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P glycoprotein

By Kai-Jye Lou, Staff Writer

NIH researchers have shown that sphingosine 1-phosphate receptor agonists such as **Novartis AG's** Gilenya fingolimod could transiently reduce P glycoprotein-mediated drug efflux and enhance drug delivery to the brain.¹ The group at NIH's **National Institute of Environmental Health Sciences** thinks the transient mode of action of these agonists could avoid the adverse effects seen with direct P glycoprotein inhibitors.

The researchers now are elucidating the underlying mechanism and evaluating the approach for improving drug delivery to brain tumors.

P glycoprotein (MDR1; ABCB1; P-gp; CD243) is an active efflux transporter protein expressed by endothelial cells that line the blood brain barrier (BBB). The transporter exerts its neuroprotective effect by pumping out a range of potentially harmful molecules that enter the CNS from the blood. However, the transporter also complicates drug delivery to the CNS because it expels many therapeutics such as paclitaxel.

In cases in which a drug is a known substrate of P-gp, a straightforward strategy to enhance brain delivery is directly inhibiting P-gp. The problem with this approach is that direct P-gp inhibitors have caused unacceptable systemic toxicity in clinical trials, and nearly all such compounds have been discontinued.

Hanmi Pharmaceutical Co. Ltd. and partner **Kinex Pharmaceuticals LLC** are the only companies left with a disclosed oral P-gp inhibitor, HM30181A, but they are steering clear of the brain. The gastrointestinal-selective P-gp inhibitor is in Phase II trials to treat gastric cancer in combination with an oral formulation of paclitaxel and is in Phase I testing to treat advanced solid malignancies in combination with oral irinotecan.

According to David Miller, head of the Intracellular Regulation Group and chief of the Laboratory of Toxicology & Pharmacology at the National Institute of Environmental Health Sciences (NIEHS), the safety issues of direct P-gp inhibitors stem from the compounds being too potent and inhibiting P-gp's function for too long.

He proposed an alternative strategy to improve CNS drug delivery: to rapidly—but transiently—reduce P-gp efflux activity.

Miller and colleagues at NIEHS have been trying to elucidate the mechanisms that modulate the expression and activity of P-gp in cells along the BBB in hopes of finding new ways to target the transporter. For example, the group published a series of studies starting in 2004 detailing a tumor necrosis factor- α (TNF- α)-activated signaling pathway that reduces P-gp activity.²⁻⁴

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Meanwhile, other academic groups have shown that TNF- α signaling in human endothelial cells stimulates the production of sphingosine 1-phosphate by activating sphingosine kinase 1 (SPHK1).^{5,6}

Putting the puzzle pieces together, the NIEHS group sought to determine whether sphingosine 1-phosphate signaling itself could reduce P-gp efflux activity.

In an *in vitro* assay using isolated rodent brain capillaries, 1 μ M of sphingosine 1-phosphate caused complete loss of P-gp activity within 30 minutes. Subsequent removal of the lipid metabolite led to restoration of P-gp function within the same time frame. The researchers also showed that sphingosine 1-phosphate acts further downstream than previously identified members of the TNF- α -activated pathway.

"We found that sphingosine 1-phosphate receptor agonists rapidly and reversibly modulate the activity of P-gp to reduce its transport of drugs out of the blood brain barrier," said Miller. "In our *in vitro* assay, we see a reduction in efflux activity within 5–10 minutes, with the full effect being achieved within 30 minutes, and we see that the time course of recovery after removing the agonist is also on the order of 30 minutes."

According to Miller, going after targets that are closer to the point of P-gp modulation should have a lower risk of side effects than hitting more upstream targets.

In rats, sphingosine 1-phosphate receptor agonists such as Gilenya increased BBB penetration of paclitaxel and the opioid receptor agonist loperamide by up to fivefold compared with delivering the two drugs without an agonist.

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

Patrick Ronaldson, an assistant professor in the Department of

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Pharmacology at **The University of Arizona College of Medicine**, noted that the rapid and transient mode of action should enable much finer control over drug delivery to the brain than earlier P-gp inhibitors.

Novartis markets Gilenya to treat relapsing forms of multiple sclerosis (MS). The pharma was not involved in the study and declined to comment on the findings.

Safety first

It remains unclear whether Gilenya itself would be a good sphingosine 1-phosphate agonist to use to enhance the brain delivery of other drugs.

Pieter Gaillard, cofounder and CSO at **to-BBB technologies B.V.**, noted that Gilenya has significant side effects.

“It is very interesting that this drug has such an effect on drug delivery to the CNS in addition to its known immunomodulatory effects,” he told *SciBX*. “But the drug itself is already associated with cardiotoxicity and infection risk, and it isn’t yet clear how widespread such effects would be.”

Gaillard said the safety concerns would be magnified by the need for high plasma concentrations to improve drug delivery across the BBB.

Miller said he is aware of the safety signals associated with Gilenya and acknowledged that the plasma concentrations in patients with MS who take the drug orally are at least an order magnitude lower than what is needed to enhance drug delivery across the BBB.

“If we are to use fingolimod, we would probably want to deliver the drug via carotid infusion to get the high local concentrations needed to enhance drug delivery across the blood brain barrier,” he said. “This also has the benefit of having a short-term effect as fingolimod will then be diluted into systemic circulation, so its effects on P-gp should quickly wear off after stopping the infusion.”

Gaillard agreed that carotid infusion could be a viable approach to achieve the high local concentrations needed, but he said the approach is more invasive than i.v. delivery and thus could restrict its use.

to-BBB uses liposomes coated with glutathione-conjugated polyethylene glycol (PEG) to improve drug delivery across the BBB. The biotech’s 2B3-101, a liposomal formulation of doxorubicin coated with glutathione-conjugated PEG, is in Phase I/IIa testing to treat brain cancer.

Picking an indication

Miller said the NIEHS group is starting to evaluate the Pieter Gaillard agonist strategy in a rodent brain tumor model.

Because Gilenya also has immunomodulatory effects, Gaillard said it will be important for the NIEHS researchers to evaluate their approach

“We found that sphingosine 1-phosphate receptor agonists rapidly and reversibly modulate the activity of P-gp to reduce its transport of drugs out of the blood brain barrier.”

**—David Miller,
National Institute of
Environmental Health Sciences**

in oncology models that include the ability to measure effects on the immune system.

“Other disease areas to consider for this approach could be multiple sclerosis, Parkinson’s disease, Alzheimer’s disease and possibly epilepsy, as many antiepileptics are known to be difficult to deliver to the brain,” Ronaldson told *SciBX*. “One other area would be in HIV where the infection has spread to the brain, as current antiretroviral drugs also have trouble getting into the brain.”

Ronaldson said dose-response studies are going to be important because the NIEHS group will need to determine what type of dosing adjustments are needed for existing drugs when they are co-delivered with a sphingosine 1-phosphate receptor agonist. Moreover, he said that it will be important to determine what other efflux and influx transporter proteins might be affected by sphingosine 1-phosphate receptor agonists.

In addition to the drug delivery studies, Miller said the group is looking downstream of the sphingosine 1-phosphate receptors to identify targets that are even closer to the observed down-modulation of P-gp-mediated drug efflux.

“This may also lead us to identify another transporter that we can modulate to enhance CNS drug delivery,” he added.

The work in the paper is unpatented.

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Buddy system for orphan disease

By Lev Osherovich, Senior Writer

The **Wellcome Trust** has launched a program to fund early stage translational research in rare and orphan diseases. Participation in the program, dubbed the Pathfinder Award Scheme, requires academics or not-for-profits to pair up with an industry partner at the outset.

Industry partners will contribute expertise and project-specific services but are not required to contribute cash. Companies participating in the scheme receive rights of first refusal for new IP arising from the partnership.

In September, Wellcome awarded 2 grants of about £100,000 (US\$160,000) each to 2 academic-industry pairs and plans to fund at least 2 more similar-sized grants within a year.

A team at **University College London** will work with **Eli Lilly and Co.** to develop cell culture models for a rare class of neurodegenerative disorders that resemble Parkinson's disease (PD). A **University of Oxford** group will work with **Pfizer Inc.** to develop methods to treat homocystinuria, a rare metabolic disease.

Bethan Hughes, a Wellcome Trust business analyst who administers the Pathfinder Scheme, said the program was conceived to finance projects that cannot compete for the Trust's other translational grant programs, which are typically £2–3 million (US\$3.2–4.8 million) and require a more advanced starting point.

"There were many times when applications would come to us in orphan or neglected diseases but were too early for those other funding schemes," said Hughes. "It was considered a great shame that these proposals didn't have access to product development expertise" to help them get to a more advanced stage.

Indeed, the rationale for engaging industry partners at the start of a project is to help the academics build the right tools and reagents for future translational efforts.

Hughes said rare disease researchers in academia often lack access to industrial expertise and do not know what milestones are relevant or how to navigate the regulatory landscape. The result can be inadequately validated disease models and wasted effort on inappropriate drug delivery methods.

"Suppose you're making a protein-based vaccine. Academic researchers may not know what kind of vector or tag would be most suitable and might be rushing to get to proof of concept with less than ideal technology," said Hughes. "It doesn't do much service in the end to put a suboptimal drug candidate into the clinic."

One caveat of the Pathfinder Award program is that it requires the industry partner to have previously brought a product to market. This effectively means researchers will need to work with pharma and large biotech rather than the small startups that populate the orphan disease space.

The reason for requiring industry partners to have prior product development experience is that "the expertise that we want these academic groups to harness may only be available" from such partners, according to Hughes.

Metal and metabolism

The UCL-Lilly team, led by molecular neuroscience professor John Hardy, will build cell culture models of neurodegeneration with brain iron accumulation (NBIA), a rare hereditary PD-like condition.

NBIA is caused by mutations in any of three genes—*pantothenate kinase 2* (*PANK2*; *NBIA1*), *phospholipase A₂ group VI* (*PLA₂G6*; *NBIA2A*) and *ferritin light polypeptide* (*FTL*; *NBIA3*). NBIA affects fewer than one in a million people and leads to clinical and histopathological features that resemble severe early onset PD. The disease is thought to be driven by excessive iron accumulation, which is observed to a lesser extent in milder forms of PD.

Hardy aims to "collect fibroblasts from NBIA patients and transform them into neurons *in vitro*," which would allow him and Lilly researchers to screen for compounds that reduce iron accumulation.

Hardy and his collaborators at Lilly hope to show that NBIA is a valid model of the sporadic form of PD.

Hardy said obtaining funding for the project through other grant mechanisms has been challenging because there is not yet a consensus about the relationship between NBIA and PD.

"It will be a while before the entire research community is convinced that this is a good model for PD," said Hardy. Funding this proposal "would be difficult if we got into peer review with people who didn't think this was any more than a small disease."

After 18 months, the grant expires and Lilly will have an option to continue the joint project under a direct collaborative research agreement.

At least one company—**Prana Biotechnology Ltd.**—aims to treat PD by reducing iron accumulation in the brain. Prana's PBT-434, a metal-binding compound, is in preclinical development for PD.

The other announced Pathfinder Award recipient is Wyatt Yue, group leader in the structural genomics of metabolic enzymes group at the **Structural Genomics Consortium** at University of Oxford.

Yue and collaborators at Pfizer will apply structural methods to develop pharmacological tools to restore the function of cystathionine β-synthase (CBS). Mutations in CBS lead to homocystinuria, in which homocysteine accumulation leads to a broad range of neurological and musculoskeletal problems.

Homocystinuria is currently treated by a combination of N,N,N-trimethylglycine, vitamin B₆ and a diet low in the amino acid methionine. Cystadane betaine anhydrous, a formulation of N,N,N-trimethylglycine, is marketed by **Rare Disease Therapeutics Inc.** in the U.S. and **Orphan Europe S.a.r.l.** elsewhere.

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COMPANIES AND INSTITUTIONS MENTIONED

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

Prana Biotechnology Ltd. (ASX:PBT; NASDAQ:PRAN), Melbourne, Victoria, Australia

Rare Disease Therapeutics Inc., Franklin, Tenn.

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Paper point of care

By *Tim Fulmer, Senior Writer*

A team of U.S. researchers has developed a postage stamp-sized diagnostic for hepatotoxicity and has used it to measure liver enzyme levels in human blood samples.¹ **Diagnostics for All** has exclusively licensed the device and is running field tests in Vietnam.

Blood tests for monitoring liver status in at-risk individuals receiving tuberculosis (TB) or HIV therapies are a standard practice.²⁻⁴ In the developing world, however, logistical limitations can make it difficult and costly to monitor therapy-associated hepatotoxicity.

As a result, there is a need for liver toxicity tests that can be rapidly implemented and interpreted in a resource-limited setting and that are affordable, stable and easy to use.⁵

Prior studies have shown that paper-based microfluidic devices are useful for conducting basic enzymatic and immunoassay tests.⁶⁻⁹ Such devices require no external pumps, instrumentation or power and are portable and disposable, making them suitable for use in the developing world. However, the devices have yet to be validated with actual patient samples.

