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Cancer cell line encyclopedias

By Tim Fulmer, Senior Writer

Two research teams have independently developed large-scale screening platforms to profile hundreds of human cancer cell lines and identify drug sensitivity biomarkers.[1,2] **Novartis AG**, a member of one of the groups, is now using the platform to guide patient selection in Phase I cancer trials.

Both platforms are patterned after the NCI60, which was the first cancer cell line panel developed to screen for cancer therapeutics. NCI60 consists of 60 human cell lines representing 9 tumor types. It was developed in the 1980s and first used in 1990.[3]

In the intervening 20 years it has become clear that the original NCI60 panel cannot capture the full diversity of cancer cell lineages and cancer genetics.[4,5] The panel "is just too small to model the incredible heterogeneity that, through genome sequencing, we now know exists across cancer mutations," Paul Workman told *SciBX*. "To cover mutations present in, say, 5% or less of human cancers, you need to have a panel of several hundred cancer cell lines."

Workman is deputy CEO and director of the **Cancer Research UK** Cancer Therapeutics Unit at **The Institute of Cancer Research**.

> **"To cover mutations present in, say, 5% or less of human cancers, you need to have a panel of several hundred cancer cell lines."**
>
> ***—Paul Workman, The Institute of Cancer Research***

Modeling that complex heterogeneity at the molecular level is important because "it helps us identify biomarkers of drug sensitivity and drug resistance that lead to personalized cancer treatments," said Ultan McDermott, corresponding author on one of the papers and group leader of the **Wellcome Trust Sanger Institute**'s Cancer Genome Project.

Thus, the first priority was to assemble a large set of cancer cell lines that might reflect the molecular and genetic heterogeneity of tumor tissues.

The Wellcome–**Massachusetts General Hospital** group, led by Andrew Futreal, Michael Stratton and Daniel Haber, collected 639 human tumor cell lines representing a range of adult and childhood cancers of epithelial, mesenchymal and hematopoietic origin. Lung, blood, CNS, GI tract, skin and breast cancers were the most highly represented in the panel.

Futreal is head of cancer genetics at Wellcome, and Stratton is director of Wellcome. Futreal and Stratton also are joint heads of Wellcome's Cancer Genome Project. Haber is professor of biological and biomedical sciences at **Harvard Medical School** and director of

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the **Massachusetts General Hospital Cancer Center**.

The Novartis–**Broad Institute of MIT and Harvard** group, led by Robert Schlegel, William Sellers and Levi Garraway, assembled a panel of 947 human cancer cell lines dubbed the Cancer Cell Line Encyclopedia (CCLE), which encompassed 36 tumor types. The most highly represented cancers in that panel were lung, colorectal, melanoma, breast, ovary, glioma and pancreatic.

Schlegel is executive director of oncology at Novartis. Sellers is VP and global head of oncology at Novartis. Garraway is a researcher at the Broad Institute, professor of biological chemistry and molecular pharmacology at Harvard Medical School and assistant professor of medicine at the **Dana-Farber Cancer Institute**.

For both groups, the number of cell lines per cancer was broadly a function of the mortality rate of a given cancer and the availability of cell lines for that cancer.

The next step for the teams was generating a set of molecular-level biomarkers. To do so, the groups characterized each cell line according to several basic genetic traits. The Wellcome-MGH group used standard capillary sequencing to measure the mutational status of 64 well-known cancer-associated genes. In addition, they measured DNA copy number and the expression of 14,500 genes.

The Novartis-Broad group used massively parallel sequencing to determine the mutational status of 1,600 cancer-associated genes, encompassing well-known cancer genes as well as genes identified in the literature and presentations as being putative oncogenes and tumor suppressors. In addition, the group measured DNA copy number and genome-wide mRNA expression.

With cancer cell lines and corresponding biomarkers in hand, the groups each screened a compound library to identify drug-sensitive and drug-resistant cell lines.

The Wellcome-MGH group selected 130 compounds, including targeted molecules and chemotherapeutics, and assayed 48,178 compound–cell line combinations, with a mean of 368 cell lines screened per compound.

For each compound–cell line combination, the effect of 72 hours of treatment was used to derive a drug sensitivity profile that incorporated the IC_{50} value and a dose-response curve. The researchers then correlated drug sensitivity and genetic traits, generating gene-compound associations that predicted sensitivity and resistance.

The screen identified highly significant correlations between known oncogenes and drugs. For example, the *BCR-ABL* gene rearrangement predicted sensitivity to BCR-ABL tyrosine kinase inhibition (p=2.54×10^{-65}); *BRAF* mutational status predicted sensitivity to BRAF inhibition (p=1.25×10^{-24}); *HER2* (*EGFR2*; *ERBB2*; *neu*) amplification predicted sensitivity to epidermal growth factor receptor (EGFR) inhibition (p<1×10^{-7}); *p53* mutational status predicted resistance to mdm2 p53 binding protein homolog (MDM2; HDM2) inhibition (p<1×10^{-36}).

As proof the platform could identify new biomarkers of drug sensitivity, the researchers found that the *Ewing sarcoma breakpoint region 1* (*EWSR1*; *EWS*)–*Friend leukemia virus integration 1* (*FLI1*) gene rearrangement predicted a previously unknown sensitivity of Ewing's sarcoma cells to poly(ADP-ribose) polymerase (PARP) inhibitors (p=1.03×10^{-26}). Subsequent cell culture studies confirmed PARP inhibition induced apoptosis in Ewing's sarcoma cell lines after 72 hours of treatment.

The Novartis-Broad group selected 24 compounds, both targeted therapies and chemotherapeutics, and screened them in 479 cell lines, generating drug sensitivity profiles for each compound–cell line combination.

Statistical analysis of those results identified many of the same known biomarkers of drug sensitivity found by the Wellcome-Harvard team's platform. The Novartis-Broad group also identified previously unknown sensitivity biomarkers: elevated expression of the *aryl hydrocarbon receptor* (*AHR*) gene in *neuroblastoma Ras viral oncogene* (*NRAS*)-mutant cells predicted sensitivity to MEK inhibition, and elevated expression of the *schlafen family member 11* (*SLFN11*) gene predicted sensitivity to topoisomerase inhibitors in multiple cell lineages. Both of those predictions were subsequently confirmed in cell culture studies.

The Wellcome-Harvard findings and the Novartis-Broad findings were published in *Nature*.

Early and late

The screening platforms may turn out to be useful both early and late in the preclinical drug development process. "Early on, these large, unbiased screens provide insight into how certain mutations drive drug sensitivity and resistance at the molecular level. In other words, they allow us to match drugs to mutations," said McDermott. "However, to account for the effects of tumor biology, angiogenesis and stroma on a drug, these screens will have to be supplemented with more complex animal models down the line."

