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Although a lot is known about how castration-resistant prostate cancers become refractory to second-generation androgen receptor antagonists, the mechanism behind resistance to CYP17 inhibitors remains a mystery. An alternative androgen synthesis pathway identified by a team from the Cleveland Clinic may change the game.

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By Lauren Martz, Staff Writer

Although numerous papers have detailed how castration-resistant prostate cancers become refractory to Xtandi enzalutamide and other second-generation androgen receptor antagonists, comparatively little is known about how the disease eventually evades CYP17 inhibitors such as Zytiga abiraterone. Findings from a **Cleveland Clinic** team could change that, as the group has detailed how some tumors engage an alternative synthesis pathway for androgen.¹

Androgen receptor antagonism and inhibition of CYP17 (cytochrome P450 17 α -hydroxylase/C17, 20 lyase) are the mainstays of castration-resistant prostate cancer (CRPC) treatment. **Medivation Inc.** and **Astellas Pharma Inc.** reported \$158 million in U.S. Xtandi sales in the first half of the year, and **Johnson & Johnson's** Zytiga posted sales of \$739 million in that period.

Both drugs face resistance issues, as most prostate tumors eventually bypass the testicular testosterone-dependent androgen synthesis pathway and circumvent CYP17 inhibitors by turning to adrenal androgen synthesis mechanisms (see **Figure 1**, "Androgen synthesis pathways in prostate cancer").

Prior studies suggested that CYP17 inhibitors may not completely shut down the CYP17-dependent pathway of androgen synthesis² and that low levels of androgen precursors may be able to progress through the pathway.

In many tumors this should not produce enough of the androgen dihydrotestosterone (DHT) to stimulate tumor growth, but tumor growth nevertheless occurs.

In a paper published in *Cell*, Nima Sharifi and colleagues have solved the mystery. The team found a mutation in the *hydroxysteroid 3 β dehydrogenase 1 (HSD3B1)* gene encoding 3 β HSD1 that catalyzes a rate-limiting step in the downstream synthesis of DHT in some CRPCs.

The mutation may be a mechanism of Zytiga drug resistance, and inhibiting its enzymatic activity could help treat CRPCs that do not respond to other therapies.

Sharifi is chair of prostate cancer research at the Cleveland Clinic. The paper also included researchers from **The University of Texas Southwestern Medical Center**, the **University of Michigan Medical School**, the **University of Washington School of Medicine** and the **Fred Hutchinson Cancer Research Center**.

The team first studied 3 β HSD1 activity in different CRPC cell lines. Whereas one cell line converted 90% of dehydroepiandrosterone (DHEA) to androstenedione in the DHT synthesis pathway in 48 hours, the other only converted 10%. Sequencing *HSD3B1* in each cell line identified an A to C nucleotide substitution that resulted in an

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asparagine to threonine amino acid substitution in the cell line with enhanced flux.

To determine the source of the mutation, the group compared germline DNA from patients with DNA from their CRPC tumors. The team found that 3 of 25 patients who were homozygous wild-type for the gene expressed the mutation in CRPC tumor DNA. This finding suggests that the mutation can arise *de novo* in tumors.

However, the mutation also occurred in the germline DNA of some patients. In 3 of 11 patients who were heterozygous for the mutation, tumors evolved to express only the mutant gene. These findings suggest that screening for the *HSD3B1* mutation could help identify patients unlikely to respond to available treatments.

Next, the team assessed whether the *HSD3B1* mutation could be responsible for resistance to Zytiga. In surgically castrated mice with *HSD3B1* wild-type tumors, two of eight animals receiving the drug developed tumors with the mutation, whereas no tumors from vehicle-treated mice acquired the mutation.

In cultured *HSD3B1*-mutant CRPC cells, small hairpin RNA targeting the mutant inhibited DHEA flux and cell proliferation and decreased DHT expression compared with shRNA control. In mice with mutant tumor xenografts, shRNA targeting the mutant gene decreased tumor growth compared with shRNA control.

Finally, the team found that the mutation increased 3 β HSD1's half-life from 2.1 to 27 hours by causing resistance to ubiquitination and degradation. These findings suggest that the mutation allows more androgen synthesis to promote tumor growth by stabilizing 3 β HSD1.

Drug development

Sharifi told *SciBX* that his team's next step is to identify a small molecule that inhibits 3 β HSD1 activity and thus cuts off the tumor's androgen supply.

Jeff Hager, senior director of biology at **Seragon Pharmaceuticals Inc.**, said that the researchers essentially will be starting from scratch.

"One problem is that there is no proof-of-concept compound with good drug-like properties that could selectively inhibit the enzyme," Hager said. "They need to determine first how druggable this enzyme is, and ideally they should look for a nonsteroidal small molecule inhibitor with improved bioavailability over steroidal compounds."

Hager said that abiraterone could alternatively be used as a starting point for medicinal chemistry in the steroid scaffold. According to the authors of the paper, the drug weakly inhibits 3 β HSD1. However, Hager cautioned that "hormonal synthesis is a complex process, and there are a lot of related enzymes and compensatory feedback. An inhibitor that is not sufficiently selective could affect other important biological processes such as aldosterone production and blood pressure."

But Douglas Jacoby, head of research at **Tokai Pharmaceuticals Inc.**, worried that "the mouse model does not accurately recapitulate

"Based on currently available data, the 3 β HSD1 pathway appears to be important in a minority of patients. The mutational status of 3 β HSD1 could serve as a biomarker to identify those patients who are likely to benefit from this mode of therapy."

—William Olson,
Progenics Pharmaceuticals Inc.

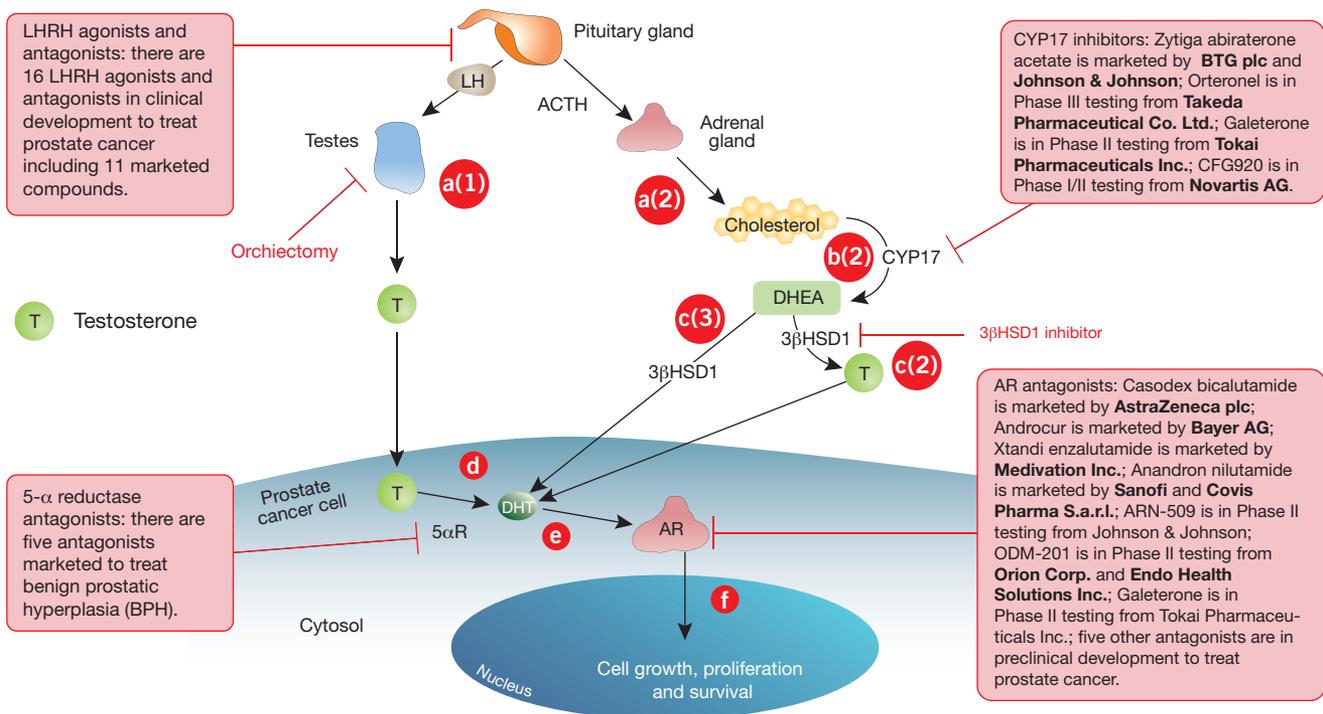


Figure 1. Androgen synthesis pathways in prostate cancer. In testicular androgen synthesis, luteinizing hormone-releasing hormone (LHRH) stimulates release of luteinizing hormone (LH) from the pituitary gland, which signals the testes to secrete testosterone [a(1)]. Testosterone enters the prostate cancer cell and is converted to the potent androgen dihydrotestosterone (DHT) by 5- α reductase (5 α R) [d]. DHT binds and activates the androgen receptor (AR) [e], which in turn initiates transcription of oncogenic genes increasing cell growth, proliferation and survival [f].

In castration-resistant androgen synthesis, the pituitary gland also signals the adrenal gland to initiate an adrenocorticotropic hormone (ACTH)-mediated androgen synthesis pathway [a(2)]. The switch from dependence on the testicular to the adrenal androgen synthesis pathway can occur following surgical or chemical castration, leading to tumor regrowth. Through a series of reactions catalyzed by cytochrome P450 17 α -hydroxylase/17, 20 lyase (CYP17), cholesterol is converted into dehydroepiandrosterone (DHEA) [b(2)]. The CYP17 inhibitor abiraterone blocks the production of DHEA and downstream androgen synthesis in the adrenal androgen synthesis pathway. However, it may incompletely inhibit this step and lead to resistance. *Hydroxysteroid 3 β dehydrogenase 1 (HSD3B1)*, the gene that encodes 3 β HSD1, catalyzes the rate-limiting step in the pathway that converts DHEA to testosterone, which is then converted to DHT to activate AR [c(2)]. DHEA may also be converted to DHT independently of testosterone through a 3 β HSD1-dependent pathway [c(3)]. A gain-of-stabilization mutation in *HSD3B1* can increase the flux from DHEA to DHT, possibly allowing sufficient production of DHT from the residual androgen precursors remaining during abiraterone treatment leading to therapeutic resistance. Inhibitors of 3 β HSD1 may prevent this resistance pathway.

the consequences of 3 β HSD1 inhibition that may occur in humans. Blocking 3 β HSD1 will inhibit not only the catalytic step converting DHEA to androstenedione but also the conversion of pregnenolone or 17-hydroxypregnenolone to steroid metabolites such as progesterone, deoxycorticosterone, corticosterone and cortisol.”

As a result, he said, it will be necessary “to strike a balance between 3 β HSD1 inhibition and other unwanted consequences resulting from 3 β HSD1 blockade. This can be determined by examining the toxicology of novel 3 β HSD1 inhibitors.”

Tokai’s Galeterone, a small molecule that disrupts androgen receptor signaling through a triple mechanism that involves antagonizing testosterone binding to the androgen receptor, inhibiting CYP17 and degrading the androgen receptor, is in Phase II testing for CRPC.

Seragon is developing selective estrogen receptor degraders including ARN-810, which is in Phase I testing to treat estrogen receptor-positive metastatic breast cancer. **Aragon Pharmaceuticals Inc.** spun out Seragon

prior to Aragon’s acquisition by J&J in September.

Aragon’s second-generation androgen receptor antagonist, ARN-509, is in Phase II testing to treat CRPC. Hager was senior director of biology at Aragon.

Added benefits

If the Cleveland Clinic generates an inhibitor of 3 β HSD1, the molecule would likely find immediate use as part of a combination therapy for CRPC.

Hager told *SciBX*, “A real advantage of this potential new target is that it adds another layer to the antiandrogen therapeutic options. Each level of therapy lowers androgen levels, and adding a 3 β HSD1 inhibitor could shut down the androgen supply more completely. One could imagine a combination of LHRH [luteinizing hormone-releasing hormone] agonists to block testicular androgen, CYP17 inhibitors to block adrenal androgen and a new 3 β HSD1-targeting agent to block the amplified DHT production that the mutation confers. If the combination

is possible from a tolerability perspective, one could imagine shutting down the hormone production more completely.”

William Olson, SVP of R&D at **Progenics Pharmaceuticals Inc.**, added that 3 β HSD1 inhibition might not only treat resistant tumors but also prevent resistance in the first place by blocking the alternative androgen source before tumors evolve to depend on it.

Progenics' PSMA ADC, an antibody-drug conjugate targeting prostate-specific membrane antigen (PSMA; FOLH1; GCPII), is in Phase II testing to treat prostate cancer.

Hager added, “There are non-overlapping mechanisms of acquired drug resistance, and altering the drug cocktail

to better target the mutations and genetics of different tumors can all be complementary, especially when coupled with predictive biomarkers. These drugs all may have their roles.”

Companionship

Olson said that the number of patients likely to benefit from 3 β HSD1 inhibition might be small. “Based on currently available data, the 3 β HSD1 pathway appears to be important in a minority of patients. The mutational status of 3 β HSD1 could serve as a biomarker to identify those patients who are likely to benefit from this mode of therapy,” he said.

But Sharifi said that the data in the paper suggest that about 20% of patients with CRPC may have either the germline mutation with loss of heterozygosity or a somatic *de novo* mutation in the enzyme.

“Our data probably underrepresent the true frequency of the mutation because some of the patients we studied were progressing but some were from an autopsy population. If we are looking specifically at

progressing tumors, the frequency might be higher,” he said.

Whatever the exact number, Hager said that given the size of the CRPC market, “north of 5%–10% affected is a reasonable opportunity and market size.”

Sharifi said that his team's next step for biomarker development is to link the *HSD3B1* biomarker to clinical trials for various types of hormone therapy to see if it predicts response.

Hager said, “Such a biomarker test could have broad importance because it could help select patients who produce high DHT levels. Whether these patients are specifically resistant to abiraterone or not, this indicates that the tumors likely still depend on androgens, which is valuable information to help guide treatment decisions. The potential to develop a biomarker test is important because it suggests an almost immediate application for the findings.”

Sharifi told *SciBX* that the Cleveland Clinic has filed two provisional patent applications covering the work that are available for licensing.

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Alternative strategies in ALS

By C. Simone Fishburn, Senior Editor

Biogen Idec Inc. and **Evotec AG** are taking opposite strategies to finding new therapies for amyotrophic lateral sclerosis, a disease with an unknown mechanism. Whereas Biogen Idec is forming partnerships with multiple academic labs to solve the biology of the disease, Evotec is partnering with the **Harvard Stem Cell Institute at Harvard University** to employ phenotypic screens that circumvent the need to understand the mechanism from the outset.

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease in which progressive loss of motor neurons leads to muscle weakness, atrophy and respiratory failure. Despite recent advances in understanding the genetics of the disease,¹ the biological trigger of the nerve cell loss remains unclear and therapeutic targets remain elusive.

About 10% of patients with ALS show familial inheritance, whereas the remaining 90% of cases are sporadic and have no clear genetic linkage. Both forms of the disease are phenotypically similar, suggesting that pathways identified by genetic mutations might also be disrupted in sporadic ALS.

Going phenotypic

In September, Evotec partnered with the Harvard Stem Cell Institute (HSCI) to combine the academic lab's expertise in creating induced pluripotent stem (iPS) cells from patients with ALS and the biotech's proprietary screening assays for the disease.

The deal is with Lee Rubin and Kevin Eggan, both faculty members at HSCI who have developed a technique for creating motor neurons from human fibroblasts. The duo also has generated cell lines from patients with ALS representing a variety of genetic backgrounds.

Evotec CSO Cord Dohrmann would not elaborate on the details of the endpoints of the company's ALS assays but told *SciBX* that the goal of the screens is to identify compounds with therapeutic potential that also can be used to explore the mechanisms underlying the degeneration of motor neurons.

The assays were developed via Evotec's in-house research on motor neurons derived from mouse embryonic stem cells.

Evotec also will use its expertise in scale-up to translate the iPS cell differentiation process to industry and enable screening of tens of thousands to hundreds of thousands of molecules. Until now, the HSCI researchers did not have a way to increase the supply of their cell lines in quantities sufficient for drug discovery.

"Scaling up the iPS cell-based motor neurons for large-scale screens is a labor-intensive and compound-intensive process," said Dohrmann.

In addition, Evotec has high-content screening capabilities, which

involve multiple simultaneous readouts from a single assay, and a Cellular Target Profiling platform obtained in the 2011 acquisition of Kinaxo Biotechnologies GmbH.

The platform integrates information from the diverse sets of assay readouts, incorporates quantitative analysis of data points such as protein binding and K_d values and then yields a few specific targets that can be investigated.

Evotec hopes the functional readouts from screens of thousands of molecules against cell lines from multiple genetic backgrounds will distill down to a manageable number of targets that can be pursued both for their therapeutic potential and to gain insights into the mechanisms underlying ALS.

According to Dohrmann, the strength of Evotec's phenotypic screening strategy is the ability to follow multiple readouts at the same time. The collaboration with HSCI will allow the company to get readouts from multiple genetic libraries, which could improve the odds of detecting new targets.

"Finding associated genes is key to understanding the mechanism, and we are interested in novel mechanisms that have not yet been identified," Dohrmann told *SciBX*.

Backing basic science

Instead of reverse engineering the biology of ALS, Biogen Idec is working from the ground up and is investing in basic science to identify pathways, mechanisms and molecules involved in axonal degeneration of motor neurons.

In January, Biogen Idec discontinued development of dexamipexole to treat ALS after the compound missed the primary endpoint of improving function and survival in the Phase III EMPOWER trial. The compound was licensed from **Knopp Biosciences LLC** after showing a dose-dependent reduction in disease progression in Phase II trials.

Dexamipexole also showed neuroprotective effects in a murine model of ALS based on a mutant form of *superoxide dismutase 1 (SOD1)*, a gene associated with about 20% of familial cases. However, the precise mechanism of action of dexamipexole was never fully elucidated.

