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Super-enhancing discovery

By *Chris Cain, Senior Writer*

Boston researchers have detailed a class of regulatory elements, dubbed super-enhancers, that control the expression of genes, including oncogenes, that are key to determining cellular identity.^{1,2} The findings may explain how some compounds that broadly inhibit particular epigenetic regulators can act selectively on oncogenes and could thus help identify new drug targets in cancer.

The team has founded **Syros Pharmaceuticals Inc.** to develop compounds that disrupt super-enhancers or the genes they regulate in cancer.³

Recent genomewide studies conducted as part of the Encyclopedia of DNA Elements (ENCODE) project have predicted hundreds of thousands to millions of enhancer elements in mammalian genomes that regulate gene expression.⁴ Complementing this effort, whole-genome maps of transcription factor binding sites in individual cell types have found that key regulators of cellular identity tend to work together to form large protein-DNA regulatory complexes at cell type-specific enhancers.

These regulators of cellular identity often control their own expression and that of their co-regulator proteins, forming positive feedback loops that help maintain a particular cellular phenotype.

The best-characterized example comes from embryonic stem cell (ESC) regulators including *OCT4*, *SOX2* and *nanog homeobox (NANOG)*. These sequence-specific DNA-binding factors occupy highly overlapping locations genomewide and control each other's expression and the expression of downstream genes that specify ESC identity.⁵

As expected, all three regulators are required to maintain ESC identity. What was unexpected was the recent demonstration that Mediator, a multisubunit protein complex that is a general coactivator of transcription in all cell types, also was important for determining ESC identity.⁶

Team leader Richard Young thus set out to understand how disrupting Mediator preferentially affects ESC-specific gene expression.

"Mediator is brought to nearly every active gene, yet when we reduce Mediator function in ESCs, it looks exactly like we reduced the levels of the key transcription factors," he said. "How is it that when you perturb a common regulator of gene expression, you can have a very specific kind of biological effect?"

Young is a member of the **Whitehead Institute for Biomedical Research**, professor of biology at the **Massachusetts Institute of Technology** and a cofounder of Syros.



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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

2008 Q Street, NW, Suite 100

Washington, DC 20009

T: +1 202 462 9582

Nature Publishing Group

New York

75 Varick Street, 9th Floor

New York, NY 10013-1917

T: +1 212 726 9200

London

The Macmillan Building

4 Crinan Street

London N1 9XW

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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To investigate this question, he teamed up with James Bradner, who was investigating a similar conundrum in multiple myeloma (MM) cells. Those cells are particularly sensitive to inhibitors of proteins in the BET bromodomain family such as bromodomain containing 4 (BRD4).

Bromodomain-containing proteins are epigenetic regulators that bind to acetylated lysines on histones; they regulate chromatin remodeling and gene transcription. Previous studies have shown that small molecule BET inhibitors selectively kill some cancer cells, including MM and acute myelogenous leukemia (AML), by downregulating *c-Myc* (MYC) expression.^{7,8}

“One would think targeting a broadly prevalent chromatin factor would have a general effect on transcription, yet when we treat these cells with a BET inhibitor, we observe that only 50–100 genes are downregulated,” Bradner said. “So how is it selective?”

Bradner is an investigator in the Department of Medical Oncology at the **Dana-Farber Cancer Institute** and assistant professor in the Department of Medicine at **Harvard Medical School**.

To understand how certain genes might be particularly sensitive to perturbation of general transcriptional regulators, Young’s group performed extensive chromatin immunoprecipitation followed by whole-genome sequencing

“We went from looking at thousands of genes to looking at the few hundred that have super-enhancers. It allows us to focus a tremendous amount of genomic data being produced every day from ChIP-Seq efforts into a more simplified version that helps us place our bets.”

*—Richard Young,
Whitehead Institute for
Biomedical Research*

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(ChIP-Seq) to map the genomewide binding of numerous proteins. The binding maps included mediator complex subunit 1 (MED1) and BRD4 in MM cells, and MED1, OCT4, SOX2 and NANOG in ESCs.

In ESCs, the researchers identified 8,794 genomic regions that were co-occupied by OCT4, SOX2 and NANOG. What stood out were 231 highly enriched DNA regions within this set that spanned large distances up to 50 kb in length. These 231 regions had a median length of more than 8.5 kb, whereas the other 8,563 regions had a median length of 0.7 kb, which is what would be expected for a typical enhancer.

Notably, these long regions were found near genes known to be critical regulators of cell identity, including *OCT4*, *SOX2* and *NANOG*.

Young dubbed these regions super-enhancers because of their length and ability to drive transcription to higher levels than typical enhancers. In addition, super-enhancer activity was more sensitive to knockdown of *MED1* than typical enhancers, and super-enhancers bound at least 10-fold the amount of *MED1* as typical enhancers. Super-enhancers were also quite heterogeneous, spanning a wide range of lengths and displaying distinct patterns of transcription factor binding.

The researchers saw similar results in an MM cell line driven by a translocation upstream of *c-Myc*. About 8,000 enhancer regions were bound by BRD4 and MED1, and of those, 308 super-enhancers were identified that were on average 15-fold larger than traditional enhancers and that bound 18-fold more MED1 and 16-fold more BRD4.

Many genes associated with MM pathology were regulated by super-enhancers, including *c-Myc*.

When treated with JQ1, a BRD4 inhibitor, super-enhancers were, on average, more depleted of BRD4

than typical enhancers, and genes controlled by super-enhancers exhibited, on average, moderate but statistically lower expression than genes regulated by typical enhancers. The expression of certain genes associated with super-enhancers, most notably *c-Myc*, was dramatically reduced by JQ1 treatment.

Young said a possible explanation for the increased sensitivity of super-enhancers is that they are regulated by more cooperative binding interactions than typical enhancers due to their size, which would render them more sensitive to changes in transcription factor concentrations.

To confirm the widespread existence of super-enhancers, the researchers generated and analyzed ChIP-Seq data from multiple additional cell lines. In glioblastoma multiforme (GBM) and small-cell lung cancer (SCLC) samples, ChIP-Seq identified large super-enhancer regions near multiple tumor-associated genes.

In an analysis of existing ChIP-Seq data from a series of normal cells of varying types, super-enhancers were found upstream of key genes associated with the identity of each respective cell type.

Results were published in two separate *Cell* papers. One focused on ESCs and normal cells,¹ and the other focused on cancer cells.² Young was corresponding author of both studies, and Bradner was a coauthor on the cancer study.

“The papers are strong on concept and data. People may have seen this type of binding before, but the authors took away a new concept from this data, and concepts are important in science,” said Kristian Helin, director of the Biotech Research & Innovation Centre at the **University of Copenhagen** and CSO of **EpiTherapeutics ApS**.

Target hunting

Young and Bradner founded Syros last year to apply insights gained from mapping super-enhancers to cancer drug development. Earlier this month, the company exited stealth mode with a \$30 million series A round led by **ARCH Venture Partners** and **Flagship Ventures**.³

CEO Nancy Simonian said the company is taking a two-pronged strategy that involves targeting super-enhancers themselves and identifying new targets that may have been previously missed by expression analysis.

“One of the important discoveries in this work is the demonstration that if you target a component of super-enhancers, you can get selective effects. It allows you to think you can disrupt components of enhancers and get preferential disruption of super-enhancer function,” she said.

Simonian said the company is interested in targeting transcriptional regulatory machinery, which could include kinases. Thus, the company’s third cofounder, Nathanael Gray, was recruited for his expertise in kinase inhibitor biochemistry. Gray is professor of biological chemistry and molecular pharmacology at Harvard Medical School.

Simonian added that the company is not developing BRD4 inhibitors and emphasized that JQ1 was used solely as proof of concept that super-enhancers could be selectively inhibited. In 2011, Bradner founded **Tensha Therapeutics Inc.** to develop derivatives of JQ1, which are in preclinical development.

Young suggested that the approach taken to characterize the precise functions of JQ1 could serve as a model for understanding the actions of compounds that inhibit other transcriptional regulators, including epigenetic targets. “Everyone seems very focused on the development of drugs against ‘epigenetic’ regulators, but for any component of enhancers that can be drugged, whether a histone-modifying enzyme or a kinase, it is now possible to map out the logic of control pathways associated with enhancers,” he said.

Helin agreed that this level of understanding is critical for epigenetic drug discovery programs and noted that companies including EpiTherapeutics already are routinely using techniques including ChIP-Seq to generate this information. “Biotechs have to do these types of experiments—it is obviously important for understanding the direct effects of your drug,” he said.

He wanted to see more work characterizing both super-enhancers and the effect of BET inhibition in additional MM cell lines, which can display varying levels of sensitivity to BET inhibitors and can drive *c-Myc* expression through a variety of distinct genetic mechanisms.

Bradner said additional experiments are ongoing to characterize super-enhancers in additional MM cells that show a range of sensitivities to JQ1, including cells with different genomic alterations that drive *c-Myc* expression.

Young said that beyond targeting the super-enhancers themselves, super-enhancers could be used to hone in on key cell fate regulators or drug targets that may have been missed by other approaches.

“The papers are strong on concept and data. People may have seen this type of binding before, but the authors took away a new concept from this data, and concepts are important in science.”

**—Kristian Helin,
University of Copenhagen**

“We went from looking at thousands of genes to looking at the few hundred that have super-enhancers,” he said. “It allows us to focus a tremendous amount of genomic data being produced every day from ChIP-Seq efforts into a more simplified version that helps us place our bets.”

Helin said the real demonstration of the utility of super-enhancer mapping will come when the approach uncovers new functional biology. “The real test is to say, can you turn this idea around, and can you find the transcription factor that is driving cell fate in a system where we don’t already know the identity of that factor,” he said.

Syros has exclusively licensed undisclosed IP covering biochemical assays and bioinformatics approaches used to identify super-enhancers, in addition to undisclosed IP from Whitehead and Dana-Farber covering two small molecule programs against undisclosed targets.

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Contact: Richard A. Young, Whitehead Institute for Biomedical Research, Cambridge, Mass.
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Contact: Richard A. Young, Whitehead Institute for Biomedical Research, Cambridge, Mass.
e-mail: young@wi.mit.edu
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COMPANIES AND INSTITUTIONS MENTIONED

ARCH Venture Partners, Chicago, Ill.
Dana-Farber Cancer Institute, Boston, Mass.
EpiTherapeutics ApS, Copenhagen, Denmark
Flagship Ventures, Cambridge, Mass.
Harvard Medical School, Boston, Mass.
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MERTK: upstream from BRAF

By Michael J. Haas, Senior Writer

U.S. researchers have shown that inhibiting c-Mer proto-oncogene tyrosine kinase, a protein that sits upstream from BRAF, reduced melanoma growth in mice.¹ Future studies will need to determine whether inhibitors of this kinase are effective in BRAF-resistant tumors.

c-Mer proto-oncogene tyrosine kinase (MERTK) is a member of the TAM receptor family of transmembrane proteins that includes TYRO3 protein tyrosine kinase (TYRO3; Sky) and AXL receptor tyrosine kinase (AXL; UFO). *MERTK* is expressed on at least three types of normal cells: platelets, for which it aids their aggregation; macrophages, which it enables to engulf target cells; and a range of epithelial cell types, for which it plays a role in survival.

Studies by multiple groups have shown that *MERTK* is overexpressed or hyperactivated—and thus a potential therapeutic target—in leukemia² and in prostate,³ brain⁴ and lung⁵ cancers. At least one study has shown that TAM and other tyrosine kinase receptors are activated in melanoma,⁶ and

two more have linked TYRO3, AXL and the TAM receptor ligand, growth arrest–specific 6 (GAS6), to melanoma tumorigenesis and invasiveness.^{7,8}

Collectively, these findings prompted Douglas Graham and colleagues to hypothesize that MERTK might also be a therapeutic target in melanoma. Graham is assistant professor of pediatrics and immunology at the University of Colorado Denver School of Medicine.

To investigate this hypothesis, Graham's team performed microarray analyses and found that *MERTK* was overexpressed in about 50% of melanomas compared with normal human melanocytes. Moreover, there was higher *MERTK* expression in metastatic melanoma than in primary tumors.

MERTK overexpression did not correlate with mutations in *BRAF* or *neuroblastoma Ras viral (v-Ras) oncogene (NRAS)*, which are found in about 50% and 20% of melanomas, respectively.

In human melanoma cell lines, a small molecule inhibitor of MERTK decreased proliferation and invasion and increased apoptosis compared with vehicle.

Mice injected with human melanoma cell lines pretreated with *MERTK* small hairpin RNA developed smaller tumors than mice injected with cells pretreated with a scrambled control shRNA. Graham said the team did not test the small molecule in mouse models because it was not suitable for *in vivo* work.

Figure 1. Downstream of MERTK.

According to a study in *The Journal of Clinical Investigation*, inhibiting c-Mer proto-oncogene tyrosine kinase (MERTK)—which lies upstream from BRAF—could help treat melanoma.

In melanoma tumor cells [a], overexpression of *MERTK* activates multiple signaling pathways. Activated Ras [b(1)] signals through BRAF, CRAF (RAF1) and other Raf proteins to activate MAP kinase kinase 1 (MAP2K1; MEK1) and MEK2 (MAP2K2). Activated JAK kinases (JAKs) [b(2)] in turn activate signal transducer and activator of transcription (STAT) proteins. Activated phosphoinositide 3-kinase (PI3K) [b(3)] induces activation of protein kinase B (PKB; PKBA; AKT; AKT1). Upregulation of any or all of these three pathways leads to melanoma growth, proliferation and survival [c].

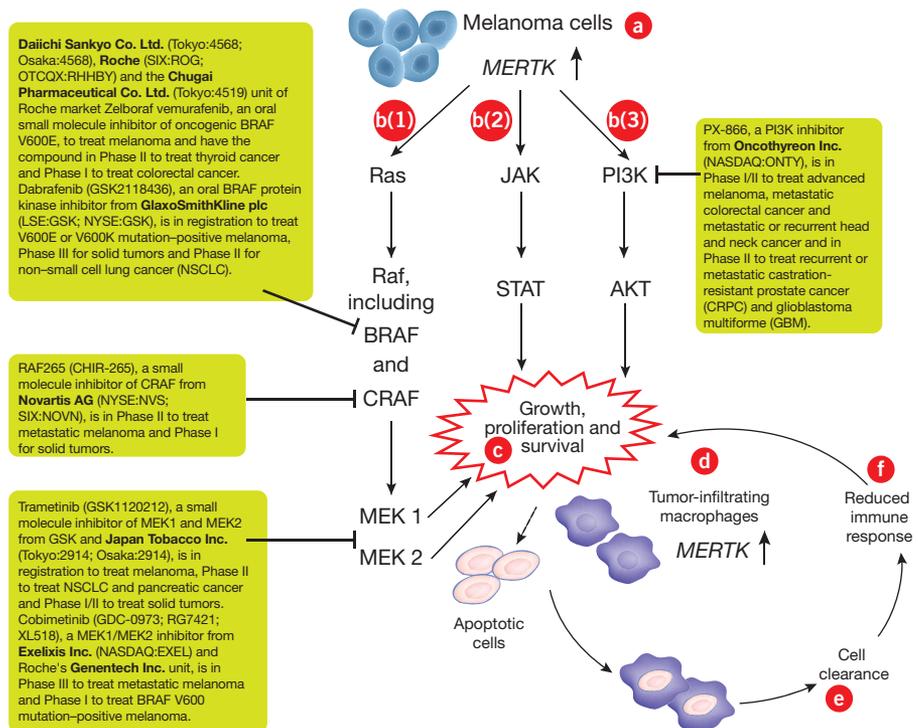
Additionally, expression of *MERTK* on tumor-infiltrating macrophages [d] may enhance their ability to engulf and clear apoptotic tumor cells [e], thereby leading to reduced immune system responses [f] and enhanced tumor survival.

Multiple companies market or are developing products that inhibit proteins in pathways [b(1)]–[b(3)] to treat melanoma.