Later in preclinical development, following animal testing, the drug sensitivity and resistance profiles could again become useful, said McDermott. "In this case, the biomarkers of drug sensitivity identified in our cell lines are now used to generate genetic profiles of patients and thus help inform trial design and patient stratification."

Novartis is already using its screening platform to help guide patient selection in its Phase I cancer trials, said Sellers. "For example, a trial for the PI3K [phosphoinositide 3-kinase] inhibitor BYL719 was focused on patients who show specific mutations in the *PI3KCA* gene in part motivated by the strength of the cancer cell line encyclopedia data." BYL719 is in Phase I testing to treat solid tumors.

Moving forward, both groups plan to build out their screening platforms with additional biomarkers and drug combinations.

"We plan to characterize our cell line panel at the level of epigenetics, looking at patterns of histone modifications and DNA methylation as potential biomarkers of drug sensitivity," said McDermott. "We also want to assay combinations of drugs in our cell lines. Finally, we want to optimize and unify our analytical methods into a single statistical algorithm."

The Novartis-Broad group "wants to include a variety of additional molecular-level biomarker profiles, including epigenetics, metabolomics, proteomics and microRNA expression levels. We also want to supplement genome sequencing with RNA sequencing," said Sellers.

Novartis also is developing a human xenograft mouse tumor encyclopedia that will supplement the cell line screen, said Sellers. "The mouse encyclopedia will encompass a wide variety of tumor types in an *in vivo* setting. It will help provide insight into how tumor stroma-epithelial interactions affect drug activity, which is impossible to assay in a cell line platform."

The findings in both papers are unpatented and are freely available to the public at http://www.broadinstitute.org/ccle and http://www.cancerrxgene.org/.

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COMPANIES AND INSTITUTIONS MENTIONED

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Cancer Research UK, London, U.K.
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Texas translation

By Lev Osherovich, Senior Writer

The taxpayer-backed **Cancer Prevention & Research Institute of Texas** is moving downstream from its initial focus on basic research in oncology. This month, the institute announced its latest round of grants—this time focusing on both translational- and commercial-stage research, the latter of which includes recruiting companies to relocate to Texas.

The Cancer Prevention & Research Institute of Texas (CPRIT) launched in 2007, after a voter-backed constitutional amendment authorized a $3 billion bond issue for cancer research and prevention within the state, and issued its first grants in 2009. In the latest round, 25 entities received about $81 million. In total, CPRIT now has given out 387 grants worth about $671 million.

"The people of Texas wanted us to prevent cancer and save lives but also to promote revenue generation in the state."

—William Gimson, Cancer Prevention & Research Institute of Texas

CPRIT has a broad remit for how to spend its money, about $300 million annually for 10 years, said Charles Tate. Tate is a member of CPRIT's Oversight Committee and chairman of CPRIT's Economic Development and Commercialization Subcommittee.

Tate said CPRIT is required to spend no more than 10% of its budget on prevention, such as colorectal and breast cancer screening programs in rural areas. The remaining 90% is to be spent at the discretion of the institute's Executive Committee. Although there are no formal milestones to mark CPRIT's progress, the institute must report annually to the Texas state legislature.

"The people of Texas wanted us to prevent cancer and save lives but also to promote revenue generation in the state," said Bill Gimson, executive director of CPRIT. "We balance this by investing in both basic and translational research as well as commercial research."

The latter two components are the major thrust of the new grants (*see* **Table 1, "Cancer Prevention & Research Institute of Texas' latest grant recipients"**). For example, the institute issued a $20 million grant to launch the Houston-Area Translational Research Consortium (HATRC) at **Rice University** and **The University of Texas MD Anderson Cancer Center**'s Institute for Applied Cancer Science (IACS).

HATRC is incubating new companies based on discoveries by Houston-area researchers and will be headed by Lynda Chin, IACS scientific director and chair of genomic medicine at MD Anderson.

CPRIT's Gimson and Tate noted that translational work requires not just financial investment but also management expertise. To help academics, clinicians and companies collaborate, CPRIT created a virtual management company called **Texas BioAlliance**.

Texas BioAlliance CEO Jacqueline Northcut said her team supports CPRIT's grant recipients with managing and developing IP and outsourcing of laboratory services.

"Texas BioAlliance helps companies or principal investigators to understand the kind of help they need" to advance technologies from the bench to the clinic, said Northcut.

Courting companies

To go even further downstream, CPRIT is looking outside the borders of Texas. The first company that has chosen to relocate to Texas is U.K. cancer immunotherapy company **Cell Medica Ltd.**

Table 1. Cancer Prevention & Research Institute of Texas' latest grant recipients.

Recipient	Program	Funding ($M)
Companies		
Asuragen Inc.	Mutational profiling of tumors by next-generation DNA sequencing	6.8
Cell Medica Ltd.	Clinical development of T cell therapies	15.6
Kalon Biotherapeutics LLC	Process development and manufacturing of biologics	7.9
Pulmotect Inc.	Clinical development of PUL-042, an inhalable immunomodulatory agent	7.1
Academic institutions		
Houston-Area Translational Research Consortium	Translational research incubator	20
The University of Texas MD Anderson Cancer Center	Targeted breast cancer therapies, cancer pain therapies, immunotherapeutics, imaging and cytometric technology, and staff recruitment	6.7
The University of Texas Southwestern Medical Center	Biomarker studies, and faculty and staff recruitment	5
The University of Texas Health Science Center at Houston	Cancer imaging	0.6
Texas A&M University	Cancer metabolism and faculty recruitment	4
Baylor College of Medicine	Development of molecular diagnostics and cancer vaccines	2
The Methodist Hospital Research Institute	Small interfering RNA therapeutics for breast cancer and immunomodulatory therapies for prostate cancer	1.9
Texas Tech University Health Science Center	Preclinical development and manufacturing of a ceramide catabolism inhibitor to treat solid tumors	1
Texas A&M University Health Science Center	Cancer metabolism	1.5
The University of Texas Health Science Center at San Antonio	NMR facility for drug discovery	1

The institute invested $15.6 million in Cell Medica as part of a $28 million series A round that was led by CPRIT. Other investors were undisclosed.

The company's ties to Texas can be traced back to 2010, when Cell Medica in-licensed T cell isolation technology from the **Baylor College of Medicine**. Baylor and Cell Medica now are running a 40-patient open-label Phase Ia trial of Cytorex EBV, an autologous cell therapy involving Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes, for lymphoproliferative malignancies.

"We were talking to Baylor about launching a company-sponsored trial of Cytorex EBV for accelerated approval. This required a physical presence in the United States," said Cell Medica CEO Gregg Sando. "Then we started talking to CPRIT and realized that they would support our efforts if we relocated to Texas."

Cell Medica's lead product is Cytovir CMV, which is in Phase II and Phase III testing to prevent latent cytomegalovirus (CMV) reinfection in patients receiving bone marrow transplants after myeloablative therapy for cancer. Cytovir CMV is already approved in the U.K. as a transplant service similar to a bone marrow transplant. The company is discussing the classification of Cytovir CMV with the FDA.

Another Cell Medica product, Cytovir ADV, will enter Phase I testing later this year to prevent awakening of latent adenovirus (ADV) in pediatric cancer patients receiving bone marrow transplants.

Sando said the company will maintain a presence in the U.K.

Gimson cited Cell Medica's fundraising as an example of how CPRIT's investments can yield an influx of outside venture capital investment into Texas companies, justifying the fund's efforts to state lawmakers even before the clinical benefits of its grants are known.

"Relocating a company to Texas is a big draw," said Gimson. "Our latest estimate is that for the $60 million invested in companies prior to this round, those companies went on to raise an additional $200 million in follow-on capital from other sources. To a decision maker, this looks pretty good, even if it's a surrogate until there are products."

Three other companies, all based in Texas, also are receiving money in the latest grant round: RNA diagnostics company **Asuragen Inc.**, biomanufacturing company **Kalon Biotherapeutics LLC** and immunomodulator play **Pulmotect Inc.** will collectively receive $21.8 million.

Streamlining manufacturing is the rationale behind CPRIT's grant to Kalon, which is owned by the **Texas A&M University** system.

President and CEO Andrew Strong said Kalon, which was founded last year, aims to rapidly develop specialized manufacturing protocols for complex biologic and cell-based therapies. "The company is working to fill the space between discovery and manufacturing," he said. "Instead of doing one particular type of manufacturing, we've developed a single facility that can use all kinds of expression systems."

Kalon's process development facility was already up and running before the CPRIT grant, but Strong said the company needed CPRIT's cash to grow its staff to accommodate an influx of business from Texas-based academic researchers seeking to scale up production of their therapeutic candidates.

"With the CPRIT money, we can look on a national and international level for the best talent and the best equipment," said Strong.

Kalon is working with teams at Baylor and MD Anderson to produce material for investigator-initiated Phase I/II trials of a therapeutic mAb and a plasmid-based gene therapy. The company did not disclose further details.

Asuragen and Pulmotect could not be reached for comment.

Long-term plans

Tate sees different time horizons for CPRIT's various investments, with prevention efforts having the most immediately evident results. CPRIT's commercial and research spending will take longer to affect public health and state revenue.

"Our prevention activities could have a short-term impact, our commercialization efforts are medium term and the research is more long term," said Tate.

Gimson said that besides the 10% earmarked for prevention, CPRIT spends 75% of its budget on academic research and the remaining 15% on commercial development. He said CPRIT hopes to increase the proportion of commercial spending in future funding rounds.

Gimson noted that companies receiving CPRIT grants must raise additional money from other investors equaling no less than 50% of CPRIT's contribution. He also noted CPRIT will determine on a case-by-case basis whether to take an equity stake in companies receiving its grants or instead require a royalty-sharing arrangement.

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COMPANIES AND INSTITUTIONS MENTIONED

Asuragen Inc., Austin, Texas
Baylor College of Medicine, Houston, Texas
Cancer Prevention & Research Institute of Texas, Austin, Texas
Cell Medica Ltd., London, U.K.
Kalon Biotherapeutics LLC, College Station, Texas
Houston-Area Translational Research Consortium, Houston, Texas
Pulmotect Inc., Houston, Texas
Rice University, Houston, Texas
Texas A&M University, College Station, Texas
Texas BioAlliance, Houston, Texas
The University of Texas MD Anderson Cancer Center, Houston, Texas

Pumping up the metabolic Rev-ERB

By Michael J. Haas, Senior Writer

Two teams have shown that the nuclear receptors Rev-ERBAα and Rev-ERBAβ play a central role in regulating the circadian clock and metabolism,[1,2] and a third group has found that agonizing both receptors treats obesity in mice.[3] Collectively, the findings suggest Rev-ErbA agonists could help treat a range of metabolic diseases.

Next, agonists with longer half-lives will need to be developed and patient populations that might benefit from the molecules will have to be identified.

The circadian clock regulates sleep/wake cycles, metabolism and other physiological parameters in relation to the 24-hour day. Previous studies have suggested that among the many regulatory components of the circadian clock, two transcription factors—Rev-ERBAα (nuclear receptor subfamily 1 group D member 1; NR1D1) and Rev-ERBAβ (nuclear receptor subfamily 1 group D member 2; NR1D2)—only played minor roles in regulating circadian cycles. Indeed, mice deficient in either Rev-erbaα or Rev-erbaβ had only mild circadian disruptions.[4,5]

> **"While there has been a lot of evidence over the past four or five years linking metabolism and the circadian clock, there have not been many papers about targeting clock proteins with small molecules."**
>
> ***—Ross Bersot, ReSet Therapeutics Inc.***

To better understand the function of the two proteins, separate teams from the **Salk Institute for Biological Studies** and the **Perelman School of Medicine at the University of Pennsylvania** conducted genomic analyses of normal mouse livers. Both groups found Rev-erbaα and Rev-erbaβ bound many of the same target genes, including genes that regulate the core circadian clock and lipid metabolism.

Additionally, both teams showed that compared with wild-type mice or those lacking only one *Rev-erba* gene, mice lacking *Rev-erbaα* and *Rev-erbaβ* had decreased nocturnal locomotor activity, which is indicative of disruptions in normal circadian rhythms. The double-knockout animals also had higher plasma levels of glucose and triglycerides and greater levels of hepatosteatosis.

Collectively, these results showed Rev-ErbAα and Rev-ErbAβ cooperated to regulate the core clock and metabolism in ways that were not evident in earlier studies that focused only on one of the proteins, the teams wrote in their respective papers.

One team was led by Ronald Evans, professor and director of the Gene Expression Laboratory at Salk and an investigator at the **Howard Hughes Medical Institute** (HHMI), and included researchers from the **University of California, San Diego School of Medicine**, **The University of Sydney**, **Westmead Hospital**, **Westmead Millennium Institute** and the **Swiss Federal Institute of Technology Lausanne**.

The other team was led by Mitchell Lazar, professor of medicine and genetics and chief of the Division of Endocrinology at Perelman and director of Perelman's Institute for Diabetes, Obesity and Metabolism.

Results were reported in *Nature* and *Genes & Development*, respectively.

Revisiting Rev-ERB

Meanwhile, a team from **The Scripps Research Institute** developed two small molecules that were dual Rev-ErbAα and Rev-ErbAβ agonists to evaluate their *in vivo* effects on the circadian clock and metabolism. In mice, the agonists delayed the onset of nocturnal locomotor activity and increased energy expenditure and decreased fat mass compared with vehicle, all without altering food intake or activity levels.

In mouse models of obesity, the agonists decreased fat mass and plasma levels of glucose, triglycerides and cholesterol compared with vehicle.

Thomas Burris, professor of molecular therapeutics at **Scripps Florida**, led the team, which included researchers from HHMI and **The University of Texas Southwestern Medical Center**.

Results were reported in *Nature*.[3]

"We've always considered Rev-Erbs as an auxiliary or backup loop in the core circadian clock, but these papers show that the receptors are probably a critical component of that clock in mammals and humans," said Timothy Willson, director of chemical biology at **GlaxoSmithKline plc**.

Willson noted that a previous Lazar-led team showed Rev-ErbAα plays a role in energy expenditure, glucose homeostasis and other liver functions.[6] "So the idea of Rev-Erb as a metabolic target is not unprecedented, and the effects of double-knockout or dual agonism on metabolic parameters shown in the three new studies is not surprising," he said. "But the effects are more profound than in previous studies using only *Rev-erbaα* knockouts."

"While there has been a lot of evidence over the past four or five years linking metabolism and the circadian clock, there have not been many papers about targeting clock proteins with small molecules," added Ross Bersot, president of **ReSet Therapeutics Inc.** "It's interesting to see data on the metabolic effects" of the Scripps team's small molecule Rev-ErbA agonists.

ReSet's lead compound is SHP-1, a small molecule that targets an undisclosed circadian clock protein. The compound is in preclinical development to treat diabetes. The company also has agonists of orexin 1 receptor (HCRTR1; OX1R) and HCRTR2 (OX2R) in lead optimization to treat narcolepsy and other sleep disorders.

ReSet was cofounded by Salk team leader Evans and Joseph Takahashi, professor and chair of neuroscience at UT Southwestern and investigator at HHMI. Takahashi was a member of the Scripps team, although ReSet was not involved in any of the Rev-Erb papers.

Metabolic shift work

Before any dual Rev-ErbAα and Rev-ErbAβ agonists are developed to treat human metabolic disorders, Willson and Bersot said animal studies are needed to determine the receptors' roles in specific tissue types and metabolic diseases.

"There is a lot of epidemiological data showing that shift workers have a higher incidence and risk of diabetes and obesity," and those data support the hypothesis that restoring normal clock function with dual Rev-ErbA agonists could treat metabolic disease, Willson said. "But a

key question is whether the circadian clock, and especially Rev-ErbAs, are deregulated in all patients with metabolic disease or just a subset" of diseases or patient populations.

He added: "This means studying the clock in metabolic disease patients you might want to treat and ascertaining what, if any, sleep disruptions or other clock perturbations they have."

Wilson said it will be hard to identify associations between circadian disruptions and metabolic disorders in a broad population. "Even in shift workers, it takes 15–20 years before there is a measurable increase in the risk of metabolic disease," whereas short-term disruptions to the circadian rhythms—such as those caused by jet lag or switching between standard time and daylight saving time—have no known effect on people's health, he said.

Bersot noted that circadian clock proteins also have differing tissue-specific metabolic functions in liver, adipose tissue, skeletal muscle and pancreas. "Thus, there are different pathways within the clock mechanism that could help treat different metabolic diseases. You'd have to compare the benefits and liabilities of targeting Rev-ErbAs with other clock components to treat a given disease" and decide which target is most feasible, he said.

He also wanted to know whether the dual agonists are effective in mouse models of diabetes and other metabolic diseases over a longer period than the Scripps team's 12-day study.

Willson said the molecules are not suitable for long-term studies. He noted that the team had to use very high doses of the dual agonists—100 mg/kg, twice daily—to see a therapeutic effect in the obesity models, because of the compounds' short *in vivo* half-lives. He said GSK has observed similarly poor pharmacokinetic properties for its own Rev-ErbAα ligands, GSK4112 and GSK5072, in normal animals.

"These types of compounds—ours and the Scripps team's dual agonists—are not useful for long-term studies," and better compounds are needed before the long-term safety and efficacy of Rev-ErbA agonists can be assessed, he said.

GSK identified GSK4112 and GSK5072 in a screen for ligands of orphan receptors and, in separate collaborations with Lazar's group at Perelman and a group at **The University of Manchester**, used the compounds to investigate Rev-ErbAα's role in metabolism[7] and inflammation,[8] respectively. After determining the compounds were not suitable drug candidates, GSK discontinued their development in 2008 and made GSK4112 available to other researchers as a tool compound. The company's ongoing work includes identifying additional Rev-ErbAα ligands to treat rheumatoid arthritis (RA), asthma and other inflammatory diseases.

Other Rev-ERB-erations

Burris disagreed that the half-lives of the dual agonists made them unsuitable for long-term studies, noting that the compounds had therapeutically relevant plasma levels in mice up to eight hours after dosing. "For the preclinical proof-of-principle studies, we dosed twice daily because we wanted to hit the targets for a long duration," he said. "I don't think this would interfere with safety studies, but these compounds would require further optimization before IND-enabling studies anyway."

Indeed, in ongoing work the team has optimized the agonists to improve their potency about 10-fold and continues to optimize their pharmacokinetic and pharmacodynamic properties, he said.

Burris said the Scripps team is investigating a range of potential metabolic indications for the dual agonists and determining the mechanism by which the agonists increased energy expenditure in the mouse models of obesity.

"We plan to take the agonists into mouse models of atherosclerosis" because the compounds suppressed cholesterol synthesis in mice, he said.

The team's follow-on studies in mice have shown that the agonists could treat sleep disorders, and those results will be reported in a forthcoming publication, he added.

The Scripps Research Institute has filed for a patent covering the dual agonists and related scaffolds and is evaluating opportunities to license the IP or spin it out into a company. "We are having discussions with specific companies, but nothing is settled yet," Burris said.

Team leaders Evans and Lazar could not be reached for comment.

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COMPANIES AND INSTITUTIONS MENTIONED

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Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa.
ReSet Therapeutics Inc., San Francisco, Calif.
Salk Institute for Biological Studies, La Jolla, Calif.
Scripps Florida, Jupiter, Fla.
The Scripps Research Institute, La Jolla, Calif.
Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland
University of California, San Diego School of Medicine, La Jolla, Calif.
The University of Manchester, Manchester, U.K.
The University of Texas Southwestern Medical Center, Dallas, Texas
The University of Sydney, Sydney, New South Wales, Australia
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TAU's cease and de-*cis*-t letter

By Lauren Martz, Staff Writer

Although it is well established that phosphorylated microtubule-associated protein-τ contributes to the pathology of Alzheimer's disease, antibodies against the target have so far been ineffective and have thus been relegated to research-only use. Now, researchers at **Harvard Medical School** have developed isoform-specific antibodies to target the protein and have shown that these can help detect, treat and prevent AD in mice.[1]

Microtubule-associated protein-τ (MAPT; TAU; FTDP-17) is a microtubule-binding protein that promotes microtubule assembly in healthy neurons. In AD patients, TAU becomes hyperphosphorylated, loses its normal physiological function and forms toxic TAU aggregates. In addition to β-amyloid (Aβ) plaques, AD is characterized by the accumulation of neurofibrillary tangles of hyperphosphorylated-τ 231 (p-τ 231), which also contributes to neurodegeneration.