Now, Biogen Idec is working with a consortium of six academic laboratories to dissect the pathways involved in motor neuron degeneration in organisms from fruit flies to humans.

The labs at **Columbia University**, **Harvard Medical School**, Harvard University, **The Rockefeller University** and the **Yale School of Medicine** are exploring molecular pathways of disease progression for motor neurons and are examining the role of specific genes and proteins in the degenerative process.

In addition to the multipronged approach to the biology of ALS, Biogen Idec is partnering with the **HudsonAlpha Institute for Biotechnology** and **Duke University** to sequence the genomes of more than 1,700 patients with sporadic ALS.

One of the Harvard labs involved in the consortium was previously headed by Spyros Artavanis-Tsakonas, who joined Biogen Idec as CSO this year and is leading the company's discovery effort in ALS.

According to Artavanis-Tsakonas, although SOD1 represents an important target in ALS, the company wants to cast a broader net and identify additional mechanisms that give rise to sporadic ALS.

At Harvard, Artavanis-Tsakonas collaborated with the labs of consortium members Steven Gygi and J. Wade Harper² to produce

"We need new ways to evaluate molecules *in vivo* to make it less cumbersome, to be able to evaluate more than 20 molecules and not just under 10 and to follow the progression of the disease over time."

—Cord Dohrmann, Evotec AG

a *Drosophila* protein interaction map, dubbed an interactome, that contains hundreds of protein complexes involved in signaling pathways.³

Artavanis-Tsakonas plans to use the interactome as a tool to expand the research findings and identify additional potential targets. “If I find a gene that is relevant to the pathway in the ALS phenotype, then I want to use the interactome to find all the proteins it interacts with, as they could be good targets too,” he said.

“If I find a gene that is relevant to the pathway in the ALS phenotype, then I want to use the interactome to find all the proteins it interacts with, as they could be good targets too.”

— *Spyros Artavanis-Tsakonas, Biogen Idec Inc.*

Translational challenges

The lessons of the recent ALS clinical trial by Biogen Idec and the fact that it has been over 17 years since the approval of **Sanofi**'s Rilutek riluzole, the sole drug indicated for ALS, point to the difficulties in making advances in the disease even when promising candidates do emerge from discovery programs.

Both Dohrmann and Artavanis-Tsakonas acknowledge the challenge

of moving to the next stage if they are successful in identifying active compounds because there are no accepted animal models of the disease that provide good predictive value for clinical studies.

Dohrmann believes that the best approach for any compound identified via iPS cell studies will be to reproduce its genetic target in mice and to test compounds for improvements in the phenotype associated with that target.

Such a mouse model may not mimic all the features of ALS in humans, but it would provide a mechanism-centric model with measurable readouts and would give an indication of the potency and efficacy of a compound that could help guide clinical trial design.

Most important, according to Dohrmann, is to create a model that enables longitudinal studies involving imaging techniques that would provide a means to evaluate compounds over an extended period of time.

“We need new ways to evaluate molecules *in vivo* to make it less cumbersome, to be able to evaluate more than 20 molecules and not just under 10 and to follow the progression of the disease over time,” he told *SciBX*.

Evotec is looking externally for animal models that could support its ALS program.

Artavanis-Tsakonas told *SciBX* that the path to the clinic for Biogen Idec will depend on the identified target and whether the best therapeutic would be a small molecule, antibody or antisense RNA because the different types of molecules require different experimental strategies.

In September, Biogen Idec signed a neurology-focused deal with **Isis Pharmaceuticals Inc.** that gives Biogen Idec access to Isis' antisense technology. Although the deal is not centered on ALS, Biogen Idec expects that antisense represents an extra tool in the search for new ALS candidates, Artavanis-Tsakonas told *SciBX*.

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COMPANIES AND INSTITUTIONS MENTIONED

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Harvard Stem Cell Institute, Cambridge, Mass.
Harvard University, Cambridge, Mass.
HudsonAlpha Institute for Biotechnology, Huntsville, Ala.
Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.
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The Broad's outlook in cancer

By Michael J. Haas, Senior Writer

When the **Broad Institute of MIT and Harvard** launched its Center for the Science of Therapeutics to develop new therapies for hard-to-hit targets and test them in the clinic, it lacked funds to take discoveries all the way to approval. The center's new collaboration with **Bayer AG** fills that gap for cancer assets and comes on the heels of its infectious disease arrangement with **AstraZeneca plc**.

Under the five-year collaboration, the partners will explore each other's compound libraries, share screening platforms and contribute medicinal chemistry expertise to discover new small molecules for cancer.

The Broad Institute and the Center for the Science of Therapeutics (CSofT) also will contribute cancer genomics capabilities, including sequencing and computational biology tools and a deep mechanistic understanding of how mutations lead to cancer.

Although the pharma will work with researchers throughout the Broad Institute—not just at CSofT—the collaboration reflects CSofT's goal of “enabling INDs and delivering new therapies to patients, not just building a preclinical pipeline,” CSofT director Stuart Schreiber told *SciBX*.

The Broad Institute could conduct proof-of-concept trials in small populations, but “we can't take new drug molecules through approval on our own. This requires corporate partnerships,” he said.

Schreiber and Matthew Meyerson, a senior associate member at the Broad Institute, are coleading the collaboration with Bayer.

Schreiber also is director of chemical biology at the Broad Institute, a professor of chemistry and chemical biology at **Harvard University** and an investigator at the **Howard Hughes Medical Institute**. Meyerson is also a professor of pathology at **Harvard Medical School** and the **Dana-Farber Cancer Institute**.

The collaboration with Bayer is not the Broad Institute's—or CSofT's—first foray into industrial partnerships. In 2012, the institute announced a two-year deal with AstraZeneca to develop new antiviral and antibacterial therapeutics.

Earlier this year, CSofT took over the institute's role in the collaboration. CSofT is screening the institute's 100,000-compound library. Despite its relatively small size, the library is customized to contain molecular shapes and structures not found in other compound libraries, thus enabling screens of challenging targets. The pharma will optimize, develop and commercialize the hits.

Schreiber said that to identify potential partners, leaders at CSofT and the Broad Institute meet periodically with pharmas and biotechs. “With Bayer it became evident after just a single meeting—less than a year ago—that the pharma's interests were extremely well aligned” with CSofT's, he said.

“We want to select and advance projects based on human biology—in particular, the inferences about potential targets and therapeutic strategies that can be drawn from cancer genome sequencing,” Schreiber said. “We will prioritize projects based on targets that are validated by

genomics information and their importance to tumor maintenance, not the ease or difficulty of hitting that target or its familiarity to us and Bayer. This means we will go after targets that might be challenging, and we will rely on innovative chemistry and chemical biology to solve the hard problems those challenges present.”

He noted that the goal of each project will be to test the therapeutic hypothesis of hitting the genetic target with a small molecule in the appropriate patient population.

Joint research and steering committees—each composed of equal numbers of members from the Broad Institute and Bayer—will make decisions about the number, type and duration of projects and their development. Schreiber said that some projects are under way, but he declined to disclose details.

The Broad Institute and Bayer will share rights to any new IP generated by the collaboration, and Bayer will have the option to license IP at the preclinical stage. Schreiber declined to disclose the financial terms of the deal.

CTRP: broad-ranging resource

Schreiber said that among the resources the partners will use to identify and validate tumor targets are The Cancer Genome Atlas (TCGA)—to which the institute contributes—and the Cancer Therapeutics Response Portal (CTRP). The latter is an online resource developed by a Broad Institute–led team that links genetic mutations in human cancer cell lines with sensitivity to small molecules.

In August, the team reported in *Cell* that CTRP was publicly available online and described the experiments that led to its development.¹

For the *Cell* study, the team measured the responses of 242 human cancer cell lines representing 19 tissue types to a set of 354 small molecules that targeted a wide range of cellular processes. The team then looked for correlations between the genetic or lineage features of a cell line and its sensitivity to the small molecules.

Such relationships could be used to develop new therapeutic hypotheses and accelerate drug discovery, the team wrote in its report.

As an example of the insights CTRP could generate, the team said that it found correlations between activating mutations in *β-catenin* (*CTNNB1*) and sensitivity to navitoclax in human colorectal, endometrial, gastric, liver and lung cancer cell lines. The study also revealed correlations between sensitivity to navitoclax and loss-of-function mutations in *AXIN1* and *casein kinase 1α* (*CSNK1A1*; *CKI-α*), which play roles in *CTNNB1* degradation.

Thus, mutations in *CTNNB1*, *AXIN1* or *CSNK1A1* could help identify tumors that would respond to navitoclax and other inhibitors of B cell lymphoma 2 (*BCL-2*; *BCL2*) family proteins, the team wrote.

AbbVie Inc. and **Roche's Genentech Inc.** unit have navitoclax (ABT-263; RG7433), a pan-inhibitor of antiapoptotic members of *BCL2* family proteins, in Phase I/II testing for small cell lung cancer and Phase I trials for solid tumors.

“We will go after targets that might be challenging, and we will rely on innovative chemistry and chemical biology to solve the hard problems those challenges present.”

—Stuart Schreiber,
Broad Institute of MIT and Harvard

(Continues on p. 8)

Advancing AD

By Lev Osherovich, Senior Writer

The vast majority of dollars from the NIH's recent Alzheimer's disease grants are for clinical research, but the institute also made a trio of awards to academics to develop a systems biology picture of the brain disorder. The teams hope to uncover new mechanisms and targets that may have been overlooked because of the field's traditional focus on β -amyloid.

Two projects are fishing expeditions to find targetable pathways upstream of β -amyloid ($A\beta$) accumulation that act early in disease. The third is focused on the hypothesis that innate immunity and inflammation contribute to late-stage disease.

In 2012, the U.S. government launched the National Alzheimer's Project, a road map to develop therapies and mitigate the social and economic costs of Alzheimer's disease (AD).

As part of the project, the NIH Office of the Director and the **National Institute on Aging** announced in September a \$37.1 million award for three clinical AD trials—a pair of Phase III prevention trials in two different types of genetically at-risk individuals and a Phase I trial of an amyloid-antagonizing steroid.

The trial news deflected attention from the \$4.9 million going to the 3 systems biology teams, which will be eligible for up to an additional \$18.9 million collectively over the next 5 years.

The teams all seek to identify age-related differences that distinguish healthy and AD-stricken brains. The groups will look at genetic markers, gene expression data and proteomic measurements from large collections of postmortem patient samples and controls.

(Continued from "The Broad's outlook in cancer," p. 7)

Paul Clemons, Alykhan Shamji and Schreiber co-led the team. Clemons is director of computational chemical biology research at CsoftI, and Shamji is the center's executive director. The team included researchers from **Columbia University** and the **Vanderbilt University School of Medicine**.

Data from the study are publicly available online at the [Cancer Therapeutics Response Portal](#).

Clemons said that the team's ongoing work includes testing navitoclax in mice with *CTNBN1*-mutant xenograft tumors and expanding CTRP with additional cancer cell lines, drug compounds and online functionalities.

The findings reported in *Cell* are unpatented and unlicensed, he said.

Last week, a separate Broad Institute team reported in *Nature Genetics* the results of a study that analyzed patterns and functional consequences of somatic copy number alterations (SCNAs) in over 4,900 cancers from TCGA.²

A key finding of the study was that SCNAs tend to reside in just 140 regions of the genome, only 35 of which contained known oncogenes or tumor suppressor genes. The team said that future studies need to identify whether the remaining regions encompass additional oncogenes or tumor suppressors or have limited functional roles in tumorigenesis.

Haas, M.J. *SciBX* 6(38); doi:10.1038/scibx.2013.1051
Published online Oct. 3, 2013

"The goal is to integrate all of these data into one analysis to identify molecular networks that are operating in disease," said one of the team's leaders, Philip De Jager, an associate professor of neurology at **Brigham and Women's Hospital**.

Brain collection

De Jager and coleader David Bennett plan to analyze the world's largest prospectively gathered collection of aged brains to discover new AD biomarkers and targets. Bennett is a professor of neurological sciences at **Rush University Medical Center** and director of the Rush Alzheimer's Disease Center.

"I'm the principal investigator of two cohort studies of common chronic diseases of aging with a focus on AD, as well as a wide range of other neurologic conditions," said Bennett. "The Religious Order cohort is of nuns and monks without dementia. The other cohort is the Rush Memory and Aging project, which is recruited from the lay population in northeastern Illinois. The condition of entry is that participants must donate their brains after death."

Since the mid-1990s, Bennett's team has conducted annual clinical evaluations and blood draws of each study participant. Bennett said that his team has gathered data from about 3,000 subjects, of whom about 1,100 have died and been autopsied.

"Prior studies have been focused on specific hypotheses about amyloid, but amyloid pathology only accounts for a part of dementia. We're looking for something completely novel."

—Philip De Jager,
Brigham and Women's Hospital

(Continues on p. 9)

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- Zack, T.I. *et al. Nat. Genet.* **45**, 1134–1140 (2013)

COMPANIES AND INSTITUTIONS MENTIONED

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AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Broad Institute of MIT and Harvard, Cambridge, Mass.
Columbia University, New York, N.Y.
Dana-Farber Cancer Institute, Boston, Mass.
Genentech Inc., South San Francisco, Calif.
Harvard Medical School, Boston, Mass.
Harvard University, Cambridge, Mass.
Howard Hughes Medical Institute, Chevy Chase, Md.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Vanderbilt University School of Medicine, Nashville, Tenn.

Now, Bennett and De Jager plan to analyze genomic and gene expression data, brain pathology, serum markers and clinical observations of memory and cognition to obtain a comprehensive view of AD progression.

The hope is that casting a wide net will identify early biological signs of AD that are independent of A β pathology. Until now, researchers have focused on amyloid plaques as the most obvious molecular hallmarks of AD, but efforts to prevent or reverse A β accumulation have failed in the clinic.

De Jager and Bennett both said that A β pathology strongly correlates with dementia but that not all dementia patients have amyloid plaque deposits and not all individuals with amyloid plaques have dementia.

“Our advantage is that we’re using an empirical, data-driven approach with no prior assumptions about amyloid,” said De Jager. “Prior studies have been focused on specific hypotheses about amyloid, but amyloid pathology only accounts for a part of dementia. We’re looking for something completely novel. Because we have such a deep, integrated dataset, we have the chance to discover something new.”

The team hopes to select a list of 300–400 candidate genes whose activity appears to be different in patients versus controls and will further characterize expression and function of these genes in human brain tissue and preclinical models of AD.

Once the team has identified likely targets involved in early stage disease, the researchers will conduct a small molecule drug screen in induced pluripotent stem (iPS) cells.

The ultimate goal is to identify targets for AD prevention. “Prevention is more tractable than therapy. Once you have clinical impairment, your brain is pretty far gone. I think it will be hard to reverse that,” said Bennett.

Big data

The second early stage grant went to a consortium led by Eric Schadt to pursue a computational approach to teasing out early AD players.

Schadt is a professor of genetics and genomic sciences and director of the Institute for Genomics and Multiscale Biology at **Mount Sinai Hospital**. His team will probe 250 AD brains and 50 controls from a brain bank at Mount Sinai Alzheimer’s Disease Research Center. The group will use an array of genomic and proteomic techniques to construct a model of gene interactions that will hopefully point to causal players in AD.

The team’s technique builds on statistically driven systems biology methods developed by Schadt while at **Merck & Co. Inc.**’s Rosetta Inpharmatics unit and **Sage Bionetworks**, a not-for-profit institute.^{1,2}

Co-principal investigators Jun Zhu and Bin Zhang of Mount Sinai told *SciBX* that the human brain tissue studies will guide subsequent preclinical studies to test hypotheses about which genes contribute to the initiation of disease. Zhu and Zhang are a professor and an associate professor of genetics and genomic sciences, respectively.

“Data generated from human genetic studies, human iPS cells, mouse models and *Drosophila* models will be used to generate, test and refine our network models,” said Zhang.

Like De Jaeger and Bennett, the Mount Sinai team is agnostic about what kind of results—markers or therapeutic targets—will arise from its analysis. Ideally, said Zhang, at least a few potential drug targets will emerge.

Innate hypothesis

Finally, a **University of Florida** team led by Todd Golde will pursue a hypothesis-driven approach, focusing on the role of innate immunity and inflammation in AD.

Golde is a professor of neuroscience and director of the University of Florida’s Center for Translational Research in Neurodegenerative Disease.

“It’s been long thought in the field that proinflammatory stimuli would make A β pathology worse, but we tested this in three models and found this not to be the case,” said Golde.³

Likewise, he cited evidence from mouse models of AD that the anti-inflammatory cytokines IL-4 and IL-10 appear to exacerbate A β pathology.

Thus, Golde suspects key aspects of inflammation are regulated differently in the brain than elsewhere in the body and go awry in AD. To identify the critical players, his group will use RNA sequencing to analyze the expression of selected inflammation-associated genes in a panel of 100 typical AD brains, 100 healthy, age-matched controls and 100 more controls with atypical AD-like pathology.

His next step will be to manipulate the expression of 15–20 of the most severely perturbed genes in mouse models of AD.

“We’ve used an adeno-associated viral transduction method to deliver things to the brain either neonatally or later in life and have been evaluating how altering innate immunity affects AD pathology in mice,” said Golde. “This grant lets us increase the throughput by identifying targets using a systems biology approach to directly test whether these changes are good or bad.”

Golde is starting from the hypothesis that inflammation plays a role in late stage disease, which is characterized by microglial activation, neuronal death and accumulation of neurofibrillary tangles of microtubule-associated protein- τ (MAPT; TAU; FTDP-17). He suspects that blocking inflammation can prevent TAU aggregation and improve neuronal activity even in patients with advanced disease.

“Our bias is that if we want a therapy that will work at a later stage of disease, we need something that affects TAU deposition,” said Golde. “There is evidence that manipulating innate immunity or using innate immune factors could improve TAU pathology and possibly neuronal viability.”

Interim results from all three teams are expected a year hence. Meanwhile, the National Alzheimer’s Project plans to fund one more discovery-oriented project this year but has not yet announced the recipient.

Osherovich, L. *SciBX* 6(38); doi:10.1038/scibx.2013.1052
Published online Oct. 3, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Brigham and Women’s Hospital, Boston, Mass.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Mount Sinai Hospital, New York, N.Y.
National Institute on Aging, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
Sage Bionetworks, Seattle, Wash.
Rush University Medical Center, Chicago, Ill.
University of Florida, Gainesville, Fla.

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)	IL-27	Studies in cell culture and mice suggest IL-27-conditioned dendritic cells (DCs) could help treat MS. In cell culture, DCs treated with the anti-inflammatory cytokine IL-27 had lower antigen presentation and autoimmunity-associated activity than DCs treated with vehicle. In a mouse model of MS, transfusion of IL-27-treated DCs decreased inflammatory cytokine levels in the brain and slowed disease progression compared with transfusion of vehicle-treated DCs. Next steps include validating the findings in human DCs.	Patent pending; available for licensing	Mascanfroni, I.D. <i>et al. Nat. Immunol.</i> ; published online Sept. 1, 2013; doi:10.1038/ni.2695 Contact: Francisco J. Quintana, Harvard Medical School, Boston, Mass. e-mail: fquintana@rics.bwh.harvard.edu
SciBX 6(38); doi:10.1038/scibx.2013.1053 Published online Oct. 3, 2013				
Cancer				
Acute lymphoblastic leukemia (ALL)	Wolf-Hirschhorn syndrome candidate 1 (WHSC1; MMSET; NSD2)	Cell culture studies suggest inhibiting MMSET could help treat patients carrying activating mutations in the protein. In an analysis of the cancer cell line encyclopedia, an E1099K mutation in MMSET was identified in eight cell lines, seven of which were of lymphoid origin. The mutant MMSET cell lines displayed globally increased lysine H3K36 dimethylation compared with wild-type MMSET cell lines. Next steps include functional studies to test whether blocking MMSET activity could help treat cancers carrying the mutation.	Unpatented; licensing status not applicable	Oyer, J.A. <i>et al. Leukemia</i> ; published online July 26, 2013; doi:10.1038/leu.2013.204 Contact: Relja Popovic, Northwestern University, Chicago, Ill. e-mail: r-popovic@northwestern.edu Contact: Jonathan D. Licht, same affiliation as above e-mail: j-licht@northwestern.edu
SciBX 6(38); doi:10.1038/scibx.2013.1054 Published online Oct. 3, 2013				
Breast cancer	Chemokine CXC motif ligand 10 (CXCL10; IP-10)	<i>In vitro</i> and mouse studies suggest antibodies targeting CXCL10 could help treat breast cancer. In human breast cancer tissue samples, $\gamma\delta$ T _{reg} cells, which suppress antitumor immunity, accumulated in tumors but not in healthy tissue. In mice bearing subcutaneous human breast tumors and adoptively transferred human $\gamma\delta$ T _{reg} cells, a CXCL10-neutralizing antibody prevented tumor $\gamma\delta$ T _{reg} cell accumulation and decreased tumor growth compared with an isotype control antibody. Next steps could include testing antibodies against CXCL10 in additional breast cancer models. Bristol-Myers Squibb Co.'s MDX-1100, a mAb targeting CXCL10, is in Phase II testing to treat inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). NovImmune S.A.'s CXCL10 mAb, NI-0801, is in Phase II testing for liver disease and cirrhosis.	Patent and licensing status unavailable	Ye, J. <i>et al. Cancer Res.</i> ; published online Aug. 19, 2013; doi:10.1158/0008-5472.CAN-13-0348 Contact: Guangyong Peng, Saint Louis University, St. Louis, Mo. e-mail: gpeng@slu.edu
SciBX 6(38); doi:10.1038/scibx.2013.1055 Published online Oct. 3, 2013				

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Thioesterase superfamily member 4 (THEM4; CTMP)	Studies in cell culture, mice and human tissue samples suggest inhibiting CTMP could help treat breast cancer. In a breast cancer cell line, small hairpin RNA knockdown of CTMP decreased proliferation compared with no knockdown. In a mouse xenograft model of breast cancer, CTMP overexpression increased tumorigenesis compared with wild-type CTMP expression. In human tissue samples, CTMP expression was higher in breast tumor cells than in normal cells, and expression of CTMP correlated with poor patient prognosis. Next steps could include designing and testing CTMP inhibitors in animal models. SciBX 6(38); doi:10.1038/scibx.2013.1056 Published online Oct. 3, 2013	Patent and licensing status unavailable	Liu, Y.-P. <i>et al. Cancer Res.</i> ; published online Aug. 13, 2013; doi:10.1158/0008-5472.CAN-13-0518 Contact: Pei-Jung Lu, National Cheng Kung University, Tainan, Taiwan e-mail: pjlu2190@mail.ncku.edu.tw
Cancer	β -Catenin (CTNNB1); B cell lymphoma 2 (BCL-2; BCL2); AXIN1; casein kinase 1 α (CSNK1A1; CKI- α)	<i>In vitro</i> studies suggest mutations in <i>CTNNB1</i> or in genes regulating its degradation may predict tumor responses to BCL2 inhibitors. In a screen of human colorectal, endometrial, gastric, liver and lung cancer cell lines treated with small molecule inhibitors, genomic profiling identified correlations between activating mutations in <i>CTNNB1</i> and sensitivity to the BCL2 inhibitor navitoclax. Genomic profiling of the treated cancer cell lines also identified correlations between sensitivity to navitoclax and loss-of-function mutations in <i>AXIN1</i> and <i>CSNK1A1</i> , which affect <i>CTNNB1</i> degradation. Ongoing work includes testing navitoclax in mice bearing <i>CTNNB1</i> -mutant xenograft tumors. AbbVie Inc. and Roche's Genentech Inc. unit have navitoclax (ABT-263; RG7433), a pan-BCL2 inhibitor, in Phase I/II testing to treat small cell lung cancer and Phase I testing to treat solid tumors. Roche and AbbVie have ABT-199 (RG7601; GDC-0199), a small molecule inhibitor of BCL2, in Phase II testing to treat chronic lymphocytic leukemia (CLL). Ascentage Pharma Group Corp. Ltd. and 3SBio Inc. have a pan-BCL2 inhibitor in Phase II testing to treat non-small cell lung cancer (NSCLC; see The Broad's outlook in cancer , page 7). SciBX 6(38); doi:10.1038/scibx.2013.1057 Published online Oct. 3, 2013	Unpatented; unlicensed	Basu, A. <i>et al. Cell</i> ; published online Aug. 29, 2013; doi:10.1016/j.cell.2013.08.003 Contact: Stuart L. Schreiber, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: stuart_schreiber@harvard.edu Contact: Alykhan F. Shamji, same affiliation as above e-mail: ashamji@broadinstitute.org Contact: Paul A. Clemons, same affiliation as above e-mail: pclemons@broadinstitute.org
Cancer	Heat shock protein 90 (Hsp90); heat shock 90 kDa protein β 1 (Hsp90B1; GP96; GRP94)	<i>In vitro</i> studies identified a purine-based specific inhibitor of the Hsp90 family protein GRP94 that could treat cancer. Pan-inhibitors of Hsp90 are known to kill cancer cells but also can trigger upregulation of other heat shock proteins. In a human breast cancer cell line, inhibition of GRP94 with small interfering RNA or a purine-based inhibitor decreased viability compared with no inhibition. In the cell line, the purine-based inhibitor did not trigger upregulation of Hsp70, which protects against apoptosis. Next steps could include evaluating the selective Hsp90 inhibitor in animal cancer models. Samus Therapeutics LLC has PU-H71, a purine-based pan-Hsp90 inhibitor, in Phase I testing. At least 19 other companies have Hsp90 inhibitors in Phase III testing or earlier to treat various cancers. SciBX 6(38); doi:10.1038/scibx.2013.1058 Published online Oct. 3, 2013	Patent application filed covering purine- scaffold Hsp90 inhibitors; PU-H71 licensed to Samus Therapeutics	Patel, P.D. <i>et al. Nat. Chem. Biol.</i> ; published online Sept. 1, 2013; doi:10.1038/nchembio.1335 Contact: Gabriela Chiosis, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: chiosisg@mskcc.org Contact: Daniel T. Gewirth, State University of New York at Buffalo, Buffalo, N.Y. e-mail: gewirth@hwi.buffalo.edu

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Histone deacetylase 6 (HDAC6)	<p><i>In vitro</i>, cell culture and mouse studies have identified an HDAC6 inhibitor that could help treat cancer.</p> <p><i>In vitro</i>, a hydroxamic acid–based small molecule inhibited HDAC6 with an IC_{50} of about 50 nM and had selectivity over other HDACs, including about 50-fold selectivity over HDAC1. In human cancer cell lines, the inhibitor decreased cell growth compared with no treatment but did not affect viability. In human cancer cells and in a mouse xenograft model of prostate cancer, the inhibitor plus the chemotherapeutics doxorubicin or etoposide increased cell death and decreased tumor growth compared with chemotherapy alone. Next steps could include testing the molecule in additional tumor models.</p> <p>Celgene Corp. and Acetylon Pharmaceuticals Inc. have ACY-1215, an HDAC6 inhibitor, in Phase I/II testing to treat multiple myeloma (MM). Karus Therapeutics Ltd. and IkerChem S.L. have HDAC6 inhibitors in preclinical development to treat cancer and inflammation.</p> <p>SciBX 6(38); doi:10.1038/scibx.2013.1059 Published online Oct. 3, 2013</p>	Patent and licensing status unavailable	<p>Lee, J.-H. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 10, 2013; doi:10.1073/pnas.1313893110</p> <p>Contact: Paul A. Marks, Memorial Sloan-Kettering Cancer Center, New York, N.Y.</p> <p>e-mail: marksp@mskcc.org</p> <p>Contact: Ronald Breslow, Columbia University, New York, N.Y.</p> <p>e-mail: rb33@columbia.edu</p>
Chronic myelogenous leukemia (CML)	Protein phosphatase 2 (PPP2CA; PP2A)	<p>Studies in patient samples and mice suggest Gilenya fingolimod and nonimmunosuppressive derivatives could help eradicate leukemic stem cells in CML, which are associated with disease relapse. In leukemic hematopoietic stem cells (HSCs) isolated from patients with CML, PP2A activity was lower than that in healthy HSCs. In the CML stem cells, Gilenya or any of three nonimmunosuppressive derivatives activated PP2A, impaired self-renewal and induced apoptosis. In mouse xenograft models of CML, Gilenya decreased leukemic stem cell numbers compared with no treatment. Next steps include designing additional PP2A activators.</p> <p>Novartis AG markets the sphingosine 1-phosphate receptor agonist Gilenya to treat relapsing forms of multiple sclerosis (MS).</p> <p>Oncotide Pharmaceuticals Inc. has SET nuclear oncogene (SET) inhibitors in preclinical development to treat various cancers. SET inhibition is designed to activate PP2A.</p> <p>SciBX 6(38); doi:10.1038/scibx.2013.1060 Published online Oct. 3, 2013</p>	Multiple patent applications filed covering nonimmunosuppressive derivatives and their use in various cancers; available for licensing and partnering from The Ohio State University Technology Commercialization and Knowledge Transfer Office	<p>Neviani, P. <i>et al. J. Clin. Invest.</i>; published online Sept. 3, 2013; doi:10.1172/JCI68951</p> <p>Contact: Danilo Perrotti, University of Maryland, College Park, Md.</p> <p>e-mail: dperrotti@som.umaryland.edu</p>
Melanoma	BRAF; neuroblastoma Ras viral (v-Ras) oncogene (NRAS)	<p><i>In vitro</i> and mouse studies have identified a pan-Raf kinase inhibitor that could help treat BRAF- or NRAS-mutant melanoma. In binding studies, the inhibitor TAK-632 bound BRAF with an IC_{50} of about 2.4 nM and with 67-fold selectivity over VEGF receptor 2 (KDR/Flk-1; VEGFR-2). In two mouse xenograft models of melanoma, TAK-632 decreased tumor volume compared with vehicle. Next steps include studying the compound in additional mutant NRAS cell lines to help determine the optimal indication for clinical testing.</p> <p>SciBX 6(38); doi:10.1038/scibx.2013.1061 Published online Oct. 3, 2013</p>	Patent filed by Takeda Pharmaceutical Co. Ltd.; licensing status undisclosed	<p>Okaniwa, M. <i>et al. J. Med. Chem.</i>; published online Aug. 1, 2013; doi:10.1021/jm400778d</p> <p>Contact: Tomoyasu Ishikawa, Takeda Pharmaceutical Co. Ltd., Kanagawa, Japan</p> <p>e-mail: tomoyasu.ishikawa@takeda.com</p> <p>Contact: Masaaki Hirose, same affiliation as above</p> <p>e-mail: masaaki.hirose@takeda.com</p> <p>Contact: Masanori Okaniwa, same affiliation as above</p> <p>e-mail: masanori.okaniwa@takeda.com</p>

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Ovarian cancer	Neuronal precursor cell expressed developmentally downregulated 8 (NEDD8); cullin 4A (CUL4A)	Cell culture and human tissue studies suggest inhibiting CUL4A could help treat ovarian cancer. In human ovarian cancer tissue, CUL4A expression is greater than that in normal tissue. In human ovarian cancer cell lines, an inhibitor of CUL4A neddylation and activity, MLN4924, or small interfering RNA against CUL4A components inhibited proliferation and increased apoptosis compared with no treatment or control siRNA. Also in cells, depletion of a CUL4A substrate rescued MLN4924-induced apoptosis, indicating that CUL4A substrates are necessary for the activity of MLN4924 in ovarian cancer cells. Next steps could include determining whether CUL4A components are biomarkers for ovarian cancer and testing MLN4924 in <i>in vivo</i> models of ovarian cancer. MLN4924 is a NEDD8 inhibitor from Takeda Pharmaceutical Co. Ltd. that is in Phase I testing to treat various cancers. SciBX 6(38); doi:10.1038/scibx.2013.1062 Published online Oct. 3, 2013	Patent and licensing status unavailable	Pan, W.-W. <i>et al. J. Biol. Chem.</i> ; published online Aug. 30, 2013; doi:10.1074/jbc.M113.495069 Contact: Heng-Yu Fan, Zhejiang University, Hangzhou, China e-mail: hyfan@zju.edu.cn Contact: Fang-Zhou Song, Chongqing Medical University, Chongqing, China e-mail: fzsongcq@163.com
Pancreatic cancer	Epidermal growth factor receptor (EGFR); HER2 (EGFR2; ErbB2; neu)	Mouse studies identified combinations of antibodies targeting HER2 and EGFR that could help treat pancreatic cancer. In mice with human pancreatic ductal adenocarcinoma xenografts, intraperitoneal injection of mAbs targeting HER2 or EGFR had a small effect on tumor growth, whereas combinations of the antibodies synergistically inhibited tumor growth and increased the fraction of tumor-free mice. Next steps include humanizing the relevant antibodies. SciBX 6(38); doi:10.1038/scibx.2013.1063 Published online Oct. 3, 2013	Patent application filed; available for licensing	Maron, R. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 3, 2013; doi:10.1073/pnas.1313857110 Contact: Michael Sela, Weizmann Institute of Science, Rehovot, Israel e-mail: michael.sela@weizmann.ac.il Contact: Yosef Yarden, same affiliation as above e-mail: yosef.yarden@weizmann.ac.il
Gastrointestinal disease				
Pancreatitis	CD38	Cell culture and mouse studies suggest antagonizing CD38 could be useful for treating pancreatitis. In cultured mouse pancreatic acinar cells, <i>Cd38</i> deletion decreased calcium release and cell injury in response to excessive stimulation compared with wild-type <i>Cd38</i> expression. In a mouse model of bile acid-induced pancreatitis, <i>Cd38</i> knockout mice had less damage than wild-type mice. Next steps include testing CD38 mAbs in cellular and mouse models of pancreatitis. Anti-CD38 mAbs in Phase I/II testing for multiple myeloma (MM) include MOR202 from Celgene Corp. and MorphoSys AG, daratumumab from Genmab A/S and Johnson & Johnson and SAR650984 from Sanofi. SciBX 6(38); doi:10.1038/scibx.2013.1064 Published online Oct. 3, 2013	Patent and licensing status undisclosed	Orabi, A.I. <i>et al. J. Biol. Chem.</i> ; published online Aug. 12, 2013; doi:10.1074/jbc.M113.494534 Contact: Sohail Z. Husain, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa. e-mail: sohail.husain@chp.edu

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Viral infection	IL-6 signal transducer (IL-6ST; gp130; CD130); IL-27; IL-27 receptor- α (IL27RA)	Mouse studies suggest increasing IL-27 signaling through gp130 and IL27RA could help control chronic viral infections. In mice infected with lymphocytic choriomeningitis virus (LCMV), <i>gp130</i> knockout in CD4 ⁺ T cells decreased CD4 ⁺ and CD8 ⁺ T cell immune responses compared with no knockout and led to chronic infection. In the same model, knockout of <i>IL27RA</i> also led to chronic infection. Next steps include testing whether inducing gp130 signaling on virus-specific T cells enhances chronic virus clearance.	Unpatented; available for licensing	Harker, J.A. <i>et al. Immunity</i> ; published online Aug. 29, 2013; doi:10.1016/j.immuni.2013.08.010 Contact: Elina I. Zuniga, University of California, San Diego, Calif. e-mail: eizuniga@ucsd.edu
Neurology				
Alzheimer's disease (AD)	β -Amyloid (A β)	<i>In vitro</i> studies identified synthetic peptides derived from Russell's viper venom that could help treat AD. Treatment of aggregated A β with synthetic peptides derived from a venom protein destabilized the aggregates and caused disassembly into nontoxic monomers. In a human neuroblastoma cell line treated with A β aggregates, pretreatment with the synthetic peptides decreased cell death and cytotoxicity of the aggregates compared with pretreatment using nonspecific control peptides. Next steps include testing the peptides in animal models of AD and for human blood brain barrier penetration.	Findings unpatented; unavailable for licensing	Bhattacharjee, P. & Bhattacharyya, D. <i>J. Biol. Chem.</i> ; published online Aug. 28, 2013; doi:10.1074/jbc.M113.511410 Contact: Debasish Bhattacharyya, CSIR-Indian Institute of Chemical Biology, Kolkata, India e-mail: debasish@iicb.res.in Contact: Payel Bhattacharjee, same affiliation as above e-mail: payel.iicb@gmail.com
Alzheimer's disease (AD)	Calcium release-activated calcium channel (CRAC)	Cell culture studies suggest agonizing CRAC could be useful for treating AD. In human embryonic kidney (HEK) cells overexpressing amyloid precursor protein (APP), overexpression of a constitutively active form of CRAC decreased β -amyloid (A β) secretion compared with wild-type CRAC expression. Next steps include identifying compounds that activate CRAC-mediated calcium entry and testing them in cultured neurons and mouse models of AD.	Unpatented; licensing status not applicable	Zeiger, W. <i>et al. J. Biol. Chem.</i> ; published online July 31, 2013; doi:10.1074/jbc.M113.473355 Contact: Gopal Thinakaran, The University of Chicago, Chicago, Ill. e-mail: gopal@uchicago.edu Contact: Mitchel L. Villereal, same affiliation as above e-mail: mwillere@bsd.uchicago.edu
Epilepsy	NMDA receptor NR1 subtype (GRIN1; NR1); GRIN2B (NR2B); GABA _A receptor α_1 (GABRA1); GABA _A receptor β_3 (GABRB3)	Human genome sequencing studies suggest modulating GABA _A receptors and NMDARs could help treat some patients with pediatric epilepsy. Exome sequencing of 264 patients with infantile spasms and Lennox-Gastaut syndrome and their parents identified <i>de novo</i> mutations in a variety of genes including <i>GABRB3</i> , <i>GABRA1</i> , <i>NR1</i> and <i>NR2B</i> . Next steps include characterizing the effects of these mutations on GABA _A receptor and NMDAR function in cell culture and testing pharmacological agents that modulate receptor activity. H. Lundbeck A/S markets Onfi clobazam, a GABA _A receptor agonist, to treat Lennox-Gastaut syndrome.	Unpatented; licensing status not applicable	Epi4K Consortium & Epilepsy Phenome/Genome Project. <i>Nature</i> ; published online Aug. 11, 2013; doi:10.1038/nature12439 Contact: David B. Goldstein, Duke University, Durham, N.C. e-mail: d.goldstein@duke.edu

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Insomnia	Orexin 2 receptor (HCRTR2; OX2R)	<i>In vitro</i> and mouse studies identified an OX2R-selective antagonist that may help treat insomnia. <i>In vitro</i> , the antagonist bound OX2R with a K_i of about 14 nM and about 30-fold selectivity over OX1R (HCRTR1). In mouse locomotor activity studies, the antagonist increased inactivity compared with vehicle. In electrical brain recording studies in mice, the antagonist increased non-rapid eye movement (NREM) sleep time compared with vehicle and had no effect on REM sleep time. Next steps could include testing the antagonist in the clinic for primary insomnia.	Patented by Novartis AG; licensing status undisclosed	Bestschart, C. <i>et al. J. Med. Chem.</i> ; published online Aug. 21, 2013; doi:10.1021/jm4007627 Contact: Claudia Betschart, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: claudia.betschart@novartis.com Contact: Samuel Hintermann, same affiliation as above e-mail: samuel.hintermann@novartis.com
		SciBX 6(38); doi:10.1038/scibx.2013.1069 Published online Oct. 3, 2013		
Stroke	Not applicable	Rodent studies suggest peritoneal dialysis could help decrease tissue damage after stroke. Ischemic brain injury causes the release of glutamate from damaged brain tissue to the blood, which causes tissue damage. In a rat model of brain ischemia, peritoneal dialysis 2.5 or 5 hours after infarction decreased plasma glutamate levels and infarct volume compared with no dialysis or dialysis that failed to remove glutamate. In the rats, the preserved brain tissue was viable and functional. Ongoing studies include a clinical safety trial of the approach.	Findings patented; available for licensing	Godino, M.D. <i>et al. J. Clin. Invest.</i> ; published online Sept. 3, 2013; doi:10.1172/JCI67284 Contact: José Sánchez-Prieto, Complutense University of Madrid, Madrid, Spain e-mail: jsprieto@vet.ucm.es Contact: Ignacio Lizasoain, same affiliation as above e-mail: ignacio.lizasoain@med.ucm.es
		SciBX 6(38); doi:10.1038/scibx.2013.1070 Published online Oct. 3, 2013		
Renal disease				
Glomerulonephritis	Chemokine CX3C motif receptor 1 (CX3CR1)	Mouse studies suggest inhibiting CX3CR1 could help treat glomerulonephritis. In a mouse model of crescentic glomerulonephritis, <i>Cx3cr1</i> knockout decreased both the number of inflammation-mediating dendritic cells in kidneys and disease severity compared with wild-type <i>Cx3cr1</i> expression. Next steps could include developing and evaluating CX3CR1 inhibitors.	Patent and licensing status unavailable	Hochheiser, K. <i>et al. J. Clin. Invest.</i> ; published online Sept. 3, 2013; doi:10.1172/JCI70143 Contact: Christian Kurts, Institute of Molecular Medicine and Experimental Immunology, Bonn, Germany e-mail: ckurts@web.de Contact: Katharina Hochheiser, University of Bonn, Bonn, Germany e-mail: khochhei@uni-bonn.de
		SciBX 6(38); doi:10.1038/scibx.2013.1071 Published online Oct. 3, 2013		

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			
Assay for single-cell DNA methylation analysis	An assay for single-cell DNA methylation analysis could be useful for understanding the heterogeneity of epigenetic modifications in diseased tissue. The assay system combines methylation-sensitive restriction digestion and multiplex, quantitative, real-time PCR in a microfluidic device. The assay showed that early stage mouse embryo cells with a deficiency in the scaffolding protein <i>tripartite motif containing 28 (Trim28)</i> exhibited variable degrees of hypomethylation at all tested genes. Next steps include developing a complete set of assays to monitor methylation status at all genes and adapting the assay for use with human cells. SciBX 6(38); doi:10.1038/scibx.2013.1072 Published online Oct. 3, 2013	Unpatented; licensing status not applicable	Lorthongpanich, C. <i>et al. Science</i> ; published online Sept. 6, 2013; doi:10.1126/science.1240617 Contact: Daniel M. Messerschmidt, Agency for Science, Technology and Research (A*STAR), Singapore e-mail: danielm@imcb.a-star.edu.sg Contact: William F. Burkholder, Nanyang Technological University, Singapore e-mail: wfburkholder@gmail.com
Low-copy <i>piggyBac (PB)</i> mutagenesis screening to identify mutated genes that drive cancer	Low-copy <i>PB</i> screening in mice could help identify genes that drive cancer when mutated. Identifying oncogenic driver genes from high-copy transposon mutagenesis has been difficult because of high background mutation rates. In mice, the low-copy <i>PB</i> mutagenesis system, which generates about four insertion mutations per tumor, was used to screen for drivers of mutant <i>BRAF</i> -expressing melanoma growth. Sequencing identified insertions in 2 known melanoma drivers, <i>microphthalmia-associated transcription factor (Mitf)</i> and <i>cyclin dependent kinase inhibitor 2A (Cdkn2a; Ink4a; Arf; p16INK4a)</i> , and 36 previously undescribed candidate driver genes. Next steps could include using the screening system for other types of cancer. SciBX 6(38); doi:10.1038/scibx.2013.1073 Published online Oct. 3, 2013	Patent and licensing information unavailable	Ni, T.K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 3, 2013; doi:10.1073/pnas.1314435110 Contact: Tian Xu, Yale School of Medicine, New Haven, Conn. e-mail: tian.xu@yale.edu
Chemistry			
Using metrics other than IC_{50} to assess cancer drug response	An analysis of cellular responses to cancer drugs suggests parameters other than potency should be considered when evaluating their efficacy. A multiparametric analysis of 64 cancer compounds in 53 breast cancer cell lines followed by single-cell analysis found variations in dose-response curves that suggest it could be useful to evaluate compounds using parameters other than IC_{50} measurements. These parameters include Hill slope (HS) and maximum effect (E_{max}) values. Next steps include replicating the findings in primary, patient-derived tumor cells and further studying the molecular mechanisms that underlie the observations. SciBX 6(38); doi:10.1038/scibx.2013.1074 Published online Oct. 3, 2013	Unpatented; licensing status not applicable	Fallahi-Sichani, M. <i>et al. Nat. Chem. Biol.</i> ; published online Sept. 8, 2013; doi:10.1038/nchembio.1337 Contact: Peter K. Sorger, Harvard Medical School, Boston, Mass. e-mail: peter_sorger@hms.harvard.edu
Disease models			
Doxycycline-inducible adipocyte labeling system for <i>in vivo</i> adipogenesis monitoring	A doxycycline-inducible adipocyte labeling system in mice could be useful for studying and monitoring adipogenesis. The engineered AdipoChaser mice enabled lineage tracing of white adipose tissues and monitoring of adipogenesis during high-fat diet feeding and cold exposure. The mouse system was able to show differences in the adipogenic potential of epididymal, subcutaneous and gonadal fat deposits. Next steps include using the AdipoChaser mice to monitor additional states of adipogenesis. SciBX 6(38); doi:10.1038/scibx.2013.1075 Published online Oct. 3, 2013	Unpatented; model available for licensing	Wang, Q.A. <i>et al. Nat. Med.</i> ; published online Sept. 1, 2013; doi:10.1038/nm.3324 Contact: Philipp E. Scherer, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: philipp.scherer@utsouthwestern.edu

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Interferon regulatory factor 4 (<i>Irf4</i>)-deficient mouse models of chronic lymphocytic leukemia (CLL)	<i>Irf4</i> -deficient mice could be used to study CLL pathogenesis. In the New Zealand Black mouse strain, heterozygous deletion of <i>Irf4</i> increased the number of animals that developed CLL within 12 months compared with wild-type <i>Irf4</i> expression. In a different mouse strain, animals with homozygous deletion of <i>Irf4</i> and knock-in of the IgG heavy chain <i>Vh11</i> developed CLL with 100% penetrance within 10 months, whereas <i>Vh11</i> knock-in models with heterozygous <i>Irf4</i> deletion or normal <i>Irf4</i> expression did not. Ongoing work includes using the models to elucidate how <i>IRF4</i> contributes to the development of CLL. SciBX 6(38); doi:10.1038/scibx.2013.1076 Published online Oct. 3, 2013	Findings from both studies unpatented; unlicensed	Ma, S. <i>et al. J. Biol. Chem.</i> ; published online July 29, 2013; doi:10.1074/jbc.M113.475913 Shukla, V. <i>et al. Blood</i> ; published online Aug. 7, 2013; doi:10.1182/blood-2013-03-492769 Contact: Runqing Lu, University of Nebraska Medical Center, Omaha, Neb. e-mail: rлу@unmc.edu
Mouse model of phosphoinositide 3-kinase catalytic subunit α -polypeptide (<i>PIK3CA</i> ; <i>p110α</i>)-mutant, HER2 (EGFR2; ErbB2; neu) ⁺ breast cancer	A mouse model of HER2 ⁺ breast cancer with a <i>PIK3CA</i> mutation could be useful for developing combination therapies to treat the disease. Mice with mammary epithelium-specific overexpression of human HER2 and a mutant form of <i>PIK3CA</i> had tumors that grew more aggressively and metastasized more readily than tumors with mammary epithelium-specific overexpression of HER2 alone. In the mice, the HER2 ⁺ , <i>PIK3CA</i> -mutant tumors were resistant to the combination of anti-HER2 antibodies Herceptin trastuzumab and Perjeta pertuzumab. Next steps include using these mice to test inhibitors of mutant <i>PIK3CA</i> in combination with HER2 antagonists. Roche's Genentech Inc. unit markets Herceptin to treat metastatic breast and gastric cancers and Perjeta to treat metastatic breast cancer. SciBX 6(38); doi:10.1038/scibx.2013.1077 Published online Oct. 3, 2013	Patent and licensing status undisclosed	Hanker, A.B. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 12, 2013; doi:10.1073/pnas.1303204110 Contact: Carlos L. Arteaga, Vanderbilt University, Nashville, Tenn. e-mail: carlos.arteaga@vanderbilt.edu Contact: Jean J. Zhao, Harvard Medical School, Boston, Mass. e-mail: jean_zhao@dfci.harvard.edu
Drug delivery			
Safety mechanism assisted by the repressor of tetracycline (SMART) oncolytic <i>Vaccinia</i> vaccines	Cell-based and mouse studies suggest tetracycline-inducible expression of interferon- γ (IFN γ ; IFN- γ) could improve the safety of <i>Vaccinia</i> virus (VACV)-based oncolytic viral therapy. SMART vectors were generated to produce low basal expression and doxycycline-inducible high expression of IFN- γ . In immunodeficient mice infected with the SMART-IFN- γ virus, compared with mice infected with a vector lacking IFN- γ , doxycycline decreased infection-associated weight loss and increased survival. Next steps include testing these viruses in mouse xenograft models of cancer and developing next-generation, smallpox-based therapeutic vaccines using the strategy. SciBX 6(38); doi:10.1038/scibx.2013.1078 Published online Oct. 3, 2013	Patent filed by University of Connecticut; available for licensing	Grigg, P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 29, 2013; doi:10.1073/pnas.1314483110 Contact: Paulo H. Verardi, University of Connecticut, Storrs, Conn. e-mail: paulo.verardi@uconn.edu Contact: Tilahun D. Yilma, University of California, Davis, Calif. e-mail: tdyilma@ucdavis.edu
Drug platforms			
Locus-specific control of histone modification using transcription activator-like (TAL) effector repeat fusion proteins	TAL effector repeats linked to chromatin-modifying enzymes could enable locus-specific chromatin modification and inform epigenetic drug development. TAL effector repeats targeting specific DNA sequences were linked to lysine-specific histone demethylase 1 (KDM1A; LSD1), which enabled locus-specific binding and reduction in levels of H3K4me2 and H3K27 acetylation, whereas a TAL effector alone did not. Next steps include using this approach to better understand how compounds that inhibit chromatin-modifying proteins function in normal and cancerous cells and to guide their development and identify potential biomarkers. SciBX 6(38); doi:10.1038/scibx.2013.1079 Published online Oct. 3, 2013	Patent application filed; available for licensing	Mendenhall, E.M. <i>et al. Nat. Biotechnol.</i> ; published online Sept. 8, 2013; doi:10.1038/nbt.2701 Contact: Bradley E. Bernstein, Massachusetts General Hospital, Boston, Mass. e-mail: bernstein.bradley@mg.harvard.edu
Mice overexpressing kidney injury molecule 1 (<i>Kim-1</i>) to model chronic kidney disease (CKD)	Mice that chronically overexpress <i>Kim-1</i> in renal epithelial cells could be used to model human CKD pathology. In patients with injured kidneys, <i>KIM-1</i> is strongly overexpressed and serves as a negative prognostic marker. Mice overexpressing <i>Kim-1</i> in renal epithelial cells developed interstitial inflammation followed by progressive fibrotic renal disease, cardiac remodeling and malfunction. In a mouse model of renal fibrosis caused by unilateral ureteral obstruction, mice expressing a mutant form of <i>Kim-1</i> did not develop renal fibroids, whereas mice with normal <i>Kim-1</i> did. Next steps include using the model in preclinical studies focused on preventing loss of glomerular filtration rates and secondary complications. SciBX 6(38); doi:10.1038/scibx.2013.1080 Published online Oct. 3, 2013	Patent applications filed; available for licensing	Humphreys, B.D. <i>et al. J. Clin. Invest.</i> ; published online Aug. 27, 2013; doi:10.1172/JCI45361 Contact: Benjamin D. Humphreys, Brigham and Women's Hospital, Boston, Mass. e-mail: bhumphreys@partners.org

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Imaging			
Combined microscopy system to image tumors during tissue-conserving surgery	A combined autofluorescence and Raman scattering microscopy system could help with the rapid identification of tumor regions during tissue-conserving surgery without a tissue preparation step. The system relies on an automated sampling strategy that uses autofluorescence imaging to select and prioritize areas for Raman spectroscopy. In patient skin tissue samples, the combined system enabled diagnosis of basal cell carcinoma (BCC) regions with 100% sensitivity and 92% specificity. The total time to diagnosis for the combined method was estimated at 20–60 minutes, whereas frozen-section histopathology has a 45–120 minute tissue preparation step plus another 10–15 minute diagnosis step. Next steps could include further optimizing the speed and accuracy of the approach and evaluating it in clinical trials. SciBX 6(38); doi:10.1038/scibx.2013.1081 Published online Oct. 3, 2013	Patent application filed; licensing status unavailable	Kong, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 3, 2013; doi:10.1073/pnas.1311289110 Contact: Ioan Notingher, The University of Nottingham, Nottingham, U.K. e-mail: ioan.notingher@nottingham.ac.uk
Secondary Cherenkov-induced fluorescence imaging (SCIFI) to detect markers of disease activity	Mouse studies suggest SCIFI could help detect and monitor markers of disease activity. SCIFI relies on the interaction between radionuclides and fluorescent nanoparticles, which generates secondary Cherenkov fluorescent signals that can be detected by their signal-to-noise ratios, which are greater than those produced by conventional fluorescent imaging. In mice with breast cancer xenografts, SCIFI selectively and noninvasively visualized tumors bound by both a radiolabeled HER2 (EGFR2; ErbB2; neu) mAb and an integrin $\alpha_v\beta_3$ (CD51/CD61)-binding fluorescent quantum dot. In mice with matrix metalloproteinase 2 (MMP2)-overexpressing tumors, SCIFI visualized MMP2 activity at tumors by detecting the interaction of ^{18}F -labeled fluorodeoxyglucose with a fluorescent nanoparticle activated by cleavage by MMP2. Next steps include toxicity studies of potential imaging agents. SciBX 6(38); doi:10.1038/scibx.2013.1082 Published online Oct. 3, 2013	Findings unpatented; unavailable for licensing	Thorek, D.L.J. <i>et al. Nat. Med.</i> ; published online Sept. 8, 2013; doi:10.1038/nm.3323 Contact: Jan Grimm, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: grimmj@mskcc.org

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