CEP-32496, a dual inhibitor of BRAF and epidermal growth factor receptor (EGFR) from **Ambit Biosciences Corp.** and **Teva Pharmaceutical Industries Ltd.**, is in preclinical testing to treat melanoma.

DP-4978, an oral small molecule dual inhibitor of mutant BRAF and CRAF from **Deciphera Pharmaceuticals LLC** and **Eli Lilly and Co.**, is in preclinical testing to treat melanoma.

Nanolipolee 007, an i.v. nanoparticle formulation containing leelamine derived from the bark of a pine tree that inhibits protein kinase Bγ (PKBγ; AKT3) and STAT3, is in preclinical testing from **Melanovus Oncology Inc.** to treat melanoma.



Additional *in vitro* studies revealed that MERTK promoted growth, proliferation and survival in melanoma cells by activating at least three signaling pathways, including the Ras/Raf/MEK/MAPK signaling cascade (see Figure 1, “Downstream of MERTK”).

Data were reported in *The Journal of Clinical Investigation*.

The team included researchers from **The University of North Carolina at Chapel Hill**, the **University of Pittsburgh School of Medicine**, **Harvard Medical School** and **Massachusetts General Hospital**.

“It is particularly noteworthy that the *JCI* study showed 28% of brain metastases of melanoma had elevated *MERTK* expression” because so little is known about how melanoma metastasizes to the brain, said Keiran Smalley. He is assistant professor in the molecular oncology program and scientific director of the Melanoma Research Center of Excellence at the **H. Lee Moffitt Cancer Center & Research Institute**.

Better with BRAF?

The immediate questions are whether a MERTK inhibitor can show efficacy

in primary melanoma tumors that have developed resistance to BRAF inhibitors—such as Zelboraf vemurafenib—and whether blocking MERTK will have additive effects in combination with inhibitors of BRAF and MEK.

“One aspect that is not yet clear is the importance of MERTK signaling relative to that of other driver oncogenes in melanoma,” such as mutant *BRAF* and *NRAS*, Smalley said.

He noted that the *JCI* team showed that *MERTK* knockdown “only delayed melanoma growth, making it likely that other drivers are also involved in tumor progression.”

Jennifer Low, group medical director at the **Genentech Inc.** unit of **Roche**, agreed that “studies specifically looking at the prevalence of MERTK activation in the general melanoma population and in patients with BRAF mutations would be of interest.”

Smalley also wanted to know whether *MERTK* expression was elevated in tumors from patients with melanoma in whom BRAF inhibitors failed. “This possibility could be explored further by determining whether *MERTK* expression mediates the increased MEK signaling in melanoma cells that are resistant to BRAF inhibition,” he said.

Graham said previous studies by his group have shown that *MERTK* expression plays a role in resistance to chemotherapy in brain cancer⁴, lung cancer⁵ and acute lymphoblastic leukemia (ALL),^{9,10} “and we are investigating whether this is also the case in melanoma. We think that MERTK inhibition might help treat melanoma that has developed resistance to BRAF inhibitors” and other therapies.

However, Low pointed out that the *JCI* study did not establish “whether inhibiting MERTK would reverse or delay progression in melanoma if combined with, or used following, a BRAF inhibitor.” Thus, she wanted to see MERTK inhibition tested in cell lines and animal models of BRAF mutation–positive melanoma that had developed resistance to BRAF inhibitors.

Smalley agreed it would be important “to determine whether the combination of MERTK and BRAF inhibitors gives a more durable

response to treatment than a BRAF inhibitor alone,” as has been observed with combined BRAF/MEK inhibition.

“It would also be wise to test MERTK inhibitors in combination with inhibitors of the MEK/ERK and PI3K/AKT [phosphoinositide 3-kinase/protein kinase B] pathways,” he added.

Graham said the team has developed a next-generation MERTK inhibitor with better bioavailability than the molecule used in the published study and is now testing it in combination with Zelboraf and an undisclosed MEK inhibitor.

“We have found these combinations increased efficacy in melanoma cell lines compared with monotherapy,” he said. “Now we plan to test the combinations in primary melanoma cells and mouse models of melanoma” and expect to publish the results this year.

Daiichi Sankyo Co. Ltd., Roche and Roche’s **Chugai Pharmaceutical Co. Ltd.** unit market Zelboraf, an oral small molecule inhibitor of oncogenic BRAF V600E.

Cobimetinib (GDC-0973; RG7421; XL518), a MAP kinase kinase 1 (MAP2K1; MEK1) and MEK2 (MAP2K2) inhibitor from **Exelixis Inc.** and Genentech, is in Phase III testing to treat metastatic melanoma and Phase I trials to treat BRAF V600 mutation–positive melanoma.

Roche and Genentech also have Zelboraf and MPDL3280A (RG7446), a human mAb against programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1), in Phase Ib testing in previously untreated patients with BRAF V600 mutation–positive melanoma.

Macrophage futures

The team has conducted follow-on studies to explore the therapeutic implications of another finding from the *JCI* study: results of microarray analyses showing that more than 50% of tumor-infiltrating macrophages highly expressed *MERTK*.

Indeed, Graham said the team has another paper in press showing that MERTK inhibition—in addition to its direct effect on tumors—has an immunomodulatory action in melanoma and other *MERTK*-expressing cancers.

“We think that the high levels of *MERTK* expressed on tumor-infiltrating macrophages may increase their efficiency at clearing apoptotic melanoma cells” and thus limit the time during which antigens from those dying cells could trigger an immune response, Graham said. Thus, MERTK inhibition could decrease macrophage-aided cell clearance and thereby stimulate immune responses to the tumor, he said.

He added, “The immunomodulatory effect of MERTK inhibition on macrophages could also be important in cancer types that themselves do not overexpress *MERTK*.”

The team also is collecting plasma serum from patients with melanoma to determine whether circulating levels of soluble MERTK or GAS6 correlate with disease progression and is planning studies to better understand the role of MERTK in cancer cell migration, invasion and metastasis, Graham said.

The University of North Carolina at Chapel Hill has patented the MERTK inhibitors and their therapeutic uses. The IP is available for licensing.

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“One aspect that is not yet clear is the importance of MERTK signaling relative to that of other driver oncogenes in melanoma.”

—Keiran Smalley,
H. Lee Moffitt Cancer
Center & Research Institute

Interfering with interferon

By Lauren Martz, Staff Writer

Type I interferon receptors are key factors that promote antiviral immunity, but two separate teams have found that elevated interferon signaling may actually be detrimental to the body's ability to fight persistent infections. Groups at **The Scripps Research Institute** and the **University of California, Los Angeles** showed that blocking type I interferon during the persistent stages of viral infections in mice can resolve the infections.^{1,2}

One key implication from the findings is that researchers should re-evaluate how to use interferon in treating HCV, as it has important antiviral benefits in acute infections but may be damaging during persistent infection.

According to David Brooks, who led the UCLA team, "There is a growing idea that dampening the constant immune activation in chronic infectious diseases has benefits. Our idea that interferon may be driving persistent infections adds one more piece to the puzzle." Brooks is assistant professor of microbiology, immunology and molecular genetics at UCLA.

Type I interferon is secreted by multiple cell types, including immune cells, and plays a key role in the antiviral immune response. Many acute viral infections are cleared by the antiviral cytotoxic T cell response that involves interferon signaling.

But some viruses, including HIV and HCV, establish persistent infections by wearing down the immune system via chronic inflammation and T cell exhaustion or by evading the immune system through the upregulation of immunosuppressive factors that dampen antiviral immunity.

Indeed, previous studies have shown that upregulation of immunosuppressive factors such as *programmed cell death 1 ligand 1* (*CD274 molecule*; *PD-L1*; *B7-H1*) or *IL-10* contribute to chronic

(Continued from "MERTK: upstream from BRAF," p. 6)

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e-mail: doug.graham@ucdenver.edu
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infections and cancers,³ and other work suggests that chronic inflammation contributes to chronic infection.⁴

Now, two separate teams have built on the prior findings by examining immune system dysfunction in chronic diseases. Both teams concluded that inhibiting interferon receptor signaling, despite known antiviral functions, may actually help clear viruses in the persistent stage of infection.

A group from Scripps led by Michael Oldstone found that antibody-mediated inhibition of type I interferon reduced chronic inflammation, immune suppression and viral load in mice with persistent viral infections.

Oldstone is professor of immunology and microbial science at Scripps. The team also included researchers from the **Washington University in St. Louis School of Medicine**.

The group infected mice with two lymphocytic choriomeningitis virus (LCMV) strains—Cl13 and Armstrong—to model human viral infections. Cl13 lasted more than 90 days and thus modeled persistent infections, whereas the Armstrong strain served as a control because it caused an acute infection that was cleared within 8 days.

In the Cl13-infected mice, serum interferon levels, dendritic cell production of interferon- β (IFN β ; IFN- β) and proinflammatory cytokine levels were higher than those in mice infected

with the Armstrong strain.

Cl13 mice receiving a prophylactic anti-type I interferon receptor antibody had lower levels of proinflammatory cytokines and chemokines and negative immune regulatory elements PD-L1 and IL-10 than untreated mice. These findings suggested that impeding interferon signaling could reduce features of immune system dysfunction responsible for persistent infection.

Prophylactic treatment with anti-interferon receptor antibodies led to undetectable viral titers in Cl13 mice by day 50 postinfection. The antibodies did cause an initial increase in viral load in both Cl13 and control animals and caused an overall increase in viral burden in the control mice.

(Continues on p. 8)

"There is a growing idea that dampening the constant immune activation in chronic infectious diseases has benefits. Our idea that interferon may be driving persistent infections adds one more piece to the puzzle."

—David Brooks,
University of California, Los Angeles

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Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan
Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568), Tokyo, Japan
Exelixis Inc. (NASDAQ:EXEL), South San Francisco, Calif.
Genentech Inc., South San Francisco, Calif.
H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of Colorado Denver School of Medicine, Denver, Colo.
The University of North Carolina at Chapel Hill, Chapel Hill, N.C.
University of Pittsburgh School of Medicine, Pittsburgh, Pa.

These findings confirmed that type I interferon does have its uses—particularly during acute infection—but also contributes to immune dysfunction later in cases of persistent infections.

The anti-interferon receptor antibodies also restored normal lymphoid architecture and were effective at clearing the virus after the onset of persistent infection.

Finally, the team found that the antibody-mediated clearance of Cl13 LCMV required CD4⁺ T cells. In the treated mice, depletion of CD4 prevented the accelerated viral clearance by anti-interferon antibodies.

Replication

Separately, a group led by Brooks obtained similar results and drew the same conclusions about the dual roles of interferon in viral infections.

Brooks is a former postdoctoral fellow in Oldstone's lab. The group also included researchers from the **Cincinnati Children's Research Foundation** and the **University of Cincinnati College of Medicine**.

The UCLA group used the same mouse models and found that type I interferon-stimulated genes and regulatory factors were initially expressed at the same levels in the acute and chronic infection models, but their levels were elevated during persistent infection.

The team also found that blocking the interferon receptor decreased chronic inflammatory signaling and immunosuppressive components during persistent infection. Cl13-infected mice receiving an anti-interferon receptor antibody had viral titers that by day 30 were either lower than those in mice given an isotype control antibody or cleared.

Similar to the Scripps findings, delivery of the antibody prior to persistent Cl13 infection of mice led to virus clearance during persistent infection, whereas delivery of the antibody during acute Armstrong infection of mice led to virus persistence.

The team also detected elevated levels of CD4⁺ T cells and type II interferon- γ (IFN γ ; IFN- γ) during persistent infections and found that antibody-mediated blockade of either CD4 or IFN- γ prevented the accelerated viral clearance by the anti-type I interferon receptor antibody.

Also, treatment with anti-interferon receptor antibody starting 25 days after infection accelerated viral clearance, suggesting that type I interferon blockade could be used to treat established persistent infections.

Both studies were published in *Science*.

Chronicles of interferon

Subpopulations of patients with HIV or HCV may be the most likely to benefit from anti-interferon therapies.

According to Brooks, "The next step is to validate the data in infections such as HIV."

Charles Nicolette, CSO and VP of R&D at **Argos Therapeutics Inc.**, told *SciBX* that "HIV may be a good choice to move forward in development. Specifically, patients with high levels of chronic inflammation driven by type I interferon would be key populations."

Argos' AGS-009, an anti-IFN- α (IFNA) antibody, recently

completed Phase I testing for systemic lupus erythematosus (SLE).

Rafick-Pierre Sékaly, co-director and scientific director of the **Vaccine & Gene Therapy Institute of Florida**, added that patients with HIV who are nonresponsive to antiretroviral therapy generally show high interferon signatures and high levels of PD-L1.

"HIV patients not on an antiretroviral therapy, and even those patients on therapy who may be experiencing an ongoing smoldering immune activation that chronically leads to immune senescence, may benefit from inhibition of the negative effects of interferon signaling," said Brooks.

Nicolette said other benefits of anti-interferon therapy include "providing relief from the damaging effects of chronic inflammation and reprogramming the immune system to better respond to the infection."

In addition to HIV, the authors of the *Science* papers think some patients with HCV could benefit from anti-interferon therapy, although it may be more difficult in the HCV setting to translate the strategy into clinical trials.

Brooks said his team does not have ongoing HCV studies but thinks the findings could be applicable to the disease.

"HCV is particularly interesting because a subset of patients is actually given interferon as a drug. In those patients, when interferon treatment fails, it is usually because they already had a high enough level of interferon to cause immune dysfunction. In these cases, adding interferon is like bringing sand to the beach. It doesn't help, and our findings suggest it may actually hurt them," he said.

Nicolette said that the problem with anti-interferon for HCV is that it is already possible to eradicate the infection with type I interferon in some patients. "It drives the immune system to higher activity," he said.

"Thinking about developing these kinds of interferon-targeted therapies is really a challenge because it is counterintuitive. You want to disable an antiviral mechanism in patients with a virus, but this type of treatment may induce an immunological change that tips the scales in favor of virus clearance," said Nicolette.

He added that it would probably be very hard to find an infectious disease doctor willing to treat patients with a strategy that is in direct opposition to a proven approach.

Regardless of indication, Brooks said, "a lot more studies are needed. Interferon is so important in regulating the immune response to infection as well as regulating homeostasis. One really has to tease apart these functions in interferon signaling to identify the best way to target it clinically. We need to preserve the antiviral role of interferon but not the immune dysfunction and chronic activation."

Brooks said UCLA has filed for a patent covering his team's work. The IP is available for licensing. The patent and licensing status for the findings from the Scripps group is unavailable.

"HIV may be a good choice to move forward in development. Specifically, patients with high levels of chronic inflammation driven by type I interferon would be key populations."

—Charles Nicolette,
Argos Therapeutics Inc.

Martz, L. *SciBX* 6(16); doi:10.1038/scibx.2013.381
Published online April 25, 2013

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Argos Therapeutics Inc., Durham, N.C.
Cincinnati Children's Research Foundation, Cincinnati, Ohio
The Scripps Research Institute, La Jolla, Calif.
University of California, Los Angeles, Calif.
University of Cincinnati College of Medicine, Cincinnati, Ohio
Vaccine & Gene Therapy Institute of Florida, Port St. Lucie, Fla.
Washington University in St. Louis School of Medicine, St. Louis, Mo.



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Regenerating the kidney

By Kai-Jye Lou, Staff Writer

Researchers at **Harvard Medical School** and **Massachusetts General Hospital** have shown that their previously described platform for creating transplantable bioengineered organs from decellularized matrices can be used to create a functional kidney.¹ The researchers are refining the process to improve kidney functionality and hope to begin large-animal testing within five years.

In the U.S., the kidney is the most commonly transplanted organ and the one for which there are the highest numbers of patients on waiting lists, according to the [Organ Procurement and Transplantation Network website](#).