Previously, a group led by Kun Ping Lu, professor of medicine at Harvard Medical School's **Beth Israel Deaconess Medical Center**, had found that protein peptidylprolyl *cis*/*trans* isomerase NIMA-interacting 1 (PIN1) binds and isomerizes p-τ 231, converting it from *cis* to *trans*.[2] The result was restoration of p-τ 231's ability to regulate microtubule assembly.

Based on those results, Lu and colleagues hypothesized that the *cis* form of p-τ 231 could be responsible for the toxic neurofibrillary tangle formation. The problem is that when p-τ 231 is synthesized chemically it exists almost entirely in the *trans* conformation.[3] Thus, antibodies developed using synthetic p-τ 231 as an antigen specifically recognize and eliminate the *trans* form.

Lu told *SciBX* that previous attempts to design antibodies that eliminate p-τ 231 pathology were ineffective because it was not known that each isoform had a different pathological function and that only the *trans* conformation of the protein was being targeted by the antibodies.

Now, Lu's team has manipulated the synthesis of p-τ 231 to lock up to 74% in the *cis* conformation. By doing so, the group was able to generate isoform-specific antibodies that targeted either the *cis* or the *trans* isoform without cross-reactivity.

In frontal cortical sections from nine healthy human brains, the antibodies detected very low levels of either *cis* or *trans* p-τ 231. In contrast, levels of *cis* p-τ 231 were elevated in brain samples from 11 AD patients and in 4 of 6 samples from patients with mild cognitive impairment. The latter findings suggested increased *cis* p-τ 231 could be an early indicator of AD.

Cis p-τ 231 had a longer half-life, greater stability and more resistance to dephosphorylation—all of which can lead to toxic aggregation—than the *trans* isoform.

Using *in vitro* assays, the group showed that adding PIN1 to p-τ 231 increased levels of *trans* p-τ 231 and decreased levels of *cis* p-τ 231. The isomerization by PIN1 further restored TAU-mediated microtubule assembly, confirming that TAU dysfunction is specifically caused by *cis* p-τ 231.

In a mouse model of AD with TAU overexpression and in Tau-overexpressing mouse neurons, Pin1 overexpression increased levels of *trans* p-τ 231 and decreased levels of *cis* p-τ 231 compared with normal Pin1 expression. Also in the AD model, Pin1 knockout caused an increase in pathogenic *cis* p-τ 231 and a decrease in *trans* p-τ 231.

"We have a way to develop new antibody technology that can be used to understand the very early stages of AD. Our antibody technology could be used for diagnostic or therapeutic applications," said Lu.

Early detection and intervention

Lu said his group's next steps include validating that the antibodies can be used to treat or prevent AD in animal models and testing whether they can identify patients with early disease.

"As Alzheimer's disease takes at least a decade to develop, early diagnosis and treatment of Alzheimer's patients before the onset of severe memory loss could offer doctors a much better chance of halting or even preventing" the disease, he added.

For example, he said, "we can use antibodies to detect *cis* p-τ 231 in spinal fluid and to determine whether the protein is a risk factor or indicator for early disease."

"Some indicators that a patient has AD include measures of phosphorylated TAU and β-amyloid above certain threshold levels. Detecting an increase in *cis* p-τ 231 could indicate that something is going wrong very early on and could be a complementary measure to the diagnostic tools that we already have."

—Gerard Griffioen, reMYND N.V.

"Some indicators that a patient has AD include measures of phosphorylated TAU and β-amyloid above certain threshold levels. Detecting an increase in *cis* p-τ 231 could indicate that something is going wrong very early on and could be a complementary measure to the diagnostic tools that we already have," noted Gerard Griffioen, CSO of **reMYND N.V.**

reMYND is developing therapeutics that prevent TAU toxicity. ReS19-T, one such compound, is in preclinical testing to treat AD and is being developed through a partnership with **Roche**.

Gerhard Koenig, SVP of research and CSO of **EnVivo Pharmaceuticals Inc.** agreed and added, "It will be key to establish the dynamic range in human cerebrospinal fluid. Additionally, it will be important to determine whether the levels of *cis* isoform are truly driving the TAU pathology as the authors suggest."

EnVivo has EVP-6124, a nicotinic acetylcholine receptor α7 (CHRNA7) agonist, in Phase II testing to treat AD. The company has exclusive worldwide rights to the compound from **Bayer AG**, and EnVivo has granted rights to **Mitsubishi Tanabe Pharma Corp.** in several Asian markets.

In addition to using anti–*cis* p-τ 231 antibodies as therapeutics, Lu thinks another approach could be to go upstream and increase PIN1 activity. "AD is complicated by other disease mechanisms as well, so blocking TAU pathology is an essential component but might not be a complete solution," he said. "PIN1 prevents TAU pathology, but in two earlier papers we also showed that it prevents β-amyloid pathology

by converting APP [amyloid precursor protein] from a *cis* to a *trans* isoform."

The problem, according to Lu, "is that it isn't clear how to specifically increase PIN1 activity in neurons. We can do this in animal models genetically, but directly targeting a PIN1 activator in humans would be very difficult."

This is because "increasing PIN1 in proliferating cells can cause cancer, while increasing its activity in nondividing cells like neurons prevents neurodegeneration."

Lu told *SciBX* that Beth Israel has filed patent applications for the diagnostic and therapeutic applications of the antibodies as well as for *cis* p-τ 231–targeting vaccines made from the team's manipulated *cis* p-τ 231 protein for treating AD at early stages. The IP is available for licensing.

Martz, L. SciBX 5(17); doi:10.1038/scibx.2012.434
Published online April 26, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

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Beth Israel Deaconess Medical Center, Boston, Mass.
EnVivo Pharmaceuticals Inc., Watertown, Mass.
Harvard Medical School, Boston, Mass.
Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508), Osaka, Japan
reMYND N.V., Leuven, Belgium
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

This week in **therapeutics**

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Autoimmune disease	Arachidonate 15-lipoxygenase (ALOX15; 15-LOX)	Mouse and cell culture studies suggest increasing 15-LOX activity could help prevent autoimmune diseases. In cultured mouse cells, 15-lox promoted the uptake of apoptotic cells by macrophages and reduced the uptake of apoptotic cells by proinflammatory monocytes. In a mouse model of systemic lupus erythematosus (SLE), mice lacking 15-lox had greater autoantibody production and glomerulonephritis than 15-lox-expressing controls. Next steps include developing small molecules that could block the uptake of apoptotic cells into proinflammatory monocytes. ***SciBX* 5(17); doi:10.1038/scibx.2012.435** **Published online April 26, 2012**	Patent application filed; unavailable for licensing	Uderhardt, S. *et al. Immunity*; published online April 12, 2012; doi:10.1016/j.immuni.2012.03.010 **Contact:** Gerhard Krönke, University of Erlangen-Nuremberg, Erlangen, Germany e-mail: gerhard.kroenke@uk-erlangen.de
Cancer				
Cancer	Serine/threonine kinase 33 (STK33); heat shock protein 90 (Hsp90)	Studies in cell culture suggest blocking the interaction between STK33 and Hsp90 could help treat tumors driven by activating mutations in *K-Ras*. Previous studies have shown divergent results on whether antagonizing STK33 kinase activity would be an effective cancer treatment. In lysates from cultured colon and lung tumor lines, Hsp90 coimmunoprecipitated with STK33. In *K-Ras*-mutant tumor lines, pharmacological inhibition or small hairpin RNA knockdown of Hsp90 decreased STK33 levels and increased apoptosis compared with those seen in control cells with wild-type *K-Ras*. In an *in vitro* tumor growth assay, overexpression of STK33 blocked Hsp90 inhibitor–mediated growth prevention. Next steps include understanding the kinase-independent roles of STK33 in promoting growth in *K-Ras*-mutant tumors. At least 12 companies have Hsp90 inhibitors in preclinical through Phase III development for cancer. ***SciBX* 5(17); doi:10.1038/scibx.2012.436** **Published online April 26, 2012**	Unpatented; licensing status not applicable	Azoitei, N. *et al. J. Exp. Med.*, published online April 9, 2012; doi:10.1084/jem.20111910 **Contact:** Claudia Scholl, University of Ulm, Ulm, Germany e-mail: claudia.scholl@uni-ulm.de **Contact:** Stefan Fröhling, same affiliation as above e-mail: stefan.froehling@uni-ulm.de
Melanoma	Phosphoinositide 3-kinase (PI3K)	Mouse and cell culture studies suggest inhibiting PI3K signaling could help improve the effects of ADI-PEG 20 in melanoma. In a human melanoma cell line, ADI-PEG 20 plus either of two PI3K inhibitors decreased proliferation compared with each compound alone. In a mouse xenograft model of melanoma, ADI-PEG 20 plus a PI3K inhibitor lowered tumor volumes compared with either compound alone. Next steps could include evaluating the combination approach in additional melanoma models. ADI-PEG 20, an arginine deiminase (ADI) formulated with polyethylene glycol from Polaris Pharmaceuticals Inc., is in Phase II/III trials to treat multiple cancers. ***SciBX* 5(17); doi:10.1038/scibx.2012.437** **Published online April 26, 2012**	Patent and licensing status unavailable	Tsai, W.-B. *et al. Cancer Res.*; published online March 29, 2012; doi:10.1158/0008-5472.CAN-11-3605 **Contact:** Macus Tien Kuo, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: tkuo@mdanderson.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	Glutathione peroxidase 3 plasma (GPX3); tumor protein p53 inducible protein 3 (TP53I3; PIG3)	*In vitro* studies suggest increasing the activity of GPX3 and PIG3 could help treat prostate cancer. In human prostate cancer cell lines and immortalized prostate epithelial cells, the tumor suppressor GPX3 colocalized with PIG3. In the same cells, anti-GPX3 and anti-PIG3 small interfering RNA decreased both reactive oxygen species (ROS) and UV-induced cell death compared with scrambled siRNA control. Next steps include additional studies of the effects of increasing PIG3 levels. ***SciBX* 5(17); doi:10.1038/scibx.2012.438** **Published online April 26, 2012**	Findings unpatented; unavailable for licensing	Wang, H. *et al. J. Biol. Chem.*; published online March 29, 2012; doi:10.1074/jbc.M111.322636 **Contact:** Yan P. Yu, University of Pittsburgh School of Medicine, Pittsburgh, Pa. e-mail: ypyu@pitt.edu
Cardiovascular disease				
Ischemia/ reperfusion injury	MicroRNA-214 (miR-214)	Mouse studies suggest increasing miR-214 levels could help protect against cardiac ischemia/reperfusion injury. In a mouse model of myocardial infarction, *miR-214* knockout increased ischemia/reperfusion injury and decreased survival compared with wild-type *miR-214* expression. Next steps could include synthesizing and evaluating miR-214 in mouse models of ischemia/ reperfusion injury. ***SciBX* 5(17); doi:10.1038/scibx.2012.439** **Published online April 26, 2012**	Patent and licensing status unavailable	Aurora, A.B. *et al. J. Clin. Invest.*; published online March 19, 2012; doi:10.1172/JCI59327 **Contact:** Eric N. Olson, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: eric.olson@utsouthwestern.edu
Endocrine/metabolic disease				
Diabetes	Inositol 1,4,5-triphosphate receptor (ITPR; IP3R)	Mouse studies suggest inhibiting IP3R could help treat diabetes. In normal mice, RNAi against *Ip3r* lowered the expression of gluconeogenic genes and circulating glucose concentrations compared with scrambled RNAi. In a mouse model of diabetes, RNAi against *Ip3r* decreased gluconeogenic gene expression and hepatic gluconeogenesis compared with nontargeting RNAi. Next steps could include screening for small molecule inhibitors of IP3R. ***SciBX* 5(17); doi:10.1038/scibx.2012.440** **Published online April 26, 2012**	Patent and licensing status unavailable	Wang, Y. *et al. Nature*; published online April 8, 2012; doi:10.1038/nature10988 **Contact:** Marc Montminy, The Salk Institute for Biological Studies, La Jolla, Calif. e-mail: montminy@salk.edu
Gastrointestinal disease				
Gastrointestinal disease	Ceramide	A study in mice identified an anticeramide antibody called 2A2 that could help prevent or reduce radiation-induced gastrointestinal syndrome. In mice, the mAb decreased radiation-induced endothelial apoptosis in the intestine and increased survival compared with antibody control. PxRadia Inc.'s 2A2 is in preclinical development for protecting against and mitigating the effects of radiation. ***SciBX* 5(17); doi:10.1038/scibx.2012.441** **Published online April 26, 2012**	Work covered by patent and filed patent applications; licensed to PxRadia	Rotolo, J. *et al. J. Clin. Invest.*; published online April 2, 2012; doi:10.1172/JCI59920 **Contact:** Richard Kolesnick, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: r-kolesnick@ski.mskcc.org
Infectious disease				
Chagas disease; leishmaniasis	Not applicable	An *in vitro* study identified derivatives of the antifungal clotrimazole that could help treat leishmaniasis and Chagas disease. *In vitro*, ruthenium complexes of clotrimazole decreased the growth of *Leishmania major* and *Trypanosoma cruzi*, the causative agent of Chagas disease, compared with the parent compound. In mouse macrophages infected with *L. major*, one of the ruthenium complexes inhibited intracellular parasite proliferation with an IC_{70} value of 29 nM. Next steps include testing the lead compounds in mouse models of cutaneous leishmaniasis and Chagas disease. ***SciBX* 5(17); doi:10.1038/scibx.2012.442** **Published online April 26, 2012**	Patent status undisclosed; licensing status not applicable	Martínez, A. *et al. J. Med. Chem.*; published online March 26, 2012; doi:10.1021/jm300070h **Contact:** Roberto A. Sánchez-Delgado, The City University of New York Brooklyn College, Brooklyn, N.Y. e-mail: rsdelgado@brooklyn.cuny.edu **Contact:** Rosa A. Maldonado, The University of Texas at El Paso, El Paso, Texas e-mail: ramaldonado@utep.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Dengue fever	Dengue virus envelope protein E (DENV_gp1)	*In vitro* studies identified small molecule inhibitors of the viral fusion protein DENV_gp1 that could help treat Dengue fever. High throughput screening and SAR studies identified a scaffold that bound DENV_gp1. In hamster kidney fibroblasts, three compounds based on the scaffold blocked infectivity of Dengue virus serotypes 2 and 4 at low micromolar to submicromolar IC_{50} values. Future studies could include testing the compounds in animal models of Dengue fever. ***SciBX* 5(17); doi:10.1038/scibx.2012.443** **Published online April 26, 2012**	Patent and licensing status unavailable	Schmidt, A.G. *et al. PLoS Pathog.*; published online April 5, 2012; doi:10.1371/journal.ppat.1002627 **Contact:** Stephen C. Harrison, Harvard Medical School, Boston, Mass. e-mail: harrison@crystal.harvard.edu
Musculoskeletal disease				
Muscular dystrophy	Heat shock 70 kDa protein 1A (Hsp72; HspA1)	Mouse studies suggest increasing Hsp72 activity could help treat muscular dystrophy. In mouse models of muscular dystrophy, a small molecule activator of Hsp72 decreased spinal curvature and increased muscle strength, diaphragm function and lifespan compared with no treatment. Next steps could include studying the Hsp72 activator in large mammal models of muscular dystrophy. ***SciBX* 5(17); doi:10.1038/scibx.2012.444** **Published online April 26, 2012**	Findings patented; licensing status undisclosed	Gehrig, S.M. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature10980 **Contact:** Gordon S. Lynch, The University of Melbourne, Melbourne, Victoria, Australia e-mail: gsl@unimelb.edu.au
Neurology				
Alzheimer's disease (AD)	Not applicable	*In vitro* studies suggest gambierol analogs could help treat AD. Gambierol is a toxin produced in limited quantities by marine *Gambierdiscus toxicus*. Two truncated skeletal analogs of the molecule were synthesized, and in primary cortical neurons, the analogs decreased β-amyloid (Aβ) accumulation and levels of phosphorylated-τ compared with no treatment. Next steps could include testing the analogs in animal models of AD. ***SciBX* 5(17); doi:10.1038/scibx.2012.445** **Published online April 26, 2012**	Patent and licensing status unavailable	Alonso, E. *et al. J. Am. Chem. Soc.*; published online April 4, 2012; doi:10.1021/ja300565t **Contact:** Luis M. Botana, University of Santiago of Compostela, Lugo, Spain e-mail: luis.botana@usc.es
Ataxia	Histone deacetylase 4 (HDAC4)	A study in mice suggests blocking the nuclear localization of HDAC4 may help treat ataxia telangiectasia, a neurodegenerative disease caused by mutation of *ataxia telangiectasia mutated* (*ATM*). In *Atm*-deficient mice, Hdac4 localized to the nucleus. Also in *Atm*-deficient mice, overexpression of Hdac4 in the cytoplasm led to decreased apoptosis in cerebellar neurons and increased motor performance compared with normal Hdac4 expression. Next steps could include strategies for blocking nuclear accumulation of HDAC4. ***SciBX* 5(17); doi:10.1038/scibx.2012.446** **Published online April 26, 2012**	Patent and licensing status unavailable	Li, J. *et al. Nat. Med.*; published online April 1, 2012; doi:10.1038/nm.2709 **Contact:** Karl Herrup, Rutgers University, Piscataway, N.J. e-mail: herrup@biology.rutgers.edu
Pain	Lysophosphatidic acid receptor 5 (LPAR5; LPA5)	Mouse studies suggest inhibiting LPAR5 could help treat neuropathic pain. In mice, *Lpar5* knockout decreased neuropathic pain following partial sciatic nerve ligation compared with wild-type *Lpar5* expression. Next steps include testing LPAR5 antagonists in proof-of-concept studies. ***SciBX* 5(17); doi:10.1038/scibx.2012.447** **Published online April 26, 2012**	Findings unpatented; research agreements available for uses including the knockout animals	Lin, M.-E. *et al. J. Biol. Chem.*; published online March 29, 2012; doi:10.1074/jbc.M111.330183 **Contact:** Jerold Chun, The Scripps Research Institute, La Jolla, Calif. e-mail: jchun@scripps.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
Assays & screens			
Comprehensive cell-line panel for predicting responses to cancer therapies	A collection of hundreds of cancer cell lines could help predict responses to cancer therapies. The panel consisted of 639 human tumor cell lines representing a range of adult and childhood cancers of epithelial, mesenchymal and hematopoietic origin. In each of the cell lines, multiple genomic technology platforms were used to determine the mutational status of 64 commonly mutated cancer genes and characterize copy number variation and profile the expression of 14,500 genes. The sensitivity of the cell lines to 132 cancer therapeutics also was measured. As proof of principle, the platform identified a previously unknown sensitivity of *Ewing sarcoma breakpoint region 1* (*EWSR1*; *EWS*)–*Friend leukemia virus integration 1* (*FLI1*)–mutant Ewing sarcoma cells to poly(ADP-ribose) polymerase (PARP) inhibitors. Next steps include characterizing some of the cell lines at the epigenetic level and studying cell responses to drug combinations (*see* **Cancer cell line encyclopedias, page 1**). ***SciBX* 5(17); doi:10.1038/scibx.2012.448** **Published online April 26, 2012**	Unpatented; licensing status not applicable	Garnett, M.J. *et al. Nature*; published online March 28, 2012; doi:10.1038/nature11005 **Contact:** Ultan McDermott, Wellcome Trust Sanger Institute, Hinxton, U.K. e-mail: um1@sanger.ac.uk **Contact:** Cyril H. Benes, Harvard Medical School, Boston, Mass. e-mail: cbenes@partners.org