Thus, a team of researchers led by Nira Pollock, Jason Rolland and George Whitesides set out to design a paper-based device that measured

liver enzyme levels in blood from patients receiving HIV and/or TB therapy and that required only the unaided eye to detect and interpret results. To do that, they relied on basic microfluidics technology previously developed in Whitesides' laboratory.^{10,11}

The study was performed on U.S. patients by U.S. clinicians and researchers.

Pollock is a researcher in the division of infectious diseases at **Beth Israel Deaconess Medical**

Center, associate medical director of the infectious diseases diagnostic laboratory at the **Boston Children's Hospital** and assistant professor of medicine at **Harvard Medical School**. Rolland is senior director of research at **Diagnostics for All**, a not-for-profit that designs low-cost point-of-care tests for use in the developing world. Whitesides is professor of chemistry at **Harvard University**.

When a drop of whole blood was applied to an opening in the cover of the device, blood cells were retained in the separation membrane while plasma diffused into the other layers and reacted with reagents. That reaction generated a color readout that indicated the presence of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the plasma. AST and ALT are two enzymes commonly associated with liver injury.

The intensity of the color readout was optimized to fall within one of three clinically relevant ranges: <3×, 3×–5× and >5× normal AST and ALT levels.

The surface of the paper also included three control zones to monitor device performance. The entire test was completed in about 15 minutes.

The researchers next tested their device on 233 blood samples from

patients with HIV and TB who had a range of AST and ALT concentrations. The device was >90% accurate using both serum and whole-blood samples.

The authors wrote that their method "can ultimately be produced at a very low cost—on the order of <\$0.10 per test." Current electronic gold standard tests cost \$4.

Results were published in *Science Translational Medicine*.

"The paper provides the first published example of clinical tests using paper-based microfluidic devices and provides convincing evidence that the basic premise of paper microfluidics is sound and worth substantial development," said Scott Phillips, assistant professor of chemistry at **Pennsylvania State University**.

Earlier this year, Phillips, Whitesides and colleagues published in *Analytical Chemistry* data on a paper-based microfluidic device that measured alkaline phosphatase, AST and total protein levels in nonclinical samples.¹²

In contrast to much previous work in paper-based diagnostics and assays, the authors "considered logistical constraints from the outset in designing their test, including cost factors, device storage and potential user error," said Barry Lutz.

They also "chose to align their test with current clinical practice, which can greatly increase the likelihood of adoption," he added.

Lutz and colleagues Paul Yager and Elain Fu at the **University of Washington** are developing paper devices for amplified immunoassays and nucleic acid amplification tests,¹³ with the goal of creating methods that "perform sophisticated biochemical tests in a format that is as easy to use as a pregnancy test."

Lutz and Fu are research assistant professors of bioengineering at the University of Washington. Yager is professor and chair of bioengineering at the university.

Good morning, Vietnam

Kenneth Hawkins, program officer and research scientist in the diagnostics group at **PATH** (Program for Appropriate Technology in Health), said the next step should be "a field-based study in one of the target markets in the developing world. The results could be very different with a different patient population and when performed by a representative group of operators in the target market."

The color reading of the device "is subjective, and the device's true ability to quantify results must be proven," added Robert Jenison, CTO at **Great Basin Corp.** "A reader device would help tremendously."

Great Basin is developing a battery-powered instrument for use in the developing world to detect mutations in TB bacteria.

"It'll be interesting to test the outcome of the assay if each patient is asked to read his or her own result," said Phillips. "The ideal point-of-care device would be one that provides a readout that is sufficiently unambiguous that anyone can read and interpret it."

Earlier this year, **Diagnostics for All** and **Beth Israel** partnered with **PATH** and **The Hospital for Tropical Diseases** (HTD) in Vietnam to carry out a preliminary study of the paper-based diagnostic, co-corresponding author Pollock told *SciBX*. "We are evaluating the performance of the diagnostic in finger-stick testing of 600 patients from the HTD HIV clinic," she said.

Initial data are expected in the next few months. The field study results "will provide data on how well local clinicians are able to read and interpret the test. Initial adoption of the test would likely be in patient clinics where

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"A particularly attractive means of doing this is to use a smart phone able to recognize and interpret colorimetric tests. This capability is something we plan to pursue in the next 1–2 years."

—*Jason Rolland, Diagnostics for All*

Transferrin PET project

By Michael J. Haas, Senior Writer

A Memorial Sloan-Kettering Cancer Center team has shown that a transferrin-based PET imaging agent detected prostate cancer in mice with greater sensitivity than ^{18}F -labeled fluorodeoxyglucose.¹ The new agent also detected a precancerous prostate condition that is not amenable to existing imaging technologies. The team now plans to take the agent into Phase I testing to detect prostate cancer.

PET imaging uses an agent labeled with a positron-emitting radionuclide. ^{18}F -labeled fluorodeoxyglucose (FDG) is the most widely used PET agent for tumor imaging because cancer cells have higher glucose uptake than normal cells and ^{18}F can be readily incorporated into glucose without significantly altering the biochemical properties of the sugar.

Another compound that could serve as the basis for a PET imaging agent is transferrin, a plasma protein that binds iron and carries it into cells via transferrin receptor protein 1 (TFRC; TFR; CD71). Most tumor types express higher levels of TFRC than normal cells, and as a result multiple studies over the past 30 years have explored the tumor-imaging potential of PET agents based on transferrin labeled with ^{18}F , ^{45}Ti , ^{97}Ru or ^{131}I .²⁻⁵

However, transferrin-based PET agents and FDG share a key limitation: rapid metabolism. The resulting radiolabeled metabolites can accumulate in normal tissues and produce background signals that make it difficult to obtain clear images of suspect tissues.

This has been especially problematic for imaging the prostate because

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(Continued from "Paper point of care," p. 5)

the test would be administered by a trained healthcare provider," Pollock added.

"Additional next steps in the work include long-term stability studies and development of quality manufacturing systems at Diagnostics for All for large-scale production of validated lots of the device," said co-corresponding author Rolland.

The researchers also are interested in using companion reader devices, said Rolland. "A particularly attractive means of doing this is to use a smart phone able to recognize and interpret colorimetric tests. This capability is something we plan to pursue in the next 1–2 years," he said.

The findings are covered by patent applications that are exclusively licensed to Diagnostics for All from Harvard.

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many metabolites of FDG and transferrin-based agents can accumulate in the nearby bladder.