Decellularization is a process in which detergents and enzymes are used to remove cells from an organ or piece of tissue. What remains is an extracellular matrix (ECM) scaffold that retains both the 3D architecture of the original part and the associated vascular networks, which can then be seeded with cells to create bioengineered organs and tissues.²

In 2008, MGH's Harald Ott and collaborators at the **University of Minnesota** first reported on the use of their platform to engineer a beating rat heart from a decellularized heart ECM.³ His group has since reported on the creation of bioengineered lungs and pancreases.^{4,5}

"Our ongoing work is focused on showing that our approach is a platform technology and not just applicable to a single organ," said Ott, a fellow in cardiothoracic surgery at MGH and an instructor in surgery at HMS.

Although replacement bladders and tracheas built upon decellularized matrices have been tested in patients by investigators and companies such as **Tengion Inc.**, such organs have relatively low functional complexity compared with most other internal organs, including the kidney.

Indeed, according to Stephen Badylak, deputy director of the **McGowan Institute for Regenerative Medicine** at the **University of Pittsburgh** and director of the institute's Center for Preclinical Tissue Engineering, the cells seeded onto the scaffolds of bioengineered bladders and tracheas support the regeneration of the organ's tissues

but do not persist to become a part of the new tissue.

"The approach taken by Dr. Ott and colleagues is different in that they would want and actually require the seeded cells to persist and

become a part of the transplanted organ," he said.

Badylak also is a professor in the Department of Surgery at the **University of Pittsburgh Medical Center**. His group is working on a bioengineered liver created with an approach similar to the one being developed by Ott.⁶

Ott added that increased complexity makes the process of repopulating the ECM scaffolds for organs such as kidneys more challenging than it is for bladders and tracheas.

To create bioengineered kidneys, Ott and his team first perfused cadaveric rat kidneys with a detergent solution to generate decellularized kidney ECMs. The resulting matrices were reseeded with a mix of rat neonatal kidney cells and human umbilical vein endothelial cells. The researchers then cultured the seeded scaffolds in a bioreactor under whole-organ culturing conditions for up to 12 days before transplantation.

In rats, the resulting bioengineered kidney grafted at an orthotopic position had filtering functionality, produced urine and did not show bleeding or clot formation for the duration of the short-term experiment. The functionality of the bioengineered kidney was higher than that of a decellularized kidney not reseeded with cells but lower than that of a cadaveric kidney.

Results were published in *Nature Medicine*.

"The real excitement from this study is in showing that the engineered organ has the ability to filter blood and form urine, which is what the kidney is supposed to do," said Badylak.

"The current study demonstrates the ability of cells introduced into a decellularized matrix to migrate to their native niche, thereby facilitating the re-creation of a very complex tissue structure," said Jeffrey Ross, VP of product development at **Miromatrix Inc.** "Many had thought the complexity of the kidney nephron would be too high to achieve functional recellularization."

Miromatrix has licensed exclusive, worldwide rights to a patent application from the University of Minnesota that covers the decellularization and recellularization process. The company is using the technology to develop engineered tissue and organ products for transplant but declined to provide details.

Badylak added that in addition to potentially addressing the shortage in donor organs, the underlying approach also could decrease the need for immunosuppressive therapy following transplant because the organ scaffolds could be seeded with a patient's own cells.

Refining protocol

Ott told *SciBX* that his group is now trying to refine the protocols for seeding and culturing the bioengineered organs. The researchers also are trying to adapt their approach to generate pig and human organs.

He said the goal is to test one of the bioengineered organs in a large-animal model within five years.

"Right now, researchers need to figure out the order in which to replace the cells during the seeding process and whether there will be a need to replace most of the cell types of the kidney or just a few of the cell types and let the body take care of the rest," said Badylak.

Badylak thinks the most immediate challenge is to maintain long-term blood flow through the bioengineered organs without also causing blood clots. He said this could be especially challenging for the kidney because the organ has an intricate vascular network.

M. Korkut Uygun, an assistant professor of surgery at HMS who is not part of Ott's team, agreed that preventing clot formation and

"I think the bioengineered organ most likely to reach human trials first will either be a kidney or a liver."

—Jeffrey Ross,
Miromatrix Inc.

"The real excitement from this study is in showing that the engineered organ has the ability to filter blood and form urine, which is what the kidney is supposed to do."

—Stephen Badylak,
University of Pittsburgh Medical Center

poor circulation remain key technical challenges that still need to be addressed. He said that ideally, the vascular network of the decellularized organ scaffold needs to be lined with endothelial cells prior to transplantation because blood clots can form at exposed patches of ECM.

Uygun also said strategies such as using heparin or giving anticlotting drugs after transplantation have produced mixed results.

He thinks the next major milestone would be to show that a bioengineered organ can rescue the host animal from problems associated with loss of the host organ's function.

"Right now, what we see is that the transplanted organs only remain functional for a short period of time, usually a few hours," said Uygun. "The next major goal would be to show that we could keep one of these engineered organs functional inside an animal for weeks, months or even years."

Uygun's group is developing a transplantable bioengineered liver created with an approach similar to the one being developed by Ott.⁷

"I think the bioengineered organ most likely to reach human trials first will either be a kidney or a liver," Ross told *SciBX*. "This is based on multiple factors including cell sourcing, prolonged organ donor waiting list times, mortality rates and the lack of end-stage therapies. An engineered liver or kidney, even providing only 20% of the original organ function, would be effective and life changing."

MGH has filed a patent application covering methods for generating the bioengineered kidney. The technology is available for licensing.

Lou, K.-J. *SciBX* **6**(16); doi:10.1038/scibx.2013.382

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Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
McGowan Institute for Regenerative Medicine, Pittsburgh, Pa.
Miromatrix Inc., Minneapolis, Minn.
Tengion Inc. (OTCQB:TNGN), Winston-Salem, N.C.
University of Minnesota, Minneapolis, Minn.
University of Pittsburgh, Pittsburgh, Pa.
University of Pittsburgh Medical Center, Pittsburgh, Pa.

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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
Cancer				
Cancer	Epoxide hydrolase 2 (EPHX2; CEH)	Cell culture and mouse studies suggest a combination of fish oil–derived epoxy docosapentaenoic acids (EDPs) and EPHX2 inhibitors could be useful for treating cancer. In a mouse model for breast cancer, EDP plus an EPHX2 inhibitor caused more potent inhibition of tumor vascularization and growth than either treatment alone. Next steps could include further preclinical evaluation of EPHX2 inhibitors in cancer models. Arete Therapeutics Inc., a company cofounded by the study's corresponding author, had EPHX2 inhibitors in Phase II testing for type 2 diabetes before ceasing operations.	Soluble epoxide hydrolase inhibitors patented; available for licensing from the University of California, Davis Contact: Barbara Boczar, University of California, Davis, Calif. e-mail: bboczar@ucdavis.edu	Zhang, G. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 3, 2013; doi:10.1073/pnas.1304321110 Contact: Bruce D. Hammock, University of California, Davis, Calif. e-mail: bdhammock@ucdavis.edu
		SciBX 6(16); doi:10.1038/scibx.2013.383 Published online April 25, 2013		
Colorectal cancer	Proteasome 26S subunit non-ATPase 10 (PSMD10; gankyrin)	Mouse and cell culture studies suggest inhibiting PSDM10 could help prevent hepatic metastasis in colorectal cancer. In samples from patients who have colorectal cancer, greater PSDM10 expression was associated with increased risk of disease metastasis to the liver. In a human colon cancer cell line, small hairpin RNA against <i>PSDM10</i> led to decreased invasiveness compared with scrambled shRNA. In mouse models for metastatic colorectal cancer, small hairpin RNA–mediated knockdown of <i>PSDM10</i> led to smaller primary tumors and fewer hepatic metastases than no knockdown. Next steps include developing small molecule PSDM10 inhibitors.	Unpatented; partnered for development of PSDM10 as risk marker for hepatic metastases in colorectal cancer; other applications available for partnering	Bai, Z.-f. <i>et al. Cancer Res.</i> ; published online April 10, 2013; doi:10.1158/0008-5472.CAN-12-4586 Contact: Tao Zhou, National Center of Biomedical Analysis, Beijing, China e-mail: tzhou@ncba.ac.cn Contact: Chenguang Wang, Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, Pa. e-mail: chenguang.wang@jefferson.edu
		SciBX 6(16); doi:10.1038/scibx.2013.384 Published online April 25, 2013		
Colorectal cancer	Tankyrase TRF1- interacting ankyrin-related ADP-ribose polymerase (TNKS); TNKS2	Mouse studies suggest small molecule inhibitors of TNKS and TNKS2 could be useful for treating colorectal cancer. In a mouse xenograft model for colorectal cancer, dual inhibitors of TNKS and TNKS2 decreased wingless-type MMTV integration site (WNT) signaling and tumor growth compared with vehicle. Next steps include improving tolerability, optimizing dosage and selecting a preclinical candidate. Novartis AG has discovery-stage TNKS and TNKS2 inhibitors for various cancers.	Patented; licensing status undisclosed	Lau, T. <i>et al. Cancer Res.</i> ; published online March 28, 2013; doi:10.1158/0008-5472.CAN-12-4562 Contact: Mike Costa, Genentech Research & Early Development, South San Francisco, Calif. e-mail: mcosta@gene.com
		SciBX 6(16); doi:10.1038/scibx.2013.385 Published online April 25, 2013		

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Melanoma	c-Mer proto-oncogene tyrosine kinase (MERTK)	<i>In vitro</i> and mouse studies suggest MERTK inhibitors could help treat melanoma. In about 50% of primary human melanoma cells, MERTK expression correlated with disease progression and was greater than that in normal melanocytes. In human melanoma cell lines, small hairpin RNA against <i>MERTK</i> or a MERTK inhibitor increased apoptosis and decreased proliferation and invasion compared with vehicle. In a mouse xenograft model for human melanoma, small hairpin RNA-mediated knockdown of <i>MERTK</i> led to decreased tumor growth compared with no knockdown. Ongoing work includes testing a MERTK inhibitor in mouse models for melanoma (<i>see MERTK: upstream from BRAF, page 5</i>).	Patented by The University of North Carolina at Chapel Hill; available for licensing or partnering	Schlegel, J. <i>et al. J. Clin. Invest.</i> ; published online April 15, 2013; doi:10.1172/JCI67816 Contact: Douglas K. Graham, University of Colorado Denver School of Medicine, Aurora, Colo. e-mail: doug.graham@ucdenver.edu
		SciBX 6(16); doi:10.1038/scibx.2013.386 Published online April 25, 2013		
Ovarian cancer	ATPase class VI type 11B (ATP11B)	Mouse and cell culture studies suggest inhibiting ATP11B could help circumvent resistance to platinum chemotherapy in ovarian cancer. In a genomic analysis of a panel of ovarian cancer cell lines, cisplatin-resistant cells had greater ATP11B expression than cisplatin-sensitive lines. In a cisplatin-resistant ovarian cancer cell line, liposome-mediated delivery of <i>ATP11B</i> -targeted small interfering RNA increased cisplatin sensitivity compared with delivery of control siRNA. In multiple mouse xenograft models for cisplatin-resistant human ovarian cancer, cisplatin plus liposome-mediated delivery of <i>ATP11B</i> -targeted siRNA decreased tumor growth compared with cisplatin plus delivery of control siRNA. Next steps include further exploring the mechanisms underlying resistance to platinum chemotherapy.	Patent application filed covering liposome-based siRNA delivery system; available for licensing from The University of Texas MD Anderson Cancer Center's Office of Technology Commercialization	Moreno-Smith, M. <i>et al. J. Clin. Invest.</i> ; published online April 15, 2013; doi:10.1172/JCI65425 Contact: Anil K. Sood, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: asood@mdanderson.org
		SciBX 6(16); doi:10.1038/scibx.2013.387 Published online April 25, 2013		
Cardiovascular disease				
Atherosclerosis	Not applicable	Patient and mouse studies suggest inhibiting intestinal microbiota-mediated metabolism of L-carnitine could help prevent atherosclerosis and other cardiovascular diseases. In a cohort of 2,595 subjects undergoing cardiac evaluation, elevated levels of L-carnitine and trimethylamine-N-oxide (TMAO) in plasma were associated with increased risk of cardiovascular diseases and the occurrence of an adverse cardiovascular event. Mouse and human gut microbiota were shown to metabolize L-carnitine to produce TMAO. In a mouse model for atherosclerosis, antibiotics prevented L-carnitine-mediated increases in disease. Next steps could include screening for compounds that inhibit production of TMAO by the microbiota.	Patent and licensing status unavailable	Koeth, R.A. <i>et al. Nat. Med.</i> ; published online April 7, 2013; doi:10.1038/nm.3145 Contact: Stanley L. Hazen, Cleveland Clinic, Cleveland, Ohio e-mail: hazens@ccf.org
		SciBX 6(16); doi:10.1038/scibx.2013.388 Published online April 25, 2013		

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cardiomyopathy; heart failure	MAP kinase 1 (MAPK1; ERK-2)	Rodent studies suggest inhibiting ERK-2 phosphorylation at threonine 188 could help prevent pathological cardiac hypertrophy. In rat cardiomyocytes, overexpression of a dominant-negative mutant ERK-2 that blocks ERK phosphorylation at threonine 188 decreased drug-induced hypertrophy compared with overexpression of wild-type ERK-2 and did not trigger apoptosis. In mice subjected to transverse aortic constriction, the dominant-negative ERK-2 prevented pathological cardiac hypertrophy and remodeling without causing adverse effects on cardiac function and cardiomyocyte survival. Next steps include developing strategies to specifically inhibit ERK phosphorylation at threonine 188. Phenylephrine is a generic over-the-counter decongestant.	Patent pending; available for licensing	Ruppert, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 15, 2013; doi:10.1073/pnas.1221999110 Contact: Kristina Lorenz, University of Wuerzburg, Wuerzburg, Germany e-mail: lorenz@toxi.uni-wuerzburg.de Contact: Martin J. Lohse, same affiliation as above e-mail: lohse@toxi.uni-wuerzburg.de
		SciBX 6(16); doi:10.1038/scibx.2013.389 Published online April 25, 2013		
Cardiovascular disease	ATP-binding cassette sub-family G member 4 (ABCG4); lyn kinase (LYN); thrombopoietin receptor (CD110; Mpl)	Cell culture and mouse studies suggest activating LYN or increasing high-density lipoprotein (HDL) levels could reduce platelet production and help prevent thrombocytosis. In mice with accelerated development of thrombocytosis from lack of <i>Abcg4</i> , bone marrow megakaryocyte progenitors produced more platelets and had greater cell surface Mpl expression than progenitors from wild-type mice. In wild-type mice with hypercholesterolemia, infusion of HDL decreased megakaryocyte progenitor proliferation, platelet counts and cell-surface Mpl expression compared with vehicle. In megakaryocyte progenitor cells lacking <i>Abcg4</i> , a small molecule LYN activator decreased Mpl expression compared with vehicle. Next steps include testing the effect of LYN activation and HDL infusion in additional mouse models.	Patent application filed; available for licensing	Murphy, A.J. <i>et al. Nat. Med.</i> ; published online April 14, 2013; doi:10.1038/nm.3150 Contact: Nan Wang, Columbia University, New York, N.Y. e-mail: nw30@columbia.edu
		SciBX 6(16); doi:10.1038/scibx.2013.390 Published online April 25, 2013		
Infectious disease				
Cytomegalovirus (CMV)	ATP-binding cassette sub-family C member 1 (ABCC1; MRP; MRP1)	Cell culture studies suggest cytotoxic drugs such as vincristine could help prevent cytomegalovirus (CMV) infection in transplant recipients. Most humans harbor latent CMV infections, but the virus can reactivate and cause severe disease in immunocompromised hosts such as transplant recipients. In a human myeloid cell line, the CMV transcript protein UL138 decreased cell surface expression of MRP1, a transporter that exports drugs including vincristine, compared with no transcript. In cultured human myeloid cells treated with vincristine, cells with latent CMV infection were more sensitive to killing than uninfected cells. Next steps include testing whether cytotoxins exported by MRP1 could help selectively deplete human CMV from populations of bone marrow cells for transplant. Vincristine is a generic chemotherapeutic.	Patent application filed; available for licensing from Cambridge Enterprise Ltd.	Weekes, M.P. <i>et al. Science</i> ; published online April 12, 2013; doi:10.1126/science.1235047 Contact: Paul J. Lehner, University of Cambridge, Cambridge, U.K. e-mail: pjl30@cam.ac.uk
		SciBX 6(16); doi:10.1038/scibx.2013.391 Published online April 25, 2013		

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Musculoskeletal disease				
Osteoporosis	Peroxisome proliferation-activated receptor- δ (PPAR δ ; PPAR δ)	<p><i>In vitro</i> and mouse studies suggest activating PPARδ could help treat osteoporosis. In cocultured osteoblasts and osteoclasts, pharmacological activation of PPARδ with GW501516 increased osteoblast differentiation and decreased osteoclastogenesis compared with no activation. In a mouse model for postmenopausal osteoporosis, GW501516 restored bone turnover and increased bone density to normal levels compared with vehicle. Next steps include studies to determine if a PPARδ agonist could be used to treat osteoporosis in patients.</p> <p>At least five companies have PPARδ agonists in clinical and preclinical testing to treat endocrine and metabolic conditions.</p> <p>GlaxoSmithKline plc discontinued development of GW501516 after finding the molecule induced tumors in rodents. The compound had completed a Phase II trial in patients with dyslipidemia.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.392 Published online April 25, 2013</p>	Findings unpatented; available for licensing	<p>Scholtyssek, C. <i>et al. Nat. Med.</i>; published online March 31, 2013; doi:10.1038/nm.3146</p> <p>Contact: Gerhard Krönke, University of Erlangen-Nuremberg, Erlangen, Germany e-mail: gerhard.kroenke@uk-erlangen.de</p>
Neurology				
Neurology	IL-5	<p><i>In vitro</i> and mouse studies suggest inhibiting eosinophil toxicity could help treat neuromyelitis optica (NMO), an autoimmune demyelinating disease. In cell culture, the NMO-causing autoantibody NMO-IgG plus eosinophils led to antibody- and complement-dependent cytotoxicity, whereas NMO-IgG or eosinophils alone did not. In mouse spinal cord slices, NMO-IgG plus eosinophils or eosinophil-secreted toxic granules induced NMO pathology, which was reversed by the antihistamine Zyrtec cetirizine. In a mouse model for NMO, cetirizine or an anti-IL-5 antibody that induces hypoeosinophilia decreased lesion severity compared with no treatment or complement control, respectively. Next steps could include testing in additional models.</p> <p>At least four companies have anti-IL-5 inhibitors in clinical testing to treat various diseases. UCB Group, Pfizer Inc. and GlaxoSmithKline plc market Zyrtec to treat allergy and rhinitis.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.393 Published online April 25, 2013</p>	Patent and licensing status unavailable	<p>Zhang, H. & Verkman, A.S. <i>et al. J. Clin. Invest.</i>; published online April 8, 2013; doi:10.1172/JCI67554</p> <p>Contact: Alan S. Verkman, University of California, San Francisco, Calif. e-mail: alan.verkman@ucsf.edu</p>

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Chemistry			
Semisynthetic synthesis of artemisinin	Biological production of artemisinic acid and chemical conversion of the acid to artemisinin could help supply first-line treatments for malaria infection at low cost. Artemisinin is naturally produced in the plant <i>Artemisia annua</i> . <i>Saccharomyces cerevisiae</i> expressing <i>A. annua</i> enzymes synthesized the artemisinin precursor artemisinic acid, which then was extracted from suspension at more than 10-fold higher titers than those produced by other methods. A 4-step chemical synthesis process was used to synthesize artemisinin from artemisinic acid with an overall yield of 40%–45% and with higher purity than plant-derived artemisinin. Next steps include commercializing the process to produce artemisinin-based combination therapies to treat malaria infection. Novartis AG markets the artemisinin-based combination therapy Coartem artemether/lumefantrine to treat malaria. Sigma-Tau Group and Pfizer Inc. market Eurartesim dihydroartemisinin/piperquine to treat malaria. Suda Ltd.'s ArTiMist, a sublingual aerosol formulation of artemisinin, is in Phase III testing for the indication.	Patent status undisclosed; Amyris Inc. exclusively licensed the technology to the Institute for OneWorld Health, which has licensed it to Sanofi; available for licensing for non-malaria indications	Paddon, C.J. <i>et al. Nature</i> ; published online April 10, 2013; doi:10.1038/nature12051 Contact: Chris J. Paddon, Amyris Inc., Emeryville, Calif. e-mail: paddon@amyris.com
	SciBX 6(16); doi:10.1038/scibx.2013.394 Published online April 25, 2013		
Simplified synthesis of pactamycin to aid analog development	A simplified process for pactamycin synthesis could facilitate the generation of less cytotoxic analogs for therapeutic evaluation. Pactamycin is a fungal-derived compound known to have antitumor and antibiotic properties but is itself considered to be too cytotoxic for clinical development. The development of analogs was complicated because the compound was previously synthesized using a 32-step process. In the current approach, a 15-step chemical-synthesis process that includes an enantioselective Mannich reaction and symmetry-breaking reduction sequence produced milligram quantities of the compound with a 1.9% overall yield. Next steps include evaluating unnatural analogs of pactamycin created using this process.	Patent application filed; available for licensing	Malinowski, J.T. <i>et al. Science</i> ; published online April 12, 2013; doi:10.1126/science.1234756 Contact: Jeffrey S. Johnson, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: jsj@unc.edu
	SciBX 6(16); doi:10.1038/scibx.2013.395 Published online April 25, 2013		
Disease models			
Mouse model for collagen type VI $\alpha 3$ (COL6A3)-related muscular dystrophies	A mouse model for COL6A3-related muscular dystrophies could help identify new treatments. In mice, a <i>Col6a3</i> mutation that caused low expression of a nonfunctional collagen chain variant resulted in collagen VI microfibril deficiency, and led to decreased muscle mass and contractions compared with what was seen in wild-type mice. In the mouse model, the collagen VI pathology was specific to tendons. Next steps include identifying signaling pathways altered in the mutant mice.	Findings unpatented; frozen sperm and breeding pairs of the mutant mice available for licensing	Pan, T.-C. <i>et al. J. Biol. Chem.</i> ; published online April 5, 2013; doi:10.1074/jbc.M112.433078 Contact: Mon-Li Chu, Thomas Jefferson University, Philadelphia, Pa. e-mail: mon-li.chu@jefferson.edu
	SciBX 6(16); doi:10.1038/scibx.2013.396 Published online April 25, 2013		
Mouse models for neurological disease controlled with cellular-scale optogenetic brain implants	Mice with cellular-scale optogenetic devices implanted in the brain could be useful for developing new models of neurological diseases. The cellular-scale device consisted of wireless, microscale, inorganic light-emitting diodes and control circuits. The device was implanted into mouse brain tissue via microneedle injection and connected to lightweight, head-mounted power and wireless systems that did not inhibit the animal's normal activities. In mice implanted with the device and expressing channelrhodopsin-2 (ChR2) in midbrain dopaminergic neurons, wireless tonic stimulation of those neurons decreased anxiety-like behaviors with an effect similar to that of nicotine. Ongoing work includes using the devices to test neural stress circuits related to depression, anxiety and addiction.	Patent status undisclosed; available for licensing or partnering	Kim, T.-i. <i>et al. Science</i> ; published online April 12, 2013; doi:10.1126/science.1232437 Contact: Michael R. Bruchas, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: bruchasm@wustl.edu Contact: John A. Rogers, University of Illinois at Urbana-Champaign, Urbana, Ill. e-mail: jrogers@uiuc.edu
	SciBX 6(16); doi:10.1038/scibx.2013.397 Published online April 25, 2013		

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Antitumor mechanism of gold nanoparticles in ovarian cancer	<p>Mouse and cell culture studies suggest gold nanoparticles could be useful for treating ovarian cancers by blocking the MAPK pathway and epithelial-to-mesenchymal transition (EMT). In three human ovarian cancer cell lines, unmodified, 20 nm gold nanoparticles had more potent antiproliferative activity than unmodified gold nanoparticles that had smaller or larger diameters. In the ovarian cancer cell lines, the 20 nm nanoparticles inhibited MAPK activation and the secretion of proteins associated with EMT. In two orthotopic mouse models for ovarian cancer, the nanoparticles decreased tumor mass compared with saline. Next steps include determining the mechanism by which the nanoparticles target cancer-associated pathways and developing methods to further enhance their efficacy.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.398 Published online April 25, 2013</p>	Unpatented; licensing status not applicable	<p>Arviso, R.R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 8, 2013; doi:10.1073/pnas.1214547110 Contact: Priyabrata Mukherjee, Mayo Medical School, Rochester, Minn. e-mail: mukherjee.priyabrata@mayo.edu</p>
Clustered, regularly interspaced short palindromic repeats (CRISPR) editing to rapidly generate stem cell models for disease	<p>A comparison of genome editing technologies suggests CRISPR-based systems could be more efficient for generating stem cell models for disease than systems that use transcription activator–like effector nucleases (TALENs). In a human pluripotent stem cell line, CRISPR systems introduced mutant alleles at 7 genomic loci with an efficiency of 51%–79%, whereas TALENs had an efficiency of 0%–34%. Next steps include determining the off-target effects of CRISPR-based genome editing.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.399 Published online April 25, 2013</p>	Patent and licensing status unavailable	<p>Ding, Q. <i>et al. Cell Stem Cell</i>; published online April 4, 2013; doi:10.1016/j.stem.2013.03.006 Contact: Kiran Musunuru, Harvard University, Cambridge, Mass. e-mail: kiranmusunuru@gmail.com</p>
Highly potent inhibitors of sirtuin 1 (SIRT1), SIRT2 and SIRT3	<p>Thieno[3,2-<i>d</i>]pyrimidine-6-carboxamide–based sirtuin inhibitors could be used as research compounds to probe the functions of SIRT1, SIRT2 and SIRT3 in human diseases. The therapeutic effects of modulating sirtuin activity have been unclear in part because weak, unselective compounds have been used to investigate sirtuin function. A lead compound from a new series of inhibitors was developed that specifically inhibited SIRT1, SIRT2 and SIRT3 with IC₅₀ values below 5 nM. Next steps include using the compounds to explore the biology of sirtuin regulation and develop new SIRT1 modulators.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.400 Published online April 25, 2013</p>	Patent applications filed; unavailable for licensing	<p>Disch, J.S. <i>et al. J. Med. Chem.</i>; published online April 9, 2013; doi:10.1021/jm400204k Contact: Ghotas Evindar, GlaxoSmithKline plc, Waltham, Mass. e-mail: ghotas.x.evindar@gsk.com Contact: Jeremy S. Disch, same affiliation as above e-mail: jdisch92@gmail.com</p>
Transplantable kidney graft from a decellularized kidney extracellular matrix (ECM)	<p>A transplantable kidney built on a decellularized kidney ECM could help guide the development of functional grafts for patients undergoing kidney transplant. A detergent solution was used to generate a decellularized rat kidney ECM matrix, which was repopulated with a mix of rat neonatal kidney cells and human umbilical vein endothelial cells. In rats, the bioengineered kidney grafted at an orthotopic position had functionality, produced urine and did not show bleeding or clot formation. Next steps include refining the culturing protocol used to generate the engineered kidney. Miromatrix Inc. is developing engineered tissues and organs for transplant using the decellularization and recellularization technology (<i>see Regenerating the kidney, page 10</i>).</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.401 Published online April 25, 2013</p>	Patent applications filed by the University of Minnesota and Massachusetts General Hospital covering the technology; University of Minnesota patent application licensed to Miromatrix; MGH patent application available for licensing	<p>Song, J.J. <i>et al. Nat. Med.</i>; published online April 14, 2013; doi:10.1038/nm.3154 Contact: Harald C. Ott, Massachusetts General Hospital, Boston, Mass. e-mail: hott@partners.org</p>

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Using chromatin immunoprecipitation followed by whole-genome sequencing (ChIP-Seq) to identify disease-associated super-enhancer regulatory elements	<p>Cell culture studies suggest mapping super-enhancers could help identify drug targets in cancer or other diseases. ChIP-Seq of mediator complex subunit 1 (MED1) in multiple myeloma (MM) cells identified 308 highly enriched sites of MED1 binding upstream of known oncogenic drivers, including c-Myc (MYC). These enriched MED1-bound regions were dubbed super-enhancers because they were bound by multiple transcriptional regulators of cell fate and drove target gene expression to higher levels than traditional enhancers. In MM cells, a bromodomain containing 4 (BRD4) inhibitor decreased expression of super-enhancer-regulated genes compared with that of genes not associated with super-enhancers. Next steps include identifying molecules to disrupt super-enhancer function and using super-enhancer mapping to identify drug targets (<i>see Super-enhancing discovery, page 1</i>).</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.402 Published online April 25, 2013</p>	Patent application filed for findings from both studies; licensed to Syros Pharmaceuticals Inc.	<p>Whyte, W.A. <i>et al. Cell</i>; published online April 11, 2013; doi:10.1016/j.cell.2013.03.035</p> <p>Lovén, J. <i>et al. Cell</i>; published online April 11, 2013; doi:10.1016/j.cell.2013.03.036</p> <p>Contact: Richard Young, Whitehead Institute for Biomedical Research, Cambridge, Mass. e-mail: young@wi.mit.edu</p>
Imaging			
Optical imaging of structural and molecular features in intact brain tissue	<p>A method of rendering intact brain tissue amenable to optical imaging could help identify new drug targets. Treatment of whole brains or brain tissue from mice, zebrafish and humans with hydrogel monomers and an electrophoretic tissue-clearing technique resulted in an optically transparent hydrogel-tissue hybrid. In transformed tissue, multiple rounds of fluorescence imaging enabled visualization of various features including long-range projections, protein complexes and neurotransmitters. In a frontal lobe sample from a deceased patient with autism, the method revealed interneuronal dendritic bridges that were not seen in normal, age-matched tissue. Next steps could include using the method to identify disease-related structural or molecular features in brain tissue from models for CNS diseases.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.403 Published online April 25, 2013</p>	Patent and licensing status unavailable	<p>Chung, K. <i>et al. Nature</i>; published online April 10, 2013; doi:10.1038/nature12107</p> <p>Contact: Karl Deisseroth, Stanford University, Stanford, Calif. e-mail: deissero@stanford.edu</p>
Markers			
Fibroblast growth factor receptor (FGFR) fusions associated with multiple cancer types	<p>Patient sample and mouse studies identified <i>FGFR</i> fusions in multiple cancers and suggest inhibiting such targets could have therapeutic benefit. Activating mutations and amplifications of <i>FGFR</i> have previously been identified as drivers in many cancers. In multiple cancer types including bladder, breast and prostate cancer, rearrangements in <i>FGFR</i> were identified. In xenograft mice with bladder cancer cells carrying <i>FGFR3</i> (<i>CD333</i>) fusions, a small molecule FGFR inhibitor decreased tumor growth compared with vehicle. Next steps could include screening additional cancers for <i>FGFR</i> fusions. At least six selective FGFR inhibitors are in Phase II testing or earlier to treat various cancers.</p> <p>SciBX 6(16); doi:10.1038/scibx.2013.404 Published online April 25, 2013</p>	Patent and licensing status unavailable	<p>Wu, Y.-M. <i>et al. Cancer Discov.</i>; published online April 4, 2013; doi:10.1158/2159-8290.CD-13-0050</p> <p>Contact: Arul M. Chinnaiyan, University of Michigan, Ann Arbor, Mich. e-mail: arul@umich.edu</p>

Erratum: Analysis: Cover Story

Osherovich, L. *SciBX* 6(15); doi:10.1038/scibx.2013.353
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The Analysis item “Targeting tankyrases” misstated the name of one of the lead compounds, one of the researcher’s titles, the description of a binding site and the name of a protein. The lead compound is G244-LM. Mike Costa is senior scientist in the Department of Cancer Targets at Genentech Inc. The tankyrase inhibitor hits a binding site that is different from that found in other PARP family members, and G244-LM and G007-LK led to higher levels of axin proteins.

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