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By *Lauren Martz, Staff Writer*

Researchers at **Virginia Commonwealth University** have found that inhibiting inflammasome formation with antagonists of the membrane receptor P2X7 could help prevent heart failure following acute myocardial infarction.<sup>1</sup> The findings point to a repurposing opportunity for P2X7 antagonists that companies have in the clinic for inflammatory indications.

About one-third of patients with acute myocardial infarction (AMI) go on to develop heart failure.<sup>2</sup> Mechanistically, the lack of blood and nutrient supply to the heart tissues after an AMI triggers inflammation, which ultimately leads to cardiac remodeling and dysfunction.

The precise mechanism of cardiac inflammation following AMI was until recently unknown, and efforts to counter inflammation involved generic inhibition of inflammatory cytokines. Early last year, Japanese researchers first reported that inflammasome formation could be responsible for cardiovascular tissue inflammation following AMI.<sup>3</sup>

The inflammasome is a multiprotein complex formed following activation of P2X7 (purinergic receptor P2X ligand-gated ion channel 7; P2RX7). Inflammasome formation leads to the activation and release of inflammatory mediators including IL-1  $\beta$ -converting enzyme (CASP1), IL-1 $\beta$  and IL-18.

Virginia Commonwealth University (VCU) is running four clinical trials of IL-1 $\beta$  inhibitors in patients with cardiovascular conditions. The inhibitors include Kineret anakinra from **Swedish Orphan Biovitrum AB** and Ilaris canakinumab from **Novartis AG**. However, inhibiting IL-1 $\beta$  only blocks one component of the inflammatory response.

Now, Antonio Abbate, lead scientist on the trials, and colleagues at VCU have uncovered additional features of the inflammasome's role—and location—following AMI (*see Figure 1, "Inflammasome activation pathway"*). Based on this, the researchers concluded that antagonizing P2X7 could be more effective at preventing inflammatory damage and heart failure than blocking IL-1 $\beta$ .

Abbate is assistant professor of medicine in the VCU Department of Internal Medicine and interim director of the Cardiac Intensive Care Unit at the VCU Pauley Heart Center.

In a mouse model of AMI, Abbate's team found that levels of Casp1 mRNA and other inflammasome components were upregulated. Notably, the components of inflammasome activation were found in leukocytes, endothelial cells and cardiomyocytes at the infarct border.

"What is newsworthy about this paper is that they have presented evidence that the cardiac myocytes can form inflammasomes. In the

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context of myocardial infarction, people did not appreciate that the inflammasome formed in this location. The inflammasome produces IL-1 $\beta$ , which we would expect to come from the immune cells infiltrating the myocardium. This is interesting because they are presenting new cell biology and new pathophysiology," said Charles Serhan, director of the Center for Experimental Therapeutics and Reperfusion Injury at **Brigham and Women's Hospital** and professor of anesthesia and dental medicine at **Harvard Medical School**.

In cultured mouse cardiomyocytes, simulation of ischemia induced inflammasome formation, Casp1 activation and cell death compared with no treatment. In the cells, inhibition of P2x7 inhibited Casp1 activity and cell death, suggesting that preventing inflammasome formation in cardiomyocytes could help decrease inflammatory damage following AMI.

In a mouse coronary artery ligation model of AMI, small interfering RNA targeting P2x7 prevented increases in Casp1 activity and lowered cardiac remodeling compared with scrambled siRNA control. In the same model, intraperitoneal administration of a noncompetitive P2X7 antagonist for seven days, beginning five minutes after the procedure, reduced cell death at the ischemic border, cardiac remodeling and cardiac enlargement compared with vehicle control administration.

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

**Taking it from the top**

Because P2X7 is necessary for the formation of the inflammasome and the release of the downstream inflammatory molecules, targeting the receptor could have wider anti-inflammatory effects than targeting IL-1 $\beta$ .

"Anti-IL-1 $\beta$  therapy only blocks a single cytokine that, albeit very important, is by no means the only component of early tissue response to damage or infection. Thus, it would be very important to be able to inhibit inflammasome activity as a whole," said Francesco Di Virgilio, professor of clinical pathology and chairman of the Department of Experimental and Diagnostic Medicine at the **University of Ferrara**.

"The problem here is that the inflammasome complex is intracellular [and] thus not easily accessible," he added. The VCU team might have found a way around this problem because P2X7 is a plasma membrane-expressed molecule.

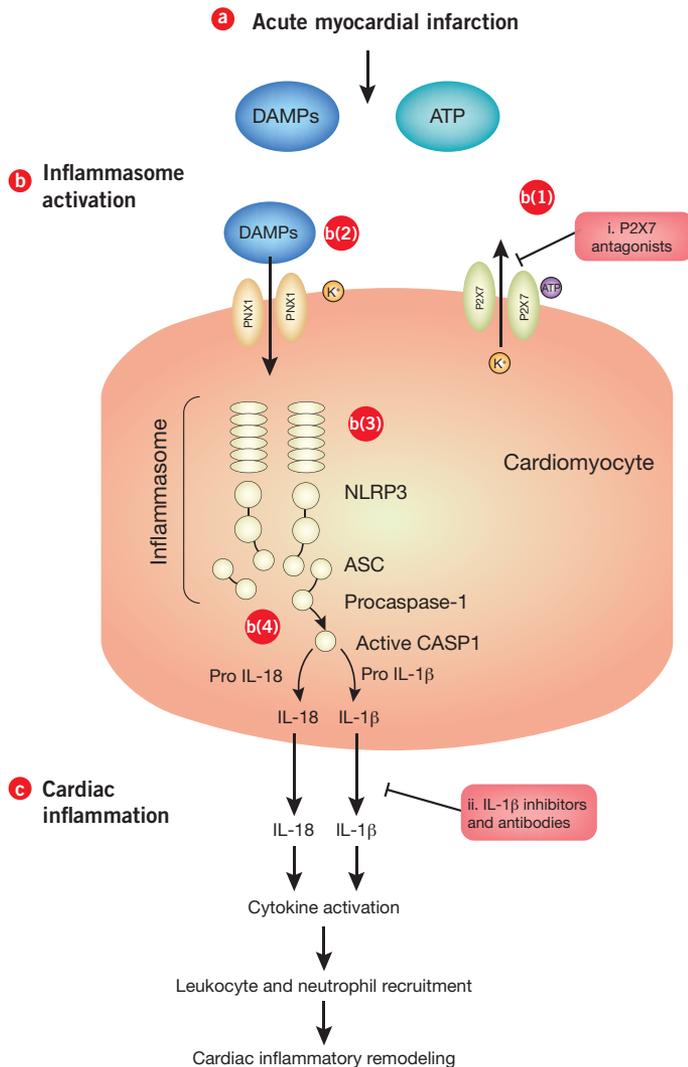
"Since low molecular weight P2X7 inhibitors with very promising drug-like properties are already available, I think that not much more is needed to develop this therapeutic approach, besides careful clinical experimentation," Di Virgilio told SciBX. "Should I decide to test the effect of inflammasome inhibition on post-AMI remodeling, I would target P2X7."

P2X7 antagonists in the clinic include **Evotec AG's** EVT 401, which is in Phase I testing to treat rheumatoid arthritis (RA), and **GlaxoSmithKline plc's** GSK1482160, which is in Phase I testing to treat pain.

Both companies declined to comment on the findings.

**"Since low molecular weight P2X7 inhibitors with very promising drug-like properties are already available, I think that not much more is needed to develop this therapeutic approach, besides careful clinical experimentation."**

**—Francesco Di Virgilio,  
University of Ferrara**



Luc St-Onge, CBO of **Affectis Pharmaceuticals AG**, wanted the VCU team to repeat its studies with a stronger P2X7 antagonist. “One problem is that in the paper, they used a research tool with potency for P2X7 that is not very high,” he said. “Also, the antagonist is nonselective for P2X7 over other purinergic receptors. The team would need to repeat the studies with an antagonist with potencies in the single-digit nanomolar range and with selectivity for the receptor, which would validate that the effects seen in the mouse models were in fact due to blocking activity against P2X7.”

Affectis is developing oral P2X7 antagonists and this year plans to submit an IND for AFC-5128 in neuropathic pain and multiple sclerosis (MS).

Serhan was interested in combining P2X7 inhibitors with other cardiovascular drugs. “I would like to see the effects of a small molecule antagonist used in combination with antiplatelet treatment. Blocking the

**Figure 1. Inflammasome activation pathway.** Acute myocardial infarction (AMI) causes the release of danger signals including damage-associated molecular pattern molecules (DAMPs) and ATP in response to tissue damage, cell death and lack of blood and nutrient supply to the heart [a].

Extracellular ATP activates purinergic receptor P2X ligand-gated ion channel 7 (P2RX7; P2X7), causing the channel to open, resulting in K<sup>+</sup> efflux from the cell [b(1)]. According to the findings from Mezzaroma *et al.*, this process occurs in cardiomyocytes. Extracellular K<sup>+</sup> activates the membrane receptor pannexin 1 (PNX1), opening the channel and allowing transport of DAMPs into the cardiomyocyte [b(2)].

DAMPs serve as direct activating ligands for NLR family pyrin domain containing 3 (NLRP3; NALP3). Activation of NLRP3 induces PYD and CARD domain containing (PYCARD; ASC) recruitment and inflammasome formation [b(3)]. Inflammasome formation causes cleavage of procaspase-1 into IL-1β-converting enzyme (CASP1), causing downstream activation of inflammatory cytokines including IL-1β and IL-18 [b(4)].

Release of IL-1β and other cytokines from cardiomyocytes ultimately induces immune cell recruitment to the heart, inflammation and cardiac remodeling [c].

Mezzaroma *et al.* show that antagonizing P2X7 prevents inflammasome formation and cardiac remodeling (i). IL-1β inhibitors block immune cell recruitment downstream, blocking some cardiovascular inflammation and remodeling (ii).

“Inflammasome formation could further help reduce damage after AMI,” he said.

Abbate said the findings reported in the paper are not patented and are unavailable for licensing.

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Harvard Medical School**, Boston, Mass.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
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# AstraZeneca's compound interest

By Lev Osherovich, Senior Writer

Academics often lament that pharma shelves full of discontinued compounds that could be useful as research tools or therapeutics repurposed for new indications. Now, the U.K.'s **Medical Research Council** has partnered with **AstraZeneca plc** to make the pharma's shelved compounds available to academics investigating basic disease mechanisms.

In December, the Medical Research Council (MRC) put out a call for proposals for its new Mechanisms of Disease grant initiative, which aims to validate proposed disease targets with pharmacological tools and obtain clinical proof of concept for targeting new disease pathways.

AstraZeneca will give academic recipients of the new MRC grants access to 22 discontinued compounds for mechanistic studies in indications beyond the ones for which the compounds were originally developed.

Christopher Watkins, head of translational research at MRC, said the grant program aims to unlock the residual value of AstraZeneca

compounds that are known to be biologically active *in vivo* but have left the pharma's pipeline because of commercial or strategic considerations.

"AstraZeneca has identified compounds that are deprioritized but are incredibly useful in studying mechanisms of human disease," said Watkins. "All of the compounds have already undergone clinical evaluation."

The compounds cover a range of targets including kinases, proteases,

neurotransmitter receptors and ion channels. AstraZeneca has publicly disclosed detailed pharmacological data about all of the compounds, thus giving researchers a sense of what can be done with them at a molecular level.

**"AstraZeneca has identified compounds that are deprioritized but are incredibly useful in studying mechanisms of human disease. All of the compounds have already undergone clinical evaluation."**

**— Christopher Watkins,  
Medical Research Council**

Clive Morris, AstraZeneca's VP of new opportunities, said the agreement gives the pharma a chance to explore alternative uses for its discontinued compounds without spending any money.

"This initiative provides AstraZeneca with access to the best of external science and many ideas that we may not have evaluated internally," said Morris.

AstraZeneca and MRC have formed a joint steering committee to review and select proposals. Watkins said 15–20 projects will receive a total of £10 million (\$15.5 million) in funding, all of which comes from MRC.

The pharma retains all commercial rights to the compounds themselves, but any IP on new uses for these molecules "is likely to be the property of the researchers, with AstraZeneca having the right to negotiate an exclusive license," said Morris.

Morris said the new funding initiative has a wider scope than typical academic-industry partnerships focused on particular disease areas or targets.

"We're calling for proposals to use these compounds as tools across the disease spectrum," noted Watkins.

In 2010, the pharma partnered with MRC's commercial arm, **Medical Research Council Technology** (MRCT), in a more focused project to screen a library of 100,000 AstraZeneca compounds and 50,000 MRCT compounds against 10 undisclosed targets in neurology, cancer, cardiovascular disease and infectious disease. The partners will retain ownership of their respective compounds and plan to negotiate licenses for projects chosen for further development.

In addition, AstraZeneca has partnered with another British biomedical research foundation, **Cancer Research UK**, to discover new targets and biomarkers in oncology.<sup>1</sup>

The next steps for the Mechanisms of Disease grant program is to review preliminary proposals in February.

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Medical Research Council**, London, U.K.  
**Medical Research Council Technology**, London, U.K.

# Fine-tuning mGluRs

By Lev Osherovich, Senior Writer

Studies by two American teams have converged on a family of metabotropic glutamate receptors as players in attention deficit hyperactivity disorder and autism spectrum disorder.<sup>1,2</sup> The findings build an argument for agonizing the receptors in patients with either ADHD or a form of ASD associated with tuberous sclerosis complex and antagonizing the targets to treat a different form of ASD associated with fragile X syndrome.

Determining which patients could benefit from which approach will require new diagnostics.

Metabotropic glutamate receptors (mGluRs) are a family of G protein-coupled receptors that influence the sensitivity of neurons to excitatory signals. Previous human genetic studies implicated mGluR mutations in various neuropsychiatric illnesses including schizophrenia, depression and anxiety.<sup>3</sup> At least 10 companies are developing mGluR modulators for neuropsychiatric and neurodegenerative indications.

The new studies by a consortium led by the **University of Pennsylvania** and **The Children's Hospital of Philadelphia** and a separate team at the **Massachusetts Institute of Technology** suggest that agonizing the receptors could be beneficial for a subset of ADHD and ASD patients.

The consortium led by the UPenn and Children's Hospital researchers ran a genomewide association study and identified deletions and mutations in several *mGluR* genes in ADHD patients. The MIT team used mouse models of two common ASD-associated genetic conditions—fragile X syndrome and tuberous sclerosis complex (TSC)—to test how modulating mGluR signaling affects brain activity and behavior.

## G'day, glutamate

The ADHD study, led by Hakon Hakonarson, associate professor of pediatrics at UPenn and director of the Center for Applied Genomics at Children's Hospital, used high-density microarrays to identify genomic copy number variants that occurred more frequently in patients compared with healthy controls.

Among 2,493 patients with ADHD and 9,222 controls, deletions in the *mGluR5* (*GRM5*) gene were found in 10 ADHD cases and 1 control ( $p=1.36 \times 10^{-6}$ ). Deletions in genes for two related receptors, mGluR7 (*GRM7*) and mGluR8 (*GRM8*), were found in six and eight cases compared with zero controls ( $p=3.52 \times 10^{-6}$  and  $p=8.14 \times 10^{-5}$ , respectively).

Results were published in *Nature Genetics*.

Hakonarson said the findings are in line with previous genomewide association studies that found mGluR mutations in ASD and schizophrenia patients, many of whom also have ADHD.<sup>4</sup>

Although previous studies had implicated mGluRs in neuropsychiatric indications, “nobody has previously shown that

deletions in these genes are significantly associated with ADHD,” said Hakonarson.

He thinks various mGluRs identified by his team could perform similar functions in keeping brain activity in balance, so mutations in any of them could lead to disturbed glutamate signaling and behavior. Thus, it may be possible to correct the defect caused by the mutations in certain mGluRs by agonizing the remaining related functional receptors.

Hakonarson plans to start an investigator-led Phase I ADHD trial of an mGluR agonist his team licensed from an undisclosed Japanese pharma.

He said the compound, which agonizes mGluR5, mGluR7 and mGluR8, previously failed Phase III testing for Alzheimer's disease (AD). The trial is expected to start this year.

Hakonarson's team also is creating cell culture models of ADHD using induced pluripotent stem cells from patients with neuropsychiatric disease who have deletions and duplications in various *mGluR* genes.

Children's Hospital has filed for patents on Hakonarson's findings, and the IP is available for licensing.

**“mGluR7 is the least investigated of these receptors, despite being the most abundant one in the CNS. It's expressed in the key areas involved in emotional reactivity and learning, so it's not surprising to see the genetic link to ADHD.”**

—Mikhail Kalinichev,  
Addex Pharmaceuticals Ltd.

## Up and down

A team led by Mark Bear, professor of neuroscience at MIT, examined the involvement of mGluR5 in mouse models of fragile X syndrome and TSC. Previous work by Bear and others has shown that antagonizing mGluR5 could decrease fragile X electrophysiological and behavioral pathology in mice,<sup>5</sup> but the involvement of glutamate signaling in TSC was unknown.

Bear's team found that brain slices from mice with low levels of tuberous sclerosis complex tumor suppressor 2 (*Tsc2*), a translational regulator that is mutated in some TSC patients, had defective mGluR5 signaling and electrophysiological functioning compared with brain slices of wild-type controls.

Compared with vehicle-treated controls, the TSC mouse brain slices treated with a positive allosteric modulator of mGluR5 had improved brain functioning *in vitro*. Also, TSC mice treated with the compound had less freezing behavior in response to new stimuli, a hallmark of ASD in the animals.

Finally, the team crossed TSC mice, which have too little mGluR5 activity, with fragile X syndrome mice, which have too much. The resulting mice had normal levels of mGluR5 signaling and resembled a wild-type mouse in behavioral assays.

Results were published in *Nature*. The patent and licensing status of Bear's findings is undisclosed.

Altogether, Bear's findings show that imbalanced mGluR activity leads to ASD-like behavior in mice.

The study “shows that you have to operate in a certain zone of mGluR activity, and if you go out of this zone to the left or right, you get an ASD-like phenotype,” said Hakonarson.

The findings “lend support for our basic working hypothesis that optimal brain function and circuit activity are tightly regulated—too

much or too little activity in a particular circuit can get you off balance,” said Randall Carpenter, cofounder, president and CEO of **Seaside Therapeutics Inc.**

Seaside’s STX107, an mGluR5 antagonist, is expected to enter Phase II testing for fragile X syndrome and other forms of ASD in the first half of this year. The company’s lead compound, arbaclofen (STX209), is a GABA<sub>B</sub> receptor antagonist that is in Phase III testing for fragile X syndrome. Bear is a Seaside cofounder.

Carpenter said mGluR5’s newly found roles in TSC and ADHD could broaden the therapeutic opportunities for the target.

**Novartis AG**’s AFQ056 is the most advanced mGluR5 antagonist for fragile X syndrome. The compound is in Phase III testing, and Novartis plans to seek approval this year.

### Common cause?

ASD, ADHD and other psychiatric disorders are often found together in the same patients. The new studies point to common genetic underpinnings for ASD and ADHD, potentially explaining the high comorbidity of these clinically distinct conditions.

In ADHD patients “where there are gene deletions, there’s a case for agonizing the functional copy of the receptor,” said Joseph Buxbaum, a professor of psychiatry, neuroscience, genetics and genomic sciences at **Mount Sinai School of Medicine**. He is a coauthor of Hakonarson’s study.

However, in patients with duplications and polymorphisms that lead to unpredictable effects on mGluR function, “you wouldn’t know whether agonism or antagonism is appropriate,” he said.

Carpenter thinks the next step is to develop diagnostics that determine which patients would benefit from mGluR agonists or antagonists.

He suggested that proteomic or gene expression profiling of mouse models of ASD could identify biomarkers of excessive or insufficient mGluR activity.

“If you could identify proteins that are most increased in the fragile X mouse and are most decreased in the TSC mouse, you could have a profile of peripheral markers” for different forms of the disease, said Carpenter.

Buxbaum noted that it is not yet clear whether abnormalities in mGluR signaling play a role in idiopathic cases of ASD or ADHD, which are far more common than cases of TSC, fragile X syndrome or ADHD associated with mGluR mutations. Thus, he said, it remains to be seen whether modulating mGluRs would be useful in ADHD or ASD patients who do not have mutations in *mGluR* genes.

Whereas Seaside is pursuing mGluR therapeutics for ASD, **Addex Pharmaceuticals Ltd.** is holding off on the indication until it becomes clear which way to modulate the targets.

Addex has a portfolio of mGluR modulators for a range of neurological indications not including ASD or ADHD.

“We don’t have any programs specifically targeting ASD,” said Sonia Poli, head of CNS and nonclinical development at Addex. “We are going for indications where you can get to registration quickly.”

“As a small biotech, we shouldn’t rush to apply these compounds in autism,” said Mikhail Kalinichev, group leader of *in vivo* pharmacology at Addex. “We’re at the early stages of understanding the neurobiological underpinnings and various subpopulations” of ASD.

The company’s most advanced candidates are the Phase II compounds dipraglurant (ADX48621), a negative allosteric modulator of mGluR5 for Parkinson’s disease (PD) and hyperkinetic movement disorder, and ADX1149, a positive allosteric modulator of mGluR2 (GRM2) for schizophrenia that is being developed in partnership with **Johnson & Johnson**.

ADX63365, a positive allosteric modulator of mGluR5, is in preclinical development for schizophrenia and cognitive dysfunction.

Kalinichev and Poli were more convinced about the prospects for using mGluR modulators to treat ADHD, an indication with more clearly defined clinical endpoints than ASD.

In addition to Hakonarson’s human genetic study, “there are preclinical data that link mGluRs to certain models of ADHD, so we were already aware of the relevance” of mGluRs, said Kalinichev.

Kalinichev and Poli think there may be an opportunity to target mGluR7 in ADHD.

“mGluR7 is the least investigated of these receptors, despite being the most abundant one in the CNS,” said Kalinichev. “It’s expressed in the key areas involved in emotional reactivity and learning, so it’s not surprising to see the genetic link to ADHD.”

“We are keen on mGluR7 because there are no other compounds available to target it besides ours,” added Poli. “We have compounds that can potentiate or inhibit its activity.”

Addex has an unnamed negative allosteric modulator of mGluR7 in discovery for depression and post-traumatic stress disorder (PTSD).

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**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
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**Mount Sinai School of Medicine**, New York, N.Y.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**Seaside Therapeutics Inc.**, Cambridge, Mass.  
**University of Pennsylvania**, Philadelphia, Pa.

# Eau de fluorescence

By Joanne Kotz, Senior Editor

Researchers from the **National Cancer Institute** and **The University of Tokyo** have developed a topical fluorescent probe that they have shown can detect residual tumor cells in mice during cancer surgery.<sup>1</sup> The researchers will next validate the method in surgical tissue from ovarian cancer patients before submitting an IND.

The rationale for using fluorescent agents to tag tumor cells during cancer surgery is clear: they improve the efficiency of resection and allow better identification of residual cancer cells that could initiate metastases and might be missed by surgeons relying on the naked eye. The difficulty has been designing the probes.

Most agents in development are systemically delivered and have a lag time on the order of hours to days between when the agent is injected into the patient and when the fluorescent signal can be observed. Another challenge has been achieving a signal-to-noise ratio sufficient to distinguish tumor tissue from normal tissue.

A team led by Hisataka Kobayashi and Yasuteru Urano set out to develop a topical imaging agent that would quickly generate a strong fluorescent signal at tumor sites during surgery.

Kobayashi is chief scientist at NCI's Molecular Imaging Program. Urano is professor in the Laboratory of Chemical Biology and Molecular Imaging at the University of Tokyo.

The first step for the team was finding a tumor-specific enzyme that could be used to activate a topical fluorescent probe. They settled on  $\gamma$ -glutamyltransferase (GGT), which is overexpressed in multiple cancers including ovarian and cervical.

The team next synthesized the actual probe,  $\gamma$ -glutamyl hydroxymethyl rhodamine green (gGlu-HMRG). The probe was engineered to contain a molecular cage that quenches fluorescence. Once the probe comes in contact with the surface of a tumor cell, GGT cleaves the glutamate moiety off the probe, uncaging the probe and triggering a fluorescent signal.

In six xenograft mouse models of disseminated human ovarian cancer, which is characterized by the presence of small metastases throughout the peritoneal cavity, the researchers sprayed gGlu-HMRG onto the peritoneal surface with an endoscopic spray catheter, which is used clinically.

In four of the mice, the probe permitted visualization of tumors as small as 1 mm in diameter within minutes. The metastases were then readily removed with forceps using fluorescence-guided endoscopy.

In the other two mice, no fluorescence above background was observed, suggesting that not all ovarian cancers overexpress GGT.

Data were published in *Science Translational Medicine*.

## Make it fast

The topical probe could be especially useful for procedures in which doctors want to visualize tumors on a limited and accessible surface.

**“Given the broad GGT expression and activity in blood, this technology will likely be restricted to topical applications. That being said, the technology is well suited for topical applications such as intraoperative identification of surface lesions.”**

— **Tito Gonzalez,**  
**Avelas Biosciences Inc.**

“One significant advance of this imaging agent is the ability to visualize tumors within 10 minutes. This fast response opens up more real-time applications, which is exciting,” said Tito Gonzalez, VP and head of R&D at **Avelas Biosciences Inc.**, which develops fluorescence approaches for intraoperative detection of tumors and metastases.

“Given the broad GGT expression and activity in blood, this technology will likely be restricted to topical applications,” Gonzalez noted. “That being said, the technology is well suited for topical applications such as intraoperative identification of surface lesions,” he added.

One possible application for the new probe during surgery could be spraying it on the remaining surface after resecting a tumor, said Gooitzen van Dam, an associate professor and surgical oncologist at **University Medical Center Groningen**.

Instead of looking at the surgical surface after resection, researchers could also look at the resected tissue itself. “After taking tissue out of the patient, you could use the spray on the specimen to see if there is a positive margin” of normal tissue around the excised cancerous tissue, he added.

Van Dam was less convinced that a topical imaging agent would be useful for cancer surgeries in which it is necessary to assess distant lymph node metastases in addition to more localized spreading. As the lymph nodes are not accessible to a topical spray, he believes that a systemic agent would be necessary in these cases.

He added that the procedure may be particularly suited for repeated diagnostic monitoring of premalignant dysplasia for possible cancerous changes. For instance, he suggested that a topical fluorescent agent could be used to look for malignancies during routine dermatology visits.

## Spraying power

The potential limitations of the new probe include tissue penetration, inactivation by an inflammation response and a potentially low signal-to-noise ratio.

“Spraying raises questions as to the homogeneity of the administration and penetration depth. For spraying approaches, diffusion into the tissue is not well controlled,” said Vasilis Ntziachristos, director of the Institute for Biological and Medical Imaging at the **German Research Center for Environmental Health** and chair for biological and medical imaging at the **Technical University Munich**.

“I am very interested in how this will behave if you have much more overlying tissue—will it penetrate well? Also, will it be hampered by an inflammatory response [in] surrounding tissue?” asked van Dam. He added that experiments using human tissue should address his questions.

“One big question will be how GGT activity in human tumors compares to GGT expression in noncancerous human tissue. Hopefully, the background will be as low as has been shown for the mouse,” said Gonzalez.

“A challenge of this approach is how variable enzyme expression levels in different cancer lines result in different fluorescence

responses. I suspect that in less homogenous models the ability to separate cancer from GGT-expressing background tissue will be more challenging,” noted Gonzalez.

The team’s next step will be to evaluate the probe in tissue from ovarian cancer patients.

“We have prepared a clinical protocol for evaluating the efficacy of this probe using fresh surgical ovarian cancer specimens in the surgery room. After this validation, we will prepare and apply for an IND,” said Kobayashi.

The researchers also are exploring the applicability of the probe to other cancers, including cervical, uterine, gastric, hepatic and colon.

Urano told *SciBX* that the University of Tokyo has filed for two patents covering the work. The IP is available for licensing.

Kotz, J. *SciBX* 5(1); doi:10.1038/scibx.2012.4

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1. Urano, Y. *et al. Sci. Transl. Med.*; published online Nov. 23, 2011; doi:10.1126/scitranslmed.3002823

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**University Medical Center Groningen**, Groningen, the Netherlands

**The University of Tokyo**, Tokyo, Japan



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## This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Multiple sclerosis (MS)	DEAD box polypeptide 58 (DDX58; RIG-I); interferon induced with helicase C domain 1 (IFIH1; MDA5)	Mouse studies suggest activating RIG-I or MDA5 could help treat MS. In a mouse model of MS, RNA ligands that activate RIG-I or MDA5 decreased inflammation, myelin damage and disease severity compared with vehicle. Next steps include determining biomarkers and endpoints for a clinical trial of one of the ligands.  <b>SciBX 5(1); doi:10.1038/scibx.2012.5</b> <b>Published online Jan. 5, 2012</b>	Patent applications filed; available for licensing	Dann, A. <i>et al. Nat. Neurosci.</i> ; published online Dec. 4, 2011; doi:10.1038/nn.2964 <b>Contact:</b> Marco Prinz, University of Freiburg, Freiburg, Germany e-mail: <a href="mailto:marco.prinz@uniklinik-freiburg.de">marco.prinz@uniklinik-freiburg.de</a>
Rheumatoid arthritis (RA)	Sphingosine 1-phosphate receptor 1 (S1PR1; S1P1; EDG1)	Mouse studies suggest an S1P1 antagonist might help treat RA and other autoimmune indications. In two mouse models of collagen-induced arthritis, the antagonist suppressed disease or decreased disease severity compared with vehicle. Next steps could include evaluating the S1P1 antagonist in additional autoimmune disease models.  <b>SciBX 5(1); doi:10.1038/scibx.2012.6</b> <b>Published online Jan. 5, 2012</b>	Patent applications filed; licensing status unavailable	Fujii, Y. <i>et al. J. Immunol.</i> ; published online Nov. 30, 2011; doi:10.4049/jimmunol.1101537 <b>Contact:</b> Yasuyuki Fujii, Taisho Pharmaceutical Co. Ltd., Saitama, Japan e-mail: <a href="mailto:y.fujii@po.rd.taisho.co.jp">y.fujii@po.rd.taisho.co.jp</a>
<b>Cancer</b>				
Acute myelogenous leukemia (AML); leukemia	<i>Neuroblastoma Ras viral oncogene (NRAS)</i> ; lysophospholipase I (LYPLA1; APT-1)	Cell culture studies suggest inhibiting APT-1 could help treat mutant <i>NRAS</i> -driven leukemias. In bone marrow cells from AML mice, treatment with a small molecule APT-1 inhibitor decreased the growth of <i>Nras</i> mutant cells compared with no treatment. The inhibitor had no effect on the growth of <i>K-Ras</i> mutant cells. Next steps include testing the inhibitor in mouse models of mutant <i>NRAS</i> -driven leukemia.  <b>SciBX 5(1); doi:10.1038/scibx.2012.7</b> <b>Published online Jan. 5, 2012</b>	Unpatented; licensing status not applicable	Xu, J. <i>et al. Blood</i> ; published online Dec. 5, 2011; doi:10.1182/blood-2011-06-358960 <b>Contact:</b> Kevin Shannon, University of California, San Francisco, Calif. e-mail: <a href="mailto:shannonk@peds.ucsf.edu">shannonk@peds.ucsf.edu</a>
Breast cancer	c-Myc (MYC); SUMO1 activating enzyme subunit 1 (SAE1); ubiquitin-like modifier activating enzyme 2 (UBA2; SAE2)	Patient tissue and mouse studies suggest inhibiting SAE1 and/or SAE2 could help treat MYC-driven breast cancers. In mouse xenograft models of MYC-dependent breast cancer, small hairpin RNA against SAE2 decreased tumor growth compared with control shRNA. In breast cancer patients with high MYC levels, those with low tumor levels of SAE1 and SAE2 had longer metastasis-free survival than patients with high tumor levels of SAE1 and SAE2. Next steps could include testing the effects of blocking SAE1 and SAE2 in other MYC-driven cancers.  <b>SciBX 5(1); doi:10.1038/scibx.2012.8</b> <b>Published online Jan. 5, 2012</b>	Patent and licensing status unavailable	Kessler, J.D. <i>et al. Science</i> ; published online Dec. 8, 2011; doi:10.1126/science.1212728 <b>Contact:</b> Thomas F. Westbrook, Baylor College of Medicine, Houston, Texas e-mail: <a href="mailto:thomasw@bcm.edu">thomasw@bcm.edu</a> <b>Contact:</b> Stephen J. Elledge, Brigham and Women's Hospital, Boston, Mass. e-mail: <a href="mailto:selledge@genetics.med.harvard.edu">selledge@genetics.med.harvard.edu</a>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Breast cancer; bone cancer	Vascular cell adhesion molecule-1 (VCAM-1); integrin $\alpha_4$ (VLA-4; CD49D)	<i>In vitro</i> , mouse and human studies suggest inhibiting VCAM-1 or its receptor VLA-4 could help prevent bone metastases in breast cancer. In patients with breast cancer, higher VCAM-1 levels in primary tumors were associated with earlier relapse. In mouse models of metastatic breast cancer, VCAM-1 small hairpin RNA and antibodies against VCAM-1 and VLA-4 decreased the formation or growth of bone metastases compared with inactive controls. Next steps include testing anti-VLA-4 compounds from undisclosed companies in mouse models of metastatic breast cancer.  Elan Corp. plc and Biogen Idec Inc. market Tysabri natalizumab, a humanized mAb against VLA-4, to treat multiple sclerosis (MS) and Crohn's disease.  Firatragrast, a VLA-4 antagonist from GlaxoSmithKline plc, is in Phase II testing to treat MS.  ELND002, a humanized mAb against VLA-4 from Elan, is in Phase I/II testing to treat MS.  <b>SciBX 5(1); doi:10.1038/scibx.2012.9</b> <b>Published online Jan. 5, 2012</b>	Patented by Princeton University; available for licensing or partnering	Lu, X. <i>et al. Cancer Cell</i> ; published online Dec. 1, 2011; doi:10.1016/j.ccr.2011.11.002 <b>Contact:</b> Yibin Kang, Princeton University, Princeton, N.J. e-mail: <a href="mailto:ykang@princeton.edu">ykang@princeton.edu</a>
Cancer	Checkpoint kinase 1 (Chk1)	Mouse and cell culture studies suggest Chk1 inhibitors should not be combined with histone deacetylase (HDAC) inhibitors to treat cancer. Earlier studies have suggested inhibiting Chk1 could increase HDAC inhibitor efficacy in cancