapeutics that can be used for allogeneic transfer,” he continued. “At this stage, cell banks could be established where large numbers of antigen-specific T cells are stored and categorized using common donor HLA [human leukocyte antigen] haplotypes, and recipients for the cells can be selected using minimal mismatch criteria to ensure histocompatibility.”

The MSKCC team now is taking a two-pronged approach to make its CARs more applicable to the allogeneic setting. The first, said Sadelain, is “disrupting endogenous TCRs using zinc finger nucleases or selecting for endogenous, virus-specific TCRs, which are less likely to cause graft-versus-host disease because the TCRs target virus proteins rather than host proteins.”

T cells with virus-specific TCRs exist in any individual who has had a viral infection. These T cells are programmed to attack virus, not host proteins, so graft-versus-host disease would not be induced through the TCR.

The second approach would involve repressing HLA expression through additional genetic modifications to ensure histocompatibility.

Before incorporating further modifications into the protocol, both Song and Jakobovits wanted to see studies showing that the engineered T cells are not tumorigenic.

“Any leftover iPS cells that do not differentiate could lead to teratoma formation,” acknowledged Sadelain. “Fortunately, immunologists are experts at sorting and isolating different subpopulations of immune cells, so if residual iPS cells remain, these cells could be removed.”

MSKCC has filed a patent application for the method, and the IP is available for licensing.

Baas, T. *SciBX* 6(36); doi:10.1038/scibx.2013.983
Published online Sept. 19, 2013

REFERENCES

1. Themeli, M. *et al. Nat. Biotechnol.*; published online Aug. 11, 2013; doi:10.1038/nbt.2678
Contact: Michel Sadelain, Memorial Sloan-Kettering Cancer Center, New York, N.Y.
e-mail: sadelaim@mskcc.org
2. Brentjens, R.J. *et al. Sci. Transl. Med.* 5, 177ra138 (2013)
3. Lei, F. *et al. Cancer Res.* 71, 4742–4747 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

Kite Pharma Inc., Los Angeles, Calif.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Pennsylvania State University Hershey College of Medicine, Hershey, Pa.

“At this stage, cell banks could be established where large numbers of antigen-specific T cells are stored and categorized using common donor HLA [human leukocyte antigen] haplotypes, and recipients for the cells can be selected using minimal mismatch criteria to ensure histocompatibility.”

—Michel Sadelain,
Memorial Sloan-Kettering
Cancer Center

Brain in a dish

By Lev Osherovich, Senior Writer

Austrian researchers grabbed headlines last month when they coaxed cultured human induced pluripotent stem cells into forming brain tissue,¹ but in actuality the approach does not offer applications beyond studying very early brain development.

Engineering stem cell–derived *in vitro* organ models for studying development and disease has made great strides for relatively simple organs such as the intestine,² lung³ and liver. For example, Japanese researchers have generated liver organoids from induced pluripotent stem (iPS) cells and shown that the *in vitro*–grown tissue was functional when transplanted into mice.⁴

Compared with other organs, the brain is much more complex and thus is considered harder to grow from scratch. Instead, efforts have focused on growing individual tissue types such as retinal⁵ and cerebellar⁶ precursors.

Now, a team led by Jürgen Knoblich has combined a variety of iPS cell culture and differentiation methods to create brain organoids—well-organized clusters of brain tissue containing the major cell layers found in embryonic brains. Knoblich is deputy scientific director of the **Institute of Molecular Biotechnology of the Austrian Academy of Science**.

The group started with off-the-shelf iPS cells and treated them with differentiation-inducing cell culture medium to yield neuroectoderm tissue, which is the embryonic precursor to the nervous system.

When implanted into a 3D growth matrix and transferred to a liquid culture bioreactor, the neuroectoderm began to separate into a brain-like, layered tissue termed neuroepithelium.

After 20–30 days of growth, the neuroepithelium formed globular organoids with layers of distinctive neurons and glial cells similar to those seen in developing human brains.

The team used RT-PCR and immunohistochemistry to show that the miniature brains had a semblance of the organization found in full-sized brains, including localized expression of markers associated with specific brain regions such as the hippocampus and choroid plexus.

Microscopy and electrophysiological studies revealed that neurons inside the brain organoids had sprouted axon-like projections and could respond to stimulation by glutamate, an excitatory neurotransmitter. The team did not report the efficiency of the organoid growth protocol or the consistency of resulting organoids.

Knoblich's team next used the brain organoids to characterize how early steps in brain development go awry in certain hereditary diseases.

The researchers grew brain organoids from iPS cells derived from a patient with a genetic form of microcephaly, a rare birth defect characterized by stunted cortical development. The cells had a loss-of-function mutation in *CDK5 regulatory subunit associated protein 2* (*CDK5RAP2*), one of several genes linked to microcephaly.

When the patient's cells were put through the brain organoid–growing protocol, the cells initially formed a seemingly normal neuroepithelium. But the neurons within this cell layer stopped dividing prematurely, leading to thinner neuronal layers and smaller organoids than were seen in a healthy control cell layer. The team obtained similar results with small hairpin RNA knockdown of *CDK5RAP2*.

Results were reported in *Nature*.

Limited development

Knoblich's findings are a step toward developing *in vitro* models of neurological disease, but the precise conditions in which the model should be applicable is up for debate.

“This system allows one to selectively up- and downregulate genes and transcripts of interest and directly observe their impact on the 3D interactions and developmental processes across cell types,” said Magali Haas, CSO and CTO of **One Mind for Research**, a not-for-profit organization that advocates for research into mental illness and brain injury.

“There are literally thousands of independent loci that seem to contribute to heritability of schizophrenia and other conditions such as autism and bipolar disorder,” she said. “Many of these conditions are known to be associated with neurodevelopmental abnormalities, but the full mechanism of these is unknown. This type of culture model may help elucidate the early roles of these genes in the neurodevelopment process.”

Mriganka Sur, a professor of neuroscience and director of the Simons Center for the Social Brain at the **Massachusetts Institute of Technology**, cautioned that brain organoid

tissue is more primitive than the highly interconnected neuronal networks found in real brains.

He noted that most common neuropsychiatric and neurodegenerative diseases involve compromised connectivity between neurons or abnormal interactions between neurons and surrounding glial cells, but neither phenomenon is evident in brain organoids.

“They show that these neurons can fire, but not that they form normal synaptic networks,” said Sur. “iPS cells are good for studying early developmental steps in neurons but not diseases of brain connectivity.”

“The system has clear limitations including the fact that other cell/tissue types are not co-developing alongside the neuronal ones,” added Haas. “Cell-cell signaling is a very important part of the development process, and this system would not fully recapitulate all those components.”

“It would be a bit premature to talk about the use of our system in an industry setting,” acknowledged Knoblich.

Aaron Chuang, research director of regenerative medicine at **GlaxoSmithKline plc**, said brain organoids appear to model only the earliest steps of embryonic brain development, whereas the complex tissues often involved in brain disease develop much later.

“Improving the technology to generate 3D brain tissue with greater maturity would improve potential utility; focusing on the generation of specific brain regions such as the hippocampus with mature state could have greater utility.”

—Aaron Chuang,
GlaxoSmithKline plc

“These organoids developed for up to two months only,” said Chuang. “These represent part of early fetal brain, but the majority of glial cells would not have been developed at this early stage. There is also no vascular system, which is known to play significant roles in brain function. Therefore, as the authors point out, their system captures only the very early stages of development.”

Chuang and Sur advocated for refining the culture method to yield more developmentally advanced brain tissue.

“Improving the technology to generate 3D brain tissue with greater maturity would improve potential utility; focusing on the generation of specific brain regions such as the hippocampus with mature state could have greater utility,” Chuang said.

“The next step is to grow synapses in a reasonable time frame and to grow different cell types,” added Sur. “At the very least there should be excitatory and inhibitory neurons.”

Knoblich said that his team is focusing on helping other laboratories learn how to make brain organoids.

“Industry should not yet be adopting this technology in its R&D pipeline procedures, but all serious CNS companies should have their discovery teams educated on these techniques to become intimately

familiar with their advantages and limitations,” concluded Haas. Patent and licensing status were not disclosed.

Oshrovich, L. *SciBX* **6(36)**; doi:10.1038/scibx.2013.984
Published online Sept. 19, 2013

REFERENCES

1. Lancaster, M. *et al. Nature*; published online Aug. 28, 2013; doi:10.1038/nature12517
Contact: Jürgen Knoblich, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria
e-mail: juergen.knoblich@imba.oeaw.ac.at
2. Sato, T. *et al. Nature* **459**, 262–265 (2009)
3. Dekkers, J.F. *et al. Nat. Med.* **19**, 939–945 (2013)
4. Takebe, T. *et al. Nature* **499**, 481–484 (2013)
5. Eiraku, M. *et al. Nature* **472**, 51–56 (2011)
6. Muguruma, K. *et al. Nat. Neurosci.* **13**, 1171–1180 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Institute of Molecular Biotechnology of the Austrian Academy of Science, Vienna, Austria
One Mind for Research, Seattle, Wash.
Massachusetts Institute of Technology, Cambridge, Mass.



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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				
Inflammatory bowel disease (IBD)	Vitamin D receptor (VDR)	Studies in mice and in patient samples suggest VDR activation could help treat IBD. In mouse models of IBD, overexpression of human VDR in intestinal epithelial cells decreased colitis severity compared with wild-type VDR expression. In <i>Vdr</i> knockout mice, expression of human VDR in intestinal epithelial cells decreased colitis severity and increased survival compared with no human VDR expression. In colonic biopsy samples from patients with IBD, VDR expression was lower than that in samples from normal subjects. Next steps could include testing VDR agonists in animal models of colitis.	Patent and licensing status unavailable	Liu, W. <i>et al. J. Clin. Invest.</i> ; published online Aug. 15, 2013; doi:10.1172/JCI65842 Contact: Yan Chun Li, The University of Chicago, Chicago, Ill. e-mail: cyan@medicine.bsd.uchicago.edu
		SciBX 6(36); doi:10.1038/scibx.2013.985 Published online Sept. 19, 2013		
Multiple sclerosis (MS)	Protein kinase C β (PRKCB)	Mouse studies suggest PRKCB inhibitors could help treat MS. PRKCB can induce hyperpermeability of the blood brain barrier (BBB). In an experimental autoimmune encephalomyelitis (EAE) mouse model of relapsed-remitting MS, the PRKCB inhibitor enzastaurin decreased migration of proinflammatory T cells across the BBB and decreased demyelination of spinal cord neurons compared with vehicle. Next steps could include testing the long-term efficacy and safety of PRKCB inhibitors in the EAE models. Eli Lilly and Co.'s Arxxant ruboxistaurin (LY333531), a synthetic PRKCB inhibitor, is under review to treat diabetic retinopathy. In May, the pharma discontinued development of enzastaurin (LY317615) after the synthetic inhibitor of PRKCB and protein kinase B (PKB; PKBA; AKT; AKT1) missed the primary endpoint in a Phase III trial to treat relapsed or refractory diffuse large B cell lymphoma (DLBCL).	Unpatented; unlicensed	Lanz, T.V. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 19, 2013; doi:10.1073/pnas.1302569110 Contact: Michael Platten, German Cancer Research Center, Heidelberg, Germany e-mail: michael.platten@med.uni-heidelberg.de
		SciBX 6(36); doi:10.1038/scibx.2013.986 Published online Sept. 19, 2013		
Rheumatoid arthritis (RA)	Endoplasmic reticulum to nucleus signaling 1 (ERN1; IRE1)	<i>In vitro</i> and mouse studies suggest inhibiting IRE1 could help treat RA. Macrophages from the synovial fluid of patients with RA showed lower IRE1 activation than macrophages from patients with osteoarthritis (OA). In a mouse model of inflammatory arthritis, myeloid-specific <i>Ire1</i> knockout or an <i>Ire1</i> -specific inhibitor protected from the disease and decreased joint inflammation compared with no knockout or with vehicle. Next steps include testing IRE1 inhibitors in large animal models of RA. MannKind Corp.'s IRE1 inhibitor MKC204 is in preclinical testing to treat multiple myeloma (MM).	Findings unpatented; unavailable for licensing	Qiu, Q. <i>et al. EMBO J.</i> ; published online Aug. 13, 2013; doi:10.1038/emboj.2013.183 Contact: Deyu Fang, Northwestern University, Chicago, Ill. e-mail: fangd@northwestern.edu Contact: Kezhong Zhang, Wayne State University School of Medicine, Detroit, Mich. e-mail: kzhang@med.wayne.edu
		SciBX 6(36); doi:10.1038/scibx.2013.987 Published online Sept. 19, 2013		

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Breast cancer	Nuclear assembly factor 1 ribonucleoprotein (NAF1); CDGSH iron sulfur domain 1 (CISD1; mitoNEET)	<i>In vitro</i> and mouse studies suggest inhibiting mitochondrial NAF1 or CISD1 could help treat breast cancer. In three human breast cancer cell lines, NAF1 and CISD1 levels were higher than those in a human epithelial breast cell line. In the cancer cell lines, small hairpin RNA against NAF1 or CISD1 increased mitochondrial iron and reactive oxygen species levels and decreased proliferation compared with scrambled shRNA. In a mouse xenograft model of human breast cancer, shRNA knockdown of NAF1 or CISD1 decreased tumor growth compared with no knockdown. Next steps could include identifying and testing pharmacological inhibitors of NAF1 and CISD1. SciBX 6(36); doi:10.1038/scibx.2013.988 Published online Sept. 19, 2013	Patent and licensing status unavailable	Sohn, Y.-S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 19, 2013; doi:10.1073/pnas.1313198110 Contact: Ron Mittler, University of North Texas, Denton, Texas e-mail: ron.mittler@unt.edu Contact: Rachel Nechushtai, The Hebrew University of Jerusalem, Jerusalem, Israel e-mail: rachel@vms.huji.ac.il Contact: Patricia A. Jennings, University of California, San Diego, La Jolla, Calif. e-mail: pajennings@ucsd.edu Contact: José N. Onuchic, Rice University, Houston, Texas e-mail: jonuchic@rice.edu
Cancer	Adenosine A _{2A} receptor (ADORA _{2A}); ADORA _{2B} ; ecto-5'-nucleotidase (NT5E; NT; CD73)	Mouse studies suggest inhibiting ADORA _{2A} or ADORA _{2B} could help prevent metastasis of CD73 ⁺ tumors. Expression of CD73 in tumor cells is known to enhance metastasis, but the downstream mechanisms underlying this effect were not known. In mouse models of breast cancer and melanoma, ectopic Cd73 expression promoted the conversion of AMP to adenosine and increased lung metastases compared with ectopic GFP expression. In a mouse model of Cd73 ⁺ metastatic melanoma, an ADORA _{2A} or ADORA _{2B} antagonist decreased lung metastases compared with no antagonists. Researchers did not disclose next steps, which could include evaluating adenosine receptor antagonists in additional animal models of CD73 ⁺ tumors. Kyowa Hakko Kirin Co. Ltd. markets Nouriasit istradefylline, an ADORA _{2A} antagonist, to treat Parkinson's disease (PD). At least eight other companies have ADORA _{2A} antagonists in Phase II testing or earlier to treat PD or other CNS disorders. SciBX 6(36); doi:10.1038/scibx.2013.989 Published online Sept. 19, 2013	Patent and licensing status undisclosed	Beavis, P.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 20, 2013; doi:10.1073/pnas.1308209110 Contact: Phillip K. Darcy, Peter MacCallum Cancer Centre, East Melbourne, Victoria Australia e-mail: phil.darcy@petermac.org
Cancer	Deoxycytidine kinase (DCK)	Mouse and <i>in vitro</i> studies identified DCK inhibitors that could help treat cancer. DCK is associated with cancer cell growth and chemotherapy resistance. High throughput screening, SAR studies and cell-based assays identified small molecules that inhibit DCK with nanomolar IC ₅₀ values. In a mouse xenograft model of human leukemia, the lead inhibitor decreased DCK activity in tumors compared with vehicle. Next steps include identifying a lead clinical candidate and carrying out IND-enabling studies. SciBX 6(36); doi:10.1038/scibx.2013.990 Published online Sept. 19, 2013	Patent application filed; licensing details available from the University of California, Los Angeles Office of Intellectual Property	Murphy, J.M. <i>et al. J. Med. Chem.</i> ; published online Aug. 15, 2013; doi:10.1021/jm400457y Contact: Caius G. Radu, University of California, Los Angeles, Calif. e-mail: cradu@mednet.ucla.edu Contact: Arnon Lavie, University of Illinois at Chicago, Chicago, Ill. e-mail: lavie@uic.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Src homology protein tyrosine phosphatase 2 (SHP-2; SHPTP2; PTPN11)	<i>In vitro</i> studies suggest cryptotanshinone could help treat Noonan syndrome and some cancers. Noonan syndrome and other cancers are caused by activating mutations in <i>SHP-2</i> . <i>In vitro</i> , cryptotanshinone directly bound and selectively inhibited SHP-2. In mouse myeloid progenitor cells and human cancer cells expressing <i>SHP-2</i> with an activating mutation, cryptotanshinone inhibited SHP-2-mediated cell signaling and decreased cell growth compared with vehicle. Next steps could include developing analogs for preclinical testing. Aardent Pharmaceuticals Inc.'s SHP-2 inhibitor, Il-B08, is in preclinical testing to treat cancers. SciBX 6(36); doi:10.1038/scibx.2013.991 Published online Sept. 19, 2013	Patent and licensing status unavailable	Liu, W. <i>et al. J. Med. Chem.</i> ; published online Aug. 19, 2013; doi:10.1021/jm400474r Contact: Cheng-Kui Qu, Case Western Reserve University, Cleveland, Ohio e-mail: cxq6@case.edu
Mesothelioma	Cyclin dependent kinase 1 (CDK1; CDC2)	Mouse and <i>in vitro</i> studies identified analogs of the <i>bis</i> (indolyl)imidazole alkaloid nortoposentin that could help treat diffuse malignant peritoneal mesothelioma (DMPM). In two human DMPM cell lines, five of the nortoposentin analogs inhibited proliferation with micromolar and submicromolar IC ₅₀ values. In a mouse xenograft model of human DMPM, the three most potent analogs decreased tumor growth compared with vehicle. In a panel of kinases, the three most potent analogs were shown to inhibit CDK1 with submicromolar IC ₅₀ values. Next steps could include testing the lead analogs in additional models of mesothelioma. Merck & Co. Inc. and Ligand Pharmaceuticals Inc. have the CDK inhibitor dinaciclib in Phase II/III testing to treat chronic lymphocytic leukemia (CLL) and Phase II or earlier testing for other cancers. At least six other companies have CDK inhibitors in Phase II or earlier testing for various cancers. SciBX 6(36); doi:10.1038/scibx.2013.992 Published online Sept. 19, 2013	Patent and licensing status unavailable	Carbone, A. <i>et al. J. Med. Chem.</i> ; published online Aug. 6, 2013; doi:10.1021/jm400842x Contact: Nadia Zaffaroni, IRCCS Foundation National Institute of Cancer, Milano, Italy e-mail: nadia.zaffaroni@istitutotumori.mi.it Contact: Patrizia Diana, University of Palermo, Palermo, Italy e-mail: patrizia.diana@unipa.it
Neurofibromatosis	p21 protein (Cdc42 Rac)-activated kinase 1 (PAK1)	<i>In vitro</i> and mouse studies identified PAK1 inhibitors that could help treat neurofibromatosis type 2 (NF2). PAK1 is highly expressed in Schwann cells in primary NF2 tumors. High throughput screening, chemistry and SAR studies identified a pyridopyrimidinone as a nanomolar-potent inhibitor of PAK1. In a Schwann cell-based model of NF2, the compound decreased proliferation compared with vehicle. In mice bearing orthotopic NF2 tumors, the compound decreased tumor growth. Ongoing work at the Genentech Inc. unit of Roche includes further optimizing the compound. SciBX 6(36); doi:10.1038/scibx.2013.993 Published online Sept. 19, 2013	Patented by the Massachusetts Institute of Technology; licensed to Genentech	Licciulli, S. <i>et al. J. Biol. Chem.</i> ; published online Aug. 19, 2013; doi:10.1074/jbc.M113.510933 Contact: Joseph L. Kissil, Scripps Florida, Jupiter, Fla. e-mail: jkissil@scripps.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Ischemia/ reperfusion injury	R-Spondin 3 (RSPO3)	<p>Mouse studies suggest RSPO3 could help treat ischemia/reperfusion injury. Ischemia/reperfusion injury causes vascular leakage that leads to tissue damage and inflammation. In a mouse model of intestinal ischemia/reperfusion injury, recombinant mouse Rspo3 decreased vascular leakage, inflammation and damage in intestinal tissue compared with no Rspo3. Next steps could include developing and testing RSPO3 mimics.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.994 Published online Sept. 19, 2013</p>	Patent and licensing status unavailable	<p>Kannan, L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 13, 2013; doi:10.1073/pnas.1309393110</p> <p>Contact: George C. Tsokos, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Mass. e-mail: gtsokos@bidmc.harvard.edu</p> <p>Contact: Lakshmi Kannan, same affiliation as above e-mail: lkannan@bidmc.harvard.edu</p>
Hematology				
Anemia	Hepcidin	<p>Mouse and nonhuman primate studies identified a humanized antihepcidin antibody that could help treat anemia of inflammation. Erythropoiesis-stimulating agents (ESAs) can help treat anemia, but inflammation-induced hepcidin can lower the efficacy of ESAs by sequestering iron. In a mouse model of anemia of inflammation with human hepcidin expression, an ESA plus a humanized, antihepcidin antibody increased iron levels and hemoglobin production in red blood cells compared with an ESA alone. In nonhuman primates, the antihepcidin antibody increased serum iron levels compared with saline. Next steps could include evaluating the antihepcidin antibody in additional animal anemia models.</p> <p>Noxxon Pharma AG's hepcidin inhibitor, NOX-H94, is in Phase II testing to treat anemia. At least two other companies have hepcidin inhibitors or antibodies in Phase I testing or earlier to treat anemia.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.995 Published online Sept. 19, 2013</p>	Patent and licensing status unavailable	<p>Cooke, K.S. <i>et al. Blood</i>; published online Aug. 14, 2013; doi:10.1182/blood-2013-06-505792</p> <p>Contact: Barbra J. Sasu, Amgen Inc., Thousand Oaks, Calif. e-mail: bajohnso@amgen.com</p>
Infectious disease				
Ebola	Ebola glycoprotein GP1; Ebola glycoprotein GP2	<p>Nonhuman primate studies suggest a cocktail of three mAbs called MB-003, which targets GP1 and GP2, could treat Ebola infection. In nonhuman primates showing symptoms of Ebola infection, MB-003 given in 3 doses 120, 170 and 250 hours after exposure resulted in survival in 3 of 7 animals. Next steps include dose optimization, pharmacology and toxicology testing. MB-003 is in preclinical development to treat Ebola infection.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.996 Published online Sept. 19, 2013</p>	Patented by the U.S. Army Medical Research Institute of Infectious Diseases; licensed to Mapp Biopharmaceutical Inc.; available for licensing and partnering through Mapp	<p>Pettitt, J. <i>et al. Sci. Transl. Med.</i>; published online Aug. 21, 2013; doi:10.1126/scitranslmed.3006608</p> <p>Contact: Gene G. Olinger, U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Md. e-mail: gene.g.olinger2.civ@mail.mil</p> <p>Contact: Larry Zeitlin, Mapp Biopharmaceutical Inc., San Diego, Calif. e-mail: larry.zeitlin@mappbio.com</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Infectious disease; respiratory syncytial virus (RSV)	Metapneumovirus F protein; RSV F protein	<p>Cell culture and mouse studies suggest the human mAb MPE8 could help treat or prevent RSV and metapneumovirus (MPV) infection. The antibody was isolated from immortalized memory B cells obtained from blood donors with high serum neutralizing antibody titers against both viruses. <i>In vitro</i> and in cell culture, MPE8 neutralized RSV and MPV by binding to the prefusion F protein. In a mouse model of RSV infection, MPE8 was 5- to 10-fold more potent than Synagis palivizumab at decreasing virus levels in the lung. Next steps could include a clinical trial of MPE8 in transplant patients who have an upper respiratory tract infection caused by RSV or MPV.</p> <p>AstraZeneca plc and Abbott Laboratories market Synagis, a humanized mAb against RSV F protein, as a prophylactic for RSV infection. AstraZeneca's motavizumab, a humanized anti-RSV F protein mAb, is in Phase III trials as a prophylactic for RSV infection.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.997 Published online Sept. 19, 2013</p>	Patent application filed; available for licensing through Humabs BioMed S.A.	<p>Corti, D. <i>et al. Nature</i>; published online Aug. 18, 2013; doi:10.1038/nature12442 Contact: Antonio Lanzavecchia, University of Lugano, Bellinzona, Switzerland e-mail: lanzavecchia@irb.usi.ch Contact: Davide Corti, Humabs BioMed S.A., Bellinzona, Switzerland e-mail: davide.corti@humabs.ch</p>
SARS-associated coronavirus	Exoribonuclease in nonstructural protein 14 (nsp14-ExoN)	<p><i>In vitro</i> studies suggest nsp14-ExoN inhibitors could help sensitize coronaviruses to RNA mutagen therapeutics including ribavirin. In murine hepatitis virus coronaviruses, knockout of the RNA proofreading gene <i>nsp14-ExoN</i> increased sensitivity to 5-fluorouracil and ribavirin by 300-fold and decreased viral replication compared with no knockout. In <i>nsp14-ExoN</i>-deficient SARS viruses, 5-fluorouracil treatment induced 16-fold more mutations than those seen in wild-type viruses. Next steps could include identifying and evaluating pharmacological nsp14-ExoN inhibitors in animal infection models.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.998 Published online Sept. 19, 2013</p>	Patent and licensing status unavailable	<p>Smith, E.C. <i>et al. PLoS Pathog.</i>; published online Aug. 15, 2013; doi:10.1371/journal.ppat.1003565 Contact: Mark R. Denison, Vanderbilt University Medical Center, Nashville, Tenn. e-mail: mark.denison@vanderbilt.edu</p>
Inflammation				
Chronic obstructive pulmonary disease (COPD)	IL-33 (NF-HEV)	<p>Mouse and human <i>ex vivo</i> studies suggest inhibiting IL-33 could help treat COPD. In a mouse model of COPD, IL-33 levels were higher in lung progenitor cells than in cells from healthy mice. In the same model, knockout of an essential IL-33 receptor subunit or treatment with a neutralizing antibody targeting that subunit both decreased disease severity compared with no knockout or with control IgG treatment. In lung tissue samples from patients with COPD, IL-33 levels were higher in lung progenitor cells than in samples from individuals without COPD. Next steps include developing inhibitors against IL-33 and its receptor.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.999 Published online Sept. 19, 2013</p>	Unpatented; licensing status not applicable	<p>Byers, D.E. <i>et al. J. Clin. Invest.</i>; published online Aug. 15, 2013; doi:10.1172/JCI65570 Contact: Michael J. Holtzman, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: holtzmanm@wustl.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Addiction	Orexin 1 receptor (HCRTR1; OX1R)	<i>In vitro</i> and rat studies identified selective, tetrahydroisoquinoline-based OX1R antagonists that could help treat addiction. In <i>in vitro</i> assays, the tetrahydroisoquinoline-based antagonists showed higher specificities and potencies for OX1R than OX2R (HCRTR2). In a rat model of addiction, one of the most potent and selective antagonists decreased cocaine-induced addiction behaviors compared with vehicle. Next steps could include further optimization of the compounds to improve their potency and selectivity. Merck & Co. Inc.'s dual OX1R and OX2R antagonist suvorexant is under review to treat insomnia. At least two other companies have OX1R antagonists in Phase II or earlier testing for neurological indications. SciBX 6(36); doi:10.1038/scibx.2013.1000 Published online Sept. 19, 2013	Patent and licensing status unavailable	Perrey, D.A. <i>et al. J. Med. Chem.</i> ; published online Aug. 13, 2013; doi:10.1021/jm400720h Contact: Yanan Zhang, RTI International, Research Triangle Park, N.C. e-mail: y Zhang@rti.org
Alzheimer's disease (AD); neurology	3-Phosphoinositide-dependent protein kinase-1 (PDPK1)	Mouse and cell culture studies suggest inhibiting PDPK1 activity could help treat AD and prion-associated diseases. In prion-infected, cultured mouse neurons and neurons from mice with amyloid plaques, a PDPK1 inhibitor led to higher levels of neuroprotective amyloid precursor protein (APP) and cellular prion protein (PrP ^{Sc} ; PrP; CD230) cleavage products than no treatment. In mouse models, the PDPK1 inhibitor decreased both AD-specific behavioral impairments and prion disease-specific motor impairments compared with no treatment. Next steps include testing other PDPK1 inhibitors and analyzing how PDPK1 is activated by pathogenic prions and amyloid peptides. Arno Therapeutics Inc.'s AR-12, a small molecule inhibitor of PDPK1, is in Phase I testing to treat lymphoma and solid tumors. Phusis Therapeutics Inc.'s PHT-427, a small molecule inhibitor of PDPK1, is in preclinical development to treat cancer. SciBX 6(36); doi:10.1038/scibx.2013.1001 Published online Sept. 19, 2013	Patent and licensing status undisclosed	Pietri, M. <i>et al. Nat. Med.</i> ; published online Aug. 18, 2013; doi:10.1038/nm.3302 Contact: Benoit Schneider, University Paris Descartes, Paris, France e-mail: benoit.schneider@parisdescartes.fr Contact: Jean-Marie Launay, Lariboisière Hospital, Paris, France e-mail: jean-marie.launay@lrb.aphp.fr
Pain	Formyl peptide receptor 1 (FPR1); α -hemolysin (α HL)	Mouse and cell culture studies suggest targeting bacterial FPR1 agonists and α HL could help treat infection-induced pain. In mouse models of pain, FPR1 agonists and α HL increased mechanical and heat hypersensitivity compared with saline. In these models, α HL-deficient bacteria caused less hypersensitivity than wild-type bacteria. In <i>Fpr1</i> -deficient mice, heat-killed bacteria had no effect on mechanical or heat sensitivity. Next steps include identifying additional bacterial mediators of pain (see <i>Bacteria's painful truth</i> , page 4). SciBX 6(36); doi:10.1038/scibx.2013.1002 Published online Sept. 19, 2013	Unpatented; licensing status not applicable	Chiu, I.M. <i>et al. Nature</i> ; published online Aug. 21, 2013; doi:10.1038/nature12479 Contact: Clifford J. Woolf, Boston Children's Hospital and Harvard Medical School, Boston, Mass. e-mail: clifford.woolf@childrens.harvard.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pain	Hyaluronan and proteoglycan link protein 1 (HAPLN1; LPP)	<i>In vitro</i> studies suggest LPP could help treat intervertebral disc degeneration-associated chronic lower back pain. Treatment of the condition is aimed at regenerating the intervertebral disc matrix to reverse the degenerative disease. In 3D cultures of primary rabbit intervertebral disc cells, a human, 16-amino-acid, N-terminal LPP peptide upregulated a chondrocyte-specific transcription factor and levels of the extracellular matrix proteins aggrecan and collagen II. Next steps include testing the potential of LPP to induce expression of disc matrix components in animal models. SciBX 6(36); doi:10.1038/scibx.2013.1003 Published online Sept. 19, 2013	Unpatented; licensing status not applicable	Wang, Z. <i>et al. J. Biol. Chem.</i> ; published online Aug. 12, 2013; doi:10.1074/jbc.M113.451948 Contact: Zili Wang, Atlanta VA Medical Center, Decatur, Ga. e-mail: zwang2@emory.edu
Rett syndrome	Methyl CpG binding protein 2 (MECP2; RTT)	Mouse studies suggest <i>MECP2</i> gene therapy could help treat Rett syndrome. Mutations in <i>MECP2</i> are the most frequent cause of Rett syndrome. In <i>Mecp2</i> ^{-/-} mice, viral delivery of <i>Mecp2</i> yielded physiologically relevant levels of <i>Mecp2</i> in the brain and restored normal neuronal soma size, and it increased survival compared with viral delivery of a control gene. In <i>Mecp2</i> ^{-/-} female mice, <i>Mecp2</i> gene transfer decreased motor impairment and seizure frequency compared with transfer of a control gene. Next steps include modifying the viral delivery vector for optimal expression of the gene. SciBX 6(36); doi:10.1038/scibx.2013.1004 Published online Sept. 19, 2013	Patent and licensing status unavailable	Garg, S.K. <i>et al. J. Neurosci.</i> ; published online Aug. 21, 2013; doi:10.1523/JNEUROSCI.1854-13.2013 Contact: Gail Mandel, Oregon Health & Science University, Portland, Ore. e-mail: mandelg@ohsu.edu
Ophthalmic disease				
Diabetic retinopathy; diabetic macular edema (DME)	Angiopoietin-like 4 (ANGPTL4)	Mouse and cell culture studies suggest inhibiting ANGPTL4 could help treat ischemic retinopathies such as DME. Increased vascular permeability is a marker of ischemic retinal diseases. In a mouse model of oxygen-induced retinopathy, hypoxic retinal Müller cells were shown to promote vascular permeability by upregulation of <i>Angptl4</i> expression. In a human Müller cell line, RNAi knockdown of ANGPTL4 inhibited the cell line's ability to promote endothelial cell permeability. Next steps include confirming the expression of ANGPTL4 in patients who have ischemic retinopathies and evaluating the effects of ANGPTL4 inhibition in animal models. SciBX 6(36); doi:10.1038/scibx.2013.1005 Published online Sept. 19, 2013	Patent application filed covering inhibition of ANGPTL4 for treatment of pathological angiogenesis in the eye; available for licensing	Xin, X. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 19, 2013; doi:10.1073/pnas.1217091110 Contact: Akrit Sodhi, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: asodhi1@jhmi.edu
Pulmonary disease				
Bronchopulmonary dysplasia (BPD)	IL-1 receptor antagonist (IL-1RA)	Mouse studies suggest IL-1RA could help treat BPD. In a mouse model of BPD, IL-1RA prevented or decreased lung inflammation and alveolar destruction compared with vehicle. In the model, IL-1RA partially prevented disease-associated decreases in immune cell levels and increases in proinflammatory cytokine levels. Next steps include testing the strategy in human infants who have BPD. SciBX 6(36); doi:10.1038/scibx.2013.1006 Published online Sept. 19, 2013	Use of anti-IL-1 strategies to treat or prevent BPD has been patented; unavailable for licensing	Nold, M.F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 14, 2013; doi:10.1073/pnas.1306859110 Contact: Claudia A. Nold-Petry, Monash University, Clayton, Victoria, Australia e-mail: claudia.nold@monash.edu

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Disease models			
A noninvasive, nonhuman primate model of schizophrenia	Nonhuman primates that receive subanesthetic doses of ketamine could be useful as noninvasive preclinical models to study schizophrenia and evaluate therapeutic candidates. Electroencephalograms in ketamine-treated rhesus monkeys produced neurophysiological measurements comparable to those seen in patients with schizophrenia. Next steps include evaluating this model in preclinical drug testing. SciBX 6(36); doi:10.1038/scibx.2013.1007 Published online Sept. 19, 2013	Patent filed by the Salk Institute for Biological Studies; available for licensing	Gil-da-Costa, R. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 19, 2013; doi:10.1073/pnas.1312264110 Contact: Ricardo Gil-da-Costa, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: ricardo@salk.edu
Mouse model of psoriasis using epidermis-selective wtless homolog (WLS; EVI; GPR177) knockout	Mouse and human skin sample studies suggest knockout of <i>Evi</i> in the mouse epidermis could model psoriasis. In mice, conditional knockout of the wingless-type MMTV integration site (Wnt) cargo receptor <i>Evi</i> in the epidermis caused features of human psoriasis, including hair loss, skin inflammation and redness and loss of skin barrier function. <i>Evi</i> knockout in the epidermis also increased inflammatory cytokine expression in the skin and immune cell infiltration compared with no knockout. In skin samples from patients with psoriasis, EVI protein and mRNA expression was lower in psoriatic lesions than in healthy skin. Next steps could include using the model to test therapeutics. SciBX 6(36); doi:10.1038/scibx.2013.1008 Published online Sept. 19, 2013	Patent and licensing status unavailable	Augustin, I. <i>et al. J. Exp. Med.</i> ; published online Aug. 5, 2013; doi:10.1084/jem.20121871 Contact: Michael Boutros, German Cancer Research Center, Heidelberg, Germany e-mail: m.boutros@dkfz.de Contact: Iris Augustin, same affiliation as above e-mail: i.augustin@dkfz.de
Mouse model of skin rash syndrome caused by anti-epidermal growth factor receptor (EGFR) therapy	A mouse model of anti-EGFR therapy-induced skin rash syndrome could be useful for developing treatment strategies. Mice were engineered with epidermal-specific knockout of <i>Egfr</i> . The mice developed progressive skin lesions that resembled those seen in patients being treated with anti-EGFR drugs. In the mouse model, localized macrophage depletion with clodronate-loaded liposomes partially reversed skin pathology compared with saline-loaded liposomes. Next steps include determining whether the anticancer effects of EGFR inhibitors are dependent on immunological mechanisms and evaluating new approaches to block macrophage function and infiltration in skin. Bayer AG markets the bisphosphonate Bonafos clodronate outside the U.S. to treat tumor-induced osteolysis and hypercalcemia. SciBX 6(36); doi:10.1038/scibx.2013.1009 Published online Sept. 19, 2013	Unpatented; model available for licensing	Mascia, F. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 21, 2013; doi:10.1126/scitranslmed.3005773 Contact: Stuart H. Yuspa, National Institutes of Health, Bethesda, Md. e-mail: yuspas@mail.nih.gov
Phlorizin-pretreated mice with streptozotocin-induced diabetes as models of diabetic nephropathy	Phlorizin pretreatment in mice with streptozotocin-induced diabetes make them useful as models to help identify new treatments for diabetic nephropathy. In mice, high doses of streptozotocin induce diabetes but also cause acute kidney injury (AKI), which makes the mice unsuitable as models of diabetic nephropathy. In the kidneys of mice given a high dose of streptozotocin, AKI markers were associated with downregulation of solute carrier family 2 facilitated glucose transporter member 2 (Slc2a2; Glut2). In mouse models of streptozotocin-induced diabetes, pretreatment with the competitive sodium-glucose cotransporter 2 (SGLT2) inhibitor phlorizin increased Glut2 levels and decreased both renal uptake of streptozotocin and consequent AKI compared with vehicle pretreatment. Next steps could include confirming that the mice develop diabetic nephropathy and using them to evaluate therapeutic candidates. SciBX 6(36); doi:10.1038/scibx.2013.1010 Published online Sept. 19, 2013	Unpatented; unlicensed	Brouwers, B. <i>et al. J. Biol. Chem.</i> ; published online Aug. 11, 2013; doi:10.1074/jbc.M113.469486 Contact: Jeroen Declercq, Catholic University Leuven, Leuven, Belgium e-mail: jeroen.declercq@med.kuleuven.be

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Transgenic scavenger receptor class B member 2 (SCARB2) mice to model enterovirus 71 (EV71) neuropathogenesis	<p>Transgenic mice that express human SCARB2 could be useful for studying the neuropathogenesis of EV71 infection and could help identify new treatments and vaccines for the disease. Current mouse models of EV71 infection do not recapitulate disease neuropathology because the virus fails to infect murine CNS tissues. In transgenic mice expressing SCARB2, a known receptor for EV71, infection with EV71 resulted in viral replication in CNS tissue, ataxia, paralysis and death, recapitulating the neuropathology of EV71 infection in humans. Next steps could include using the model to evaluate candidate therapies and vaccines against EV71 infection.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.1011 Published online Sept. 19, 2013</p>	Patent and licensing status unavailable	<p>Fujii, K. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 19, 2013; doi:10.1073/pnas.1217563110 Contact: Satoshi Koike, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan e-mail: koike-st@igakuken.or.jp</p>
Drug platforms			
Crystal structure of a ternary complex including bacitracin A to guide analog development	<p>A crystal structure of the peptide antibiotic bacitracin A in complex with zinc and a geranyl pyrophosphate ligand could help inform the rational design of new topical antibiotics. The structure of bacitracin A in complex with zinc and geranyl pyrophosphate was solved at 1.1 Å resolution. The structure showed that bacitracin A envelopes the pyrophosphate group of its ligand and zinc ion. The structure also showed that direct bacitracin A–ligand interactions are mediated by hydrogen bonds between the peptide backbone and side chain amide groups of bacitracin A with oxygen atoms of the ligand. Next steps include using the structural information to rationally design and generate candidate molecules for affinity and activity testing.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.1012 Published online Sept. 19, 2013</p>	Unpatented; available for licensing	<p>Economou, N.J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 12, 2013; doi:10.1073/pnas.1308268110 Contact: Patrick J. Loll, Drexel University College of Medicine, Philadelphia, Pa. e-mail: ploll@drexelmed.edu</p>
Cyclic GMP-AMP (cGAMP) as a viral vaccine adjuvant	<p>Cell culture and mouse studies suggest cGAMP could be used as an adjuvant for viral vaccines. cGAMP synthase (cGAS) was recently identified as a cytosolic DNA sensor that produces cGAMP, which then activates the type I interferon pathway through the transmembrane protein 173 (STING; TMEM173) adaptor protein. In cultured, HIV-infected, human monocytes, small hairpin RNA against cGAS or STING decreased the production of type I interferon compared with control shRNA. In mice infected with herpes simplex virus (HSV), knocking out cGAS decreased immune responses and survival compared with no knockout. In mice, immunization with cGAMP plus ovalbumin increased B and T cell responses compared with immunization using ovalbumin alone. Next steps could include testing formulations of HIV or HSV vaccines with cGAMP adjuvants.</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.1013 Published online Sept. 19, 2013</p>	Patent applications filed; licensing status undisclosed	<p>Gao, D. <i>et al. Science</i>; published online Aug. 8, 2013; doi:10.1126/science.1240933 Li, X.-D. <i>et al. Science</i>; published online Aug. 29, 2013; doi:10.1126/science.1244040 Contact: Zhijian J. Chen, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: zhijian.chen@utsouthwestern.edu</p>
Induced pluripotent stem (iPS) cell-derived, chimeric antigen receptor (CAR)-expressing T cells for immunotherapy	<p>iPS cell-derived, CAR-expressing T cells could be used for immunotherapy in patients when suitable autologous or allogeneic T cells are unavailable. In peripheral blood T lymphocytes, viral vector-mediated expression of four factors reprogrammed the cells into iPS cells. These iPS cells were then transduced with a viral vector encoding a CD19-specific CAR and differentiated into highly cytotoxic T lymphocytes. In a mouse model of Burkitt's lymphoma, expanded, iPS cell-derived, CD19-specific CAR T lymphocytes conferred a survival advantage comparable to that of parent CD19-specific CAR T lymphocytes. Next steps include further optimization of the method for generating iPS cell-derived, CAR-expressing T cells for autologous or allogeneic therapies (<i>see Supersizing adoptive T cell transfer, page 6</i>).</p> <p>SciBX 6(36); doi:10.1038/scibx.2013.1014 Published online Sept. 19, 2013</p>	Patent application filed; available for licensing	<p>Themeli, M. <i>et al. Nat. Biotechnol.</i>; published online Aug. 11, 2013; doi:10.1038/nbt.2678 Contact: Michel Sadelain, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: sadelaim@mskcc.org</p>

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