A way around the prostate-imaging problem emerged a few years ago from a pair of studies by the Memorial Sloan-Kettering team. In 2009, the group reported that desferrioxamine (DFO) labeled with the positron-emitting radionuclide ^{89}Zr was stable in *ex vivo* human serum for up to seven days and produced high-resolution PET images in healthy mice.⁶

In 2010, the team showed that ^{89}Zr -DFO conjugated to an antibody against prostate-specific membrane antigen (PSMA; FOLH1; GCP11) was metabolically stable and produced high-contrast PET images of xenograft prostate tumors in mice.⁷

These findings led the team to postulate that ^{89}Zr -DFO conjugated to transferrin might also be stable and thus more broadly useful as a tumor-imaging agent than the ^{89}Zr -DFO-antibody conjugate.

First, the team showed that conjugates of ^{89}Zr -DFO and human transferrin were metabolically stable in *ex vivo* human blood for up to four days. Similarly, conjugates using mouse transferrin were stable for the same duration in the circulation of healthy mice.

The team also confirmed the conjugates' mode of action by showing uptake in mouse and human cancer cell lines expressing c-Myc (MYC)—a transcription factor that upregulates TFRC.

For its subsequent experiments with ^{89}Zr -DFO-transferrin, the team focused on prostate tumors, because these presented the greatest challenge to existing PET agents.

The group showed that PET imaging with ^{89}Zr -DFO-transferrin could distinguish between xenograft prostate tumors in mice with differing levels of TFRC activity. In addition, the agent detected high-grade prostatic intraepithelial neoplasia (PIN) in four-month-

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COMPANIES AND INSTITUTIONS MENTIONED

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old mice—about eight months before these animals develop prostate tumors—whereas FDG-PET did not.

PIN is thought to be a precursor to prostate cancer but is currently detectable only by histological analysis. Thus, it is usually found in biopsies taken from patients already suspected of having prostate cancer.

A key advantage of ^{89}Zr -DFO-transferrin is its metabolic stability, team coleader Jason Lewis told *SciBX*. “This allowed us to quantify fairly modest changes in MYC activity and TFRC expression to image tumors in a region of the animal that has been notoriously challenging to image,” he said.

Another advantage is the long half-life of ^{89}Zr , which allows “imaging over time spans far more appropriate for capturing the pharmacology of long-circulating molecules like transferrin” than what was possible with other transferrin-based PET imaging agents, he said.

Lewis is vice chair for basic research, chief attending radiochemist and director of the cyclotron core in the Department of Radiology at Memorial Sloan-Kettering. He also holds a joint appointment in the **Sloan-Kettering Institute’s** molecular pharmacology and chemistry program.

Charles Sawyers, chair of the human oncology and pathogenesis program at Memorial Sloan-Kettering and investigator at the **Howard Hughes Medical Institute**, co-led the team.

Data were reported in *Nature Medicine*.¹

Aggressive images

Despite the ability of ^{89}Zr -DFO-transferrin to detect PIN, the agent probably would not find utility as a tool to screen for the risk of prostate cancer because “there is no unmet clinical need to detect and image PIN,” Lewis said.

Instead, he said, the agent could be used to distinguish between indolent and aggressive prostate cancer at the time of diagnosis because existing tools—such as levels of prostate-specific antigen (KLK3; PSA)—are not reliable predictors of aggressive cancer.

“We know aggressive disease can be MYC-driven, and it’s likely that all tumors with MYC amplification will be aggressive,” he said. “So ^{89}Zr -DFO-transferrin could be used to profile patients according to MYC status” and identify those whose cancer is likely to be aggressive.

However, Lewis noted that ^{89}Zr -DFO-transferrin would not be strictly limited to detection of MYC-dependent cancers because other proteins and pathways can also upregulate TFRC. As an example, he cited the team’s study of the agent in xenograft models of glioblastoma multiforme (GBM) in which TFRC is upregulated by aberrant phosphoinositide 3-kinase (PI3K) signaling. Those results are in press with the *Journal of Nuclear Medicine*, he said.

He declined to disclose whether the team has tested ^{89}Zr -DFO-transferrin in mice with additional tumor types, but he said there are many good animal models of MYC-dependent—and thus TFRC-expressing—lymphoma and other cancers in which the PET agent could be tested.

The team is now running IND-enabling studies of ^{89}Zr -DFO-transferrin and is raising funds for a Phase I trial of the agent in patients with prostate cancer that it expects to begin in about a year, he said.

Memorial Sloan-Kettering spokesperson Andrea Molinatti declined to disclose who will fund the trial because that funding is under review by the NIH, she said.

Lewis added that the team is starting with prostate cancer because the “abundance of patients coming through Memorial Sloan-Kettering for treatment” will make trial enrollment easy. After completing the prostate cancer trial, the team plans to test ^{89}Zr -DFO-transferrin in patients with lymphoma, he said.

Lewis said the findings reported in *Nature Medicine* are unpatented.

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Published online Oct. 4, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

Howard Hughes Medical Institute, Chevy Chase, Md.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
National Institutes of Health, Bethesda, Md.
Sloan-Kettering Institute, New York, N.Y.

“This allowed us to quantify fairly modest changes in MYC activity and TFRC expression to image tumors in a region of the animal that has been notoriously challenging to image.”