Comprehensive cell-line panel for predicting responses to cancer therapies	A collection of nearly 1,000 cancer cell lines could help predict responses to cancer therapies. The Cancer Cell Line Encyclopedia (CCLE) consists of 947 human cancer cell lines that encompass 36 tumor types. Multiple genomic technology platforms were used to characterize each of the cell lines according to three broad metrics: the mutational status of more than 1,600 genes, DNA copy number variation and mRNA expression. Based on those metrics, the sensitivity of the cell lines to 24 known cancer therapeutics was measured. As proof of principle, many cell lines were sensitive to broadly active compounds such as a histone deacetylase (HDAC) inhibitor, whereas fewer cell lines were sensitive to more selective compounds such as a BRAF inhibitor. Next steps include using the platform to guide patient selection for Novartis AG's Phase I cancer trials (*see* **Cancer cell line encyclopedias, page 1**). ***SciBX* 5(17); doi:10.1038/scibx.2012.449** **Published online April 26, 2012**	Unpatented; licensing status not applicable	Barretina, J. *et al. Nature*; published online March 28, 2012; doi:10.1038/nature11003 **Contact:** Levi A. Garraway, Dana-Farber Cancer Institute, Boston, Mass. e-mail: levi_garraway@dfci.harvard.edu **Contact:** Robert Schlegel, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: robert.schlegel@novartis.com
Computational models			
Computational model for estimating intracranial pressure	A computational model for estimating intracranial pressure could improve the diagnosis of brain injuries. The model uses noninvasive measurements of peripheral arterial blood pressure and blood flow velocity in the middle cerebral artery to estimate intracranial pressure. In 37 patients with traumatic brain injury, the computational model estimated intracranial pressure with a mean error of 1.6 mmHg and standard deviation of 7.6 mmHg relative to invasively measured values. Next steps could include using the model to estimate intracranial pressure in patients who have other types of neurological conditions, such as stroke or brain tumors. ***SciBX* 5(17); doi:10.1038/scibx.2012.450** **Published online April 26, 2012**	Patent and licensing status unavailable	Kashif, F.M. *et al. Sci. Transl. Med.*; published online April 11, 2012; doi:10.1126/scitranslmed.3003249 **Contact:** Thomas Heldt, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: thomas@mit.edu **Contact:** Faisal M. Kashif, same affiliation as above e-mail: fmkashif@mit.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
Dendrimer-based drug delivery to treat cerebral palsy	Studies in rabbits identified a dendrimer–small molecule conjugate that crossed the blood brain barrier and could help treat cerebral palsy. In a newborn rabbit model of cerebral palsy, systemic delivery of a conjugate consisting of a dendrimer delivery vehicle linked to the small molecule anti-inflammatory compound N-acetyl-cysteine (NAC) decreased neuroinflammation and increased motor function compared with delivery of vehicle. Imaging studies showed the conjugate localized to microglia and astrocytes in the brain. Next steps include identifying the optimal dosing regimen of the conjugate. The generic NAC is marketed to treat acetaminophen-induced liver injury. ***SciBX* 5(17); doi:10.1038/scibx.2012.451** **Published online April 26, 2012**	Patented; available for licensing	Kannan, S. *et al. Sci. Transl. Med.*; published online April 18, 2012; doi:10.1126/scitranslmed.3003162 **Contact:** Rangaramanujam M. Kannan, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: krangar1@jhmi.edu **Contact:** Roberto Romero, National Institute of Child Health and Human Development, Detroit, Mich. e-mail: romeror@mail.nih.gov
Drug platforms			
Controlled microfluidic formulation of small interfering RNA–containing lipid nanoparticles	Controlled microfluidic formulation of siRNA-containing lipid nanoparticles could aid the development of siRNA-based therapeutics. The system promotes the self-assembly of siRNA lipid nanoparticles by using microfluidic channels with trenches and ridges to mix an ethanol solution containing cationic lipids with an equal volume of siRNA in aqueous solution. Using this system, 7 siRNA-containing lipid nanoparticle formulations were generated that achieved more than 90% gene silencing in mice at a 1 mg/kg dose. Next steps could include studies to compare the knockdown efficacy of conventional siRNA-loaded nanoparticles with those created using the microfluidic system. ***SciBX* 5(17); doi:10.1038/scibx.2012.452** **Published online April 26, 2012**	Patent and licensing status unavailable	Chen, D. *et al. J. Am. Chem. Soc.*; published online April 5, 2012; doi:10.1021/ja301621z **Contact:** Daniel G. Anderson, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: dgander@mit.edu
Imaging			
Brain tumor imaging via triple-modal MRI, photoacoustic and Raman nanoparticles	A triple-modality approach to imaging nanoparticles could help improve surgical resection of brain tumors. In mouse models of brain cancer, modified gold nanoparticles preferentially accumulated in tumors and produced three types of signals—MRI, photoacoustic and Raman—which enabled whole-brain imaging of tumors and high-resolution definition of tumor margins. During surgical resection of mouse brain tumors, photoacoustic and Raman detection of the nanoparticles guided each resection step and confirmed removal of tumor tissue. Future studies could include developing handheld instruments that use the method. ***SciBX* 5(17); doi:10.1038/scibx.2012.453** **Published online April 26, 2012**	Patent and licensing status unavailable	Kircher, M.F. *et al. Nat. Med.*; published online April 15, 2012; doi:10.1038/nm.2721 **Contact:** Sanjiv S. Gambhir, Stanford University, Stanford, Calif. e-mail: sgambhir@stanford.edu
Markers			
Intercellular adhesion molecule-1 (ICAM-1; CD54) as a marker of treatment response for congenital disorders of glycosylation	Patient sample studies suggest ICAM-1 could be useful as a marker for congenital disorders of glycosylation, which are caused by inherited genetic defects in N-linked glycosylation. In patient fibroblasts, ICAM-1 levels were lower than those in normal cells. In one of the patient cell lines, addition of mannose, which relieves disease symptoms, increased ICAM-1 expression compared with no addition. Next steps include testing ICAM-1 as a marker for detecting improvements in glycosylation activity in cells. ***SciBX* 5(17); doi:10.1038/scibx.2012.454** **Published online April 26, 2012**	Provisional patent application filed; available for licensing from the Sanford-Burnham Medical Research Institute **Contact:** Paul Laikind, Sanford-Burnham Medical Research Institute, La Jolla, Calif. phone: 858-646-3116 e-mail: plaikind@sanfordburnham.org	He, P. *et al. J. Biol. Chem.*; published online April 11, 2012; doi:10.1074/jbc.M112.355677 **Contact:** Hudson H. Freeze, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: hudson@sanfordburnham.org

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