**—Jason Lewis,
Memorial Sloan-Kettering
Cancer Center**

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				
Multiple sclerosis (MS)	Sphingosine 1-phosphate receptor 1 (S1PR1; S1P1; EDG1)	<p>Mouse and cell culture studies suggest the S1P1-selective antagonist NIBR-0213 could help treat MS. <i>In vitro</i>, NIBR-0213 selectively inhibited S1P1 with an IC₅₀ value of 2.5 nM and was inactive against S1P2 (S1PR2; EDG5), S1P3 (S1PR3; EDG3) and S1P4 (S1PR4; EDG6). In a mouse model of experimental autoimmune encephalitis (EAE), NIBR-0213 decreased disease scores compared with vehicle and showed efficacy comparable to that of the marketed S1PR agonist Gilenya fingolimod, which acts by downregulating the receptor. Next steps could include evaluating NIBR-0213 in additional mouse MS models.</p> <p>Mitsubishi Tanabe Pharma Corp. and Novartis AG market Gilenya to treat MS.</p> <p>Exelixis Inc. has XL541, an S1P1 antagonist, in preclinical development to treat cancer.</p> <p>Noxxon Pharma AG's NOX-S91, an L-aptamer that antagonizes sphingosine 1-phosphate, is in preclinical development to treat age-related macular degeneration (AMD).</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1023 Published online Oct. 4, 2012</p>	Patent application filed; licensing status unavailable	<p>Quancard, J. <i>et al. Chem. Biol.</i>; published online Sept. 21, 2012; doi:10.1016/j.chembiol.2012.07.016</p> <p>Contact: Jean Quancard, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: jean.quancard@novartis.com</p>
Cancer				
Breast cancer	Phosphoinositide-3 kinase (PI3K); poly(AD-ribose) polymerase (PARP); breast cancer 1 early onset (BRCA1); BRCA2	<p><i>In vitro</i> and mouse studies suggest combining PARP and PI3K inhibitors could help treat metastatic breast cancer. In a mouse model of BRCA1-related breast cancer, inhibition of PI3K with BKM120 decreased angiogenesis compared with vehicle but increased activity in other cancer-associated pathways. In the same model and in mice with BRCA1-driven breast cancer xenografts, BKM120 plus the PARP inhibitor olaparib prevented the compensatory pathway upregulation and delayed tumor growth better than either treatment alone.</p> <p>In a second study, small interfering RNA targeting a PI3K isoform in triple receptor-negative breast cancer cells decreased BRCA1 and BRCA2 levels compared with no treatment and sensitized the cells to PARP inhibitor-induced cell death. In mice with triple receptor-negative breast cancer xenografts, BKM120 plus olaparib inhibited tumor growth more than either treatment alone.</p> <p>Next steps could include testing the combination in the clinic.</p> <p>Novartis AG's BKM120 is in Phase II testing for various cancers. At least 18 other companies have PI3K inhibitors in clinical and preclinical testing to treat multiple types of cancer.</p> <p>AstraZeneca plc's olaparib is in Phase II testing to treat solid tumors. At least seven other companies have PARP inhibitors in clinical and preclinical testing to treat multiple types of cancer.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1024 Published online Oct. 4, 2012</p>	Patent and licensing status unavailable	<p>Juvekar, A. <i>et al. Cancer Discov.</i>; published online Aug. 22, 2012; doi:10.1158/2159-8290.CD-11-0336</p> <p>Contact: Gerburg M. Wulf, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: gwulf@bidmc.harvard.edu</p> <p>Ibrahim, Y.H. <i>et al. Cancer Discov.</i>; published online Aug. 22, 2012; doi:10.1158/2159-8290.CD-11-0348</p> <p>Contact: José Baselga, Massachusetts General Hospital, Boston, Mass. e-mail: jbaselga@partners.org</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Transforming growth factor- β (TGFB; TGF β); TGF β receptor II (TGF β -RII; TGFBR2)	<p>Mouse studies suggest inhibiting TGFβ signaling could help improve chemotherapy efficacy in breast cancer. In two orthotopic mammary carcinoma mouse models, inhibition of TGFβ signaling with a TGFβ-neutralizing mAb or overexpression of soluble TGFBR2 decreased tumor growth and metastasis compared with no inhibition or normal TGFBR2 expression. In these mouse models, compared with wild-type mice, the TGFβ-neutralizing mAb and soluble TGFBR2 overexpression both increased the intratumoral distribution and effects of Doxil doxorubicin. Next steps could include testing TGFβ-neutralizing mAbs in combination with chemotherapy in additional types of cancer.</p> <p>Johnson & Johnson markets Doxil liposomal doxorubicin to treat various cancers.</p> <p>At least four companies have compounds that inhibit TGFβ signaling in Phase II testing or earlier to treat various cancers.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1025 Published online Oct. 4, 2012</p>	Patent and licensing status unavailable	<p>Liu, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 20, 2012; doi:10.1073/pnas.1117610109</p> <p>Contact: Lei Xu, Massachusetts General Hospital and Harvard Medical School, Boston, Mass. e-mail: lei@steele.mgh.harvard.edu</p> <p>Contact: Rakesh K. Jain, same affiliation as above e-mail: jain@steele.mgh.harvard.edu</p>
Cancer	p21 Protein (Cdc42 Rac)-activated kinase 1 (PAK1)	<p><i>In vitro</i> and mouse studies suggest inhibiting PAK1 could help treat K-Ras-driven tumors. In human squamous cell carcinoma (SCC) samples, high levels of PAK1 were associated with advanced disease. In a transgenic mouse model of mutant K-Ras-driven SCC, <i>Pak1</i> knockout delayed tumor growth and decreased progression compared with normal <i>Pak1</i> expression. In mice with established mutant K-Ras-driven SCC tumors, Pak1 inhibitors led to greater tumor regression than vehicle control. Next steps include clinical testing of PAK1 inhibitors.</p> <p>Afraxis Inc. has a PAK inhibitor in the discovery stage to treat CNS disorders.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1026 Published online Oct. 4, 2012</p>	Findings unpatented; <i>Pak1</i> knockout mice available for licensing	<p>Chow, H.Y. <i>et al. Cancer Res.</i>; published online Sept. 14, 2012; doi:10.1158/0008-5472.CAN-12-2246</p> <p>Contact: Jonathan Chernoff, Fox Chase Cancer Center, Philadelphia, Pa. e-mail: j_chernoff@fccc.edu</p>
Cancer	Unknown	<p>Mouse and cell culture studies suggest a derivative of griseofulvin that inhibits centrosomal clustering could help treat cancer. In a panel of cancer cell lines, the derivative inhibited proliferation with IC₅₀ values of 1–2.5 μM. In mouse xenograft models of multiple myeloma and colon cancer, intraperitoneal injection of the griseofulvin derivative decreased tumor growth and increased survival compared with vehicle injection. Next steps include optimizing the compound and evaluating toxicity.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1027 Published online Oct. 4, 2012</p>	Patented for use in treating malignant conditions; available for licensing	<p>Raab, M.S. <i>et al. Cancer Res.</i>; published online Aug. 31, 2012; doi:10.1158/0008-5472.CAN-12-2026</p> <p>Contact: Marc S. Raab, German Cancer Research Center, Heidelberg, Germany e-mail: m.raab@dkfz.de</p>

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This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Diffuse large B cell lymphoma (DLBCL)	Cyclin dependent kinase (CDK); p53	<p><i>In vitro</i> and mouse studies identified DLBCL gene signatures that could help predict prognosis and guide targeted therapy. In primary DLBCL samples, genotyping and analysis of transcriptional profiles and pathways identified a signature of copy number alterations that decreased p53 activity and increased cell cycle progression. In patients with the signature, the 5-year survival rate was 62%, whereas all patients without the signature survived. In mice implanted with cells from DLBCL patients containing the signature, pan-CDK inhibition decreased proliferation and tumor growth compared with no inhibition. Next steps include developing an assay to detect the gene signature.</p> <p>At least five companies have CDK inhibitors in clinical and preclinical development to treat multiple types of cancer.</p> <p>At least four companies have p53-activating compounds in clinical and preclinical development to treat multiple types of cancer.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1028 Published online Oct. 4, 2012</p>	Patent application filed; available for licensing	<p>Monti, S. <i>et al. Cancer Cell</i>; published online Sept. 11, 2012; doi:10.1016/j.ccr.2012.07.014</p> <p>Contact: Margaret A. Shipp, Dana-Farber Cancer Institute, Boston, Mass. e-mail: margaret_shipp@dfci.harvard.edu</p>
Leukemia	Myeloid leukemia cell differentiation protein (MCL1)	<p><i>In vitro</i> studies identified a small molecule MCL1 inhibitor that could help treat leukemia. A competitive screen identified the small molecule MCL1 inhibitor molecule 1 (MIM1) as an MCL1 inhibitor. In MCL1-dependent acute lymphoblastic leukemia (ALL) cells, MIM1 induced caspase activity and decreased viability compared with vehicle.</p> <p>In ALL cells expressing both MCL1 and Bcl-x_L, the B cell lymphoma 2 (BCL-2; BCL2) family inhibitor ABT-737 plus MIM1 led to synergistic cytotoxicity and decreased cell viability compared with either treatment alone. Ongoing work includes optimizing the potency of MIM1.</p> <p>ABT-737 is a research reagent from Abbott Laboratories.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1029 Published online Oct. 4, 2012</p>	Patent applications filed covering screening strategy and compounds identified by the screen, including MIM1; available for licensing	<p>Cohen, N.A. <i>et al. Chem. Biol.</i>; published online Sept. 21, 2012; doi:10.1016/j.chembiol.2012.07.018</p> <p>Contact: Loren D. Walensky, Dana-Farber Cancer Institute, Boston, Mass. e-mail: loren_walensky@dfci.harvard.edu</p>
Lung cancer	Enhancer of zeste homolog 2 (EZH2); poly(ADP-ribose) polymerase-1 (PARP-1)	<p>A study in cell culture and in patient tissue suggests inhibiting PARP-1 or EZH2 could help treat small cell lung cancer (SCLC). SCLC cell lines expressed higher protein levels of PARP-1 and EZH2 than non-small cell lung cancer (NSCLC) cell lines. Tumor tissue from patients with SCLC had higher levels of PARP-1 protein than tumor tissue from patients with NSCLC. In SCLC cell lines, a PARP-1 inhibitor or small hairpin RNA against PARP-1 or EZH2 decreased cell proliferation compared with no treatment or control shRNA. Next steps could include testing PARP-1 or EZH2 inhibitors in mouse models of SCLC.</p> <p>At least 10 companies have preclinical or clinical programs targeting PARP-1 for cancer.</p> <p>Epizyme Inc. and partner Eisai Co. Ltd. have a preclinical program targeting EZH2 in breast cancer and non-Hodgkin's lymphoma (NHL).</p> <p>Constellation Pharmaceuticals Inc. has a discovery-stage program targeting EZH2 in cancer.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1030 Published online Oct. 4, 2012</p>	Patent and licensing status unavailable	<p>Byers, L.A. <i>et al. Cancer Discov.</i>; published online Sept. 6, 2012; doi:10.1158/2159-8290.CD-12-0112</p> <p>Contact: John V. Heymach, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: jvheymach@mdanderson.org</p> <p>Contact: Lauren Averett Byers, same affiliation as above e-mail: lbyers@mdanderson.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Not applicable	Human studies suggest genomic profiling of gut microbiota might help predict risk for type 2 diabetes. A genomics analysis of gut microbiota found a smaller population of butyrate-producing bacteria and a higher population of opportunistic pathogens in patients with diabetes than in healthy individuals. In the same study group and in an additional cohort of Chinese patients with diabetes and controls, a panel of 50 microbiota gene markers correctly distinguished between patients with diabetes and healthy individuals. Ongoing work includes validation of the microbiota markers in additional cohorts of patients with diabetes and control subjects.	Patented by BGI; available for licensing or partnering	Qin, J. <i>et al. Nature</i> ; published online Sept. 26, 2012; doi:10.1038/nature11450 Contact: Jun Wang, BGI, Shenzhen, China e-mail: wangj@genomics.org.cn
SciBX 5(39); doi:10.1038/scibx.2012.1031 Published online Oct. 4, 2012				
Infectious disease				
Influenza	Mucin 5AC oligomeric mucus/gel-forming (MUC5AC)	Mouse studies suggest increasing MUC5AC levels in the lungs could help protect against influenza infection. In transgenic mice overexpressing Muc5ac, compared with wild-type mice, infection with a mouse-adapted influenza virus decreased lung viral loads. Next steps include determining signal pathways that induce mucin secretion in the lungs and selecting compounds that regulate mucin gene transcription.	Model unpatented; unlicensed	Ehre, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 24, 2012; doi:10.1073/pnas.1206552109 Contact: Camille Ehre, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: cehre@med.unc.edu
SciBX 5(39); doi:10.1038/scibx.2012.1032 Published online Oct. 4, 2012				
Inflammation				
Asthma	Solute carrier family 26 member 9 (SLC26A9)	A mouse and patient genetic study suggests activating SLC26A9 could help treat asthma-associated mucus obstruction. In genetic studies, SNPs located upstream of SLC26A9, which blunted gene expression in a cell-based assay, were associated with childhood asthma. In a mouse model of IL-13-induced asthma, <i>Slc26a9</i> knockout mice had greater airway mucus obstruction than wild-type mice. Next steps include developing a pharmacological approach for activating SLC26A9 and identifying patients with asthma that have reduced SLC26A9 function.	Unpatented; licensing status not applicable	Anagnostopoulou, P. <i>et al. J. Clin. Invest.</i> ; published online Sept. 4, 2012; doi:10.1172/JCI60429 Contact: Marcus A. Mall, Heidelberg University, Heidelberg, Germany e-mail: marcus.mall@med.uni-heidelberg.de
SciBX 5(39); doi:10.1038/scibx.2012.1033 Published online Oct. 4, 2012				
Musculoskeletal disease				
Bone repair	Bone morphogenetic protein 2 (BMP2)	Rat studies identified a benzoic acid-based BMP2 stimulator that could be useful for bone repair. In rats with drill-hole fractures, the BMP2 stimulator increased new bone formation and fracture repair compared with vehicle. Next steps could include evaluating and optimizing the benzoic acid-based molecule in additional models of bone fracture.	Patent and licensing status unavailable	Balaramnavar, V.M. <i>et al. J. Med. Chem.</i> ; published online Sept. 14, 2012; doi:10.1021/jm300985d Contact: Anil K. Saxena, CSIR-Central Drug Research Institute, Lucknow, India e-mail: anilsak@gmail.com
SciBX 5(39); doi:10.1038/scibx.2012.1034 Published online Oct. 4, 2012				
Neurology				
Alzheimer's disease (AD)	β -Amyloid 42	A high throughput screen identified small molecule inhibitors of β -amyloid 42 aggregation that could help treat AD. In rat neuronal cells, the lead inhibitor lowered β -amyloid 42-induced toxicity compared with no inhibitor. In a fruit fly model of AD, the inhibitor decreased locomotor deficits and increased lifespan compared with no treatment. Next steps include developing optimized derivatives and testing them in mouse models of AD.	Unpatented; available for partnering and collaboration	McKoy, A.F. <i>et al. J. Biol. Chem.</i> ; published online Sept. 19, 2012; doi:10.1074/jbc.M112.348037 Contact: Michael H. Hecht, Princeton University, Princeton, N.J. e-mail: hecht@princeton.edu
SciBX 5(39); doi:10.1038/scibx.2012.1035 Published online Oct. 4, 2012				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Rett syndrome	Methyl CpG binding protein 2 (MECP2; RTT)	<p>Mouse studies suggest ketamine could help treat Rett syndrome. In a <i>Mecp2</i> knockout mouse model of Rett syndrome, ketamine rescued sensorimotor dysfunction and markers of disease, whereas vehicle did not. Next steps were undisclosed but could include evaluating ketamine in patients with Rett syndrome.</p> <p>Ketamine is a generic drug approved to treat severe and chronic pain.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1036 Published online Oct. 4, 2012</p>	Patent and licensing status undisclosed	<p>Kron, M. <i>et al. J. Neurosci.</i>; published online Oct. 3, 2012; doi:10.1523/JNEUROSCI.2159-12.2012 Contact: David Katz, Case Western Reserve University, Cleveland, Ohio e-mail: david.katz@case.edu</p>
Spinal cord injury (SCI)	Not applicable	<p>A study in rats suggests neural stem cell transplantation could help treat SCI. In rats with transected spinal cords, transplantation of rat or human neural stem cells embedded in a growth factor-seeded matrix led to engraftment. Rats receiving neural transplantation showed axonal growth that filled the spinal cord lesion cavity and had greater locomotive recovery than rats not given a transplantation. Next steps include conducting longer-term studies and testing the approach in larger animal models.</p> <p>SciBX 5(39); doi:10.1038/scibx.2012.1037 Published online Oct. 4, 2012</p>	Patent application filed covering composition of matter and technique; available for licensing	<p>Lu, P. <i>et al. Cell</i>; published online Sept. 14, 2012; doi:10.1016/j.cell.2012.08.020 Contact: Mark Tuszynski, University of California, San Diego, La Jolla, Calif. e-mail: mtuszynski@ucsd.edu Contact: Paul Lu, same affiliation as above e-mail: plu@ucsd.edu</p>

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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			
Ligand-based, receptor-capturing (LRC) technology to identify cell surface receptors of therapeutic or pathologic ligands	LRC technology could be used to identify cell surface receptor targets of ligands. The technology uses a chemoreactive reagent that contains a glycosylated cell surface-binding moiety, a biotin tag and an amino-reactive moiety, which binds to a ligand of interest. In cell culture or tissue, the ligand-bound chemoreactive agent attached to the ligand's cell surface receptor and the biotin tag was used to purify the receptor for identification using mass spectroscopy. In various cells, receptors for ligands, including insulin and transferrin, were identified. In cell culture, the LRC technology identified five surface-binding proteins for vaccinia virus, which were verified using small interfering RNA-mediated knockout of the receptors. Next steps include using the platform for drug development. SciBX 5(39); doi:10.1038/scibx.2012.1038 Published online Oct. 4, 2012	Patent application filed; available for licensing	Frei, A.P. <i>et al. Nat. Biotechnol.</i> ; published online Sept. 16, 2012; doi:10.1038/nbt.2354 Contact: Bernd Wollscheid, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: bernd.wollscheid@imsb.biol.ethz.ch
Transforming growth factor- α (TGFA; TGF α) shedding assay to detect G protein-coupled receptor (GPR) ligands	A TGF α shedding assay could help identify GPR ligands. TGF α shedding occurs downstream of GPR activation when certain G α subunits are activated. In cell culture, the TGF α shedding assay detected receptor activity for 104 out of 116 GPRs. In cells expressing histamine receptor subtypes, only ligands that selectively activated a particular receptor subtype induced shedding. Next steps include modifying the platform to involve fewer steps. SciBX 5(39); doi:10.1038/scibx.2012.1039 Published online Oct. 4, 2012	Findings unpatented; unavailable for licensing	Inoue, A. <i>et al. Nat. Methods</i> ; published online Sept. 16, 2012; doi:10.1038/nmeth.2172 Contact: Junken Aoki, Tohoku University, Sendai, Japan e-mail: jaoki@m.tohoku.ac.jp
Disease models			
Mice with conditional B cell-specific knockout of <i>TANK-binding kinase 1 (Tbk1)</i>	Mice with conditional B cell-specific knockout of <i>Tbk1</i> could be useful for identifying new targets and treatments for autoimmune diseases. The <i>Tbk1</i> knockout mice showed aberrant production of IgA and autoantibodies and deposition of antibodies in kidney glomeruli, which is a marker of nephropathy. A series of cell culture studies showed that TBK1 controlled IgA production via negative regulation of noncanonical NF- κ B signaling. Next steps include further evaluating the role of TBK1 in regulating mucosal immunity and identifying associations between TBK1 deficiency and autoimmune diseases. SciBX 5(39); doi:10.1038/scibx.2012.1040 Published online Oct. 4, 2012	Model unpatented; licensing details available from Lexicon Pharmaceuticals Inc.	Jin, J. <i>et al. Nat. Immunol.</i> ; published online Sept. 30, 2012; doi:10.1038/ni.2423 Contact: Shao-Cong Sun, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: ssun@mdanderson.org
Mouse model for neurological features of myotonic dystrophy type 1 (DM1)	A mouse model for DM1 could be useful for studying neurological features of the disease. Mice lacking <i>muscleblind-like 1 (Mbnl1)</i> , the homolog of a human gene whose activity is impaired in DM1, showed defective RNA splicing and neurological deficits but not DM1-associated impaired muscle function. Next steps could include testing the effect of candidate DM1 therapeutics on neurological function in <i>Mbnl1</i> knockout mice. SciBX 5(39); doi:10.1038/scibx.2012.1041 Published online Oct. 4, 2012	Patent and licensing status undisclosed	Charizanis, K. <i>et al. Neuron</i> ; published online Aug. 9, 2012; doi:10.1016/j.neuron.2012.05.029 Contact: Maurice S. Swanson, University of Florida, Gainesville, Fla. e-mail: mswanson@ufl.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<i>Xenopus</i> model for oligodendrocyte myelination	A <i>Xenopus</i> model for myelination could help identify multiple sclerosis (MS) therapeutics. Transgenic <i>Xenopus laevis</i> were engineered to express a construct consisting of a fluorescent reporter linked to the <i>Escherichia coli</i> gene type 1 nitroreductase (<i>ntr</i>). The construct was then placed under the control of a regulatory sequence specific to mature oligodendrocytes. In the model, metronidazole, a generic prodrug that is converted into a cytotoxin by <i>ntr</i> , induced oligodendrocyte apoptosis and demyelination, resulting in a lower fluorescent signal than vehicle. Also in the model, the myelinating compound retinoic acid induced oligodendrocyte proliferation and remyelination, resulting in a greater fluorescent signal than vehicle. Next steps could include using the model to test new MS therapeutics. SciBX 5(39); doi:10.1038/scibx.2012.1042 Published online Oct. 4, 2012	Patent and licensing status unavailable	Kaya, F. <i>et al. J. Neurosci.</i> ; published online Sept. 12, 2012; doi:10.1523/JNEUROSCI.2252-12.2012 Contact: Andre Mazabraud, University of South Paris XI, Orsay, France e-mail: andre.mazabraud@u-psud.fr
Zebrafish model for narcolepsy	A zebrafish model for narcolepsy could be used to identify new targets or therapeutic leads for the sleep disorder. In zebrafish, selective disruption of hypothalamic hypocretin neurons increased both sleep time during the day and fragmented sleep during the night compared with no disruption. Next steps could include genetic or pharmacological screens to identify targets or compounds that reverse these sleep alterations. SciBX 5(39); doi:10.1038/scibx.2012.1043 Published online Oct. 4, 2012	Patent and licensing status undisclosed	Elbaz, I. <i>et al. J. Neurosci.</i> ; published online Sept. 12, 2012; doi:10.1523/JNEUROSCI.1284-12.2012 Contact: Lior Appelbaum, Bar-Ilan University, Ramat-Gan, Israel e-mail: lior.appelbaum@biu.ac.il
Imaging			
⁸⁹ Zr-transferrin agent for <i>in vivo</i> PET imaging of transferrin receptor protein 1 (TFRC; TFR; CD71)-expressing cancers	A ⁸⁹ Zr-transferrin PET imaging agent could help detect prostate and other cancers. The TFRC-binding agent consisted of ⁸⁹ Zr-labeled desferrioxamine (DFO) conjugated to human transferrin. In mice with TFRC-expressing xenografts or spontaneous prostate tumors, PET imaging of tumors with the ⁸⁹ Zr-transferrin agent provided higher signal-to-noise ratios than ¹⁸ F-labeled fluorodeoxyglucose (FDG)-PET. In the spontaneous tumor model, PET imaging with ⁸⁹ Zr-transferrin detected high-grade prostate intraepithelial neoplasia (PIN), whereas ¹⁸ F-FDG PET did not. Ongoing work includes IND-enabling studies of the agent to image undisclosed cancers (<i>see Transferrin PET project, page 6</i>). SciBX 5(39); doi:10.1038/scibx.2012.1044 Published online Oct. 4, 2012	Unpatented; unlicensed	Holland, J.P. <i>et al. Nat Med.</i> ; published online Sept. 23, 2012; doi:10.1038/nm.2935 Contact: Jason S. Lewis, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: lewisj2@mskcc.org Contact: Charles L. Sawyers, same affiliation as above e-mail: sawyersc@mskcc.org



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¹⁸F 6

⁴⁵Ti 6

⁸⁹Zr 6,14

⁹⁷Ru 6

¹³¹I 6

A

ABCB1 1

ABT-737 10

Alanine aminotransferase 5

Alkaline phosphatase 5

ALT 5

Aspartate aminotransferase 5

AST 5

B

β -Amyloid 42 11

B cell lymphoma 2 10

BCL-2 10

BCL2 10

Bcl-x_L 10

Benzoic acid 11

Betaine anhydrous 4

BKM120 8

BMP2 11

Bone morphogenetic protein 2 11

BRCA1 8

BRCA2 8

Breast cancer 1 early onset 8

Butyrate 11

C

CBS 4

CD71 6,14

CD243 1

CDK 10

c-Myc 6

Cyclin dependent kinase 10

Cystadane 4

Cystathionine β -synthase 4

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Desferrioxamine 6,14

DFO 6,14

Doxil 9

Doxorubicin 3,9

E

EDG1 8

EDG3 8

EDG5 8

EDG6 8

Enhancer of zeste homolog 2 10

EZH2 10

F

FDG 6,14

Ferritin light polypeptide 4

Fingolimod 1,8

Fluorodeoxyglucose 6,14

FOLH1 6

FTL 4

G

GCPII 6

Gilenya 1,8

Glucose 6

Glutathione 3

GPR 13

G protein-coupled receptor 13

Griseofulvin 9

H

Histamine receptor 13

HM30181A 1

I

IL-13 11

Insulin 13

Irinotecan 1

K

Ketamine 12

KLK3 7

K-Ras 9

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Loperamide 2

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Mbn1 13

MCL1 10

MCL1 inhibitor molecule 1 10

MDR1 1

MECP2 12

Methionine 4

Methyl CpG binding protein 2 12

Metronidazole 14

MIM1 10

MUC5AC 11

Mucin 5AC oligomeric mucus/gel-forming 11

Muscleblind-like 1 13

MYC 6

Myeloid leukemia cell differentiation protein 10

N

NBIA1 4

NBIA2A 4

NBIA3 4

NF- κ B 13

NIBR-0213 8

N,N,N-Trimethylglycine 4

NOX-S91 8

Ntr 14

O

Olaparib 8

Opioid receptor 2

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p21 Protein (Cdc42 Rac)-activated kinase 1 9

Paclitaxel 1

PAK 9

PAK1 9

PANK2 4

Pantothenate kinase 2 4

PARP 8

PARP-1 10

PBT-434 4

PEG 3

P-gp 1

p53 10

P glycoprotein 1

Phosphoinositide 3-kinase 7,8

Phospholipase A₂ group VI 4

PI3K 7,8

PLA₂G6 4

Poly(ADP-ribose) polymerase-1 10

Poly(AD-ribose) polymerase 8

Polyethylene glycol 3

Prostate-specific antigen 7

Prostate-specific membrane antigen 6

PSA 7

PSMA 6

R

Retinoic acid 14

RTT 12

S

S1P1 8

S1P2 8

S1P3 8

S1P4 8

S1PR 8

S1PR1 8

S1PR2 8

S1PR3 8

S1PR4 8

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TGFB 9

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TGF β -RII 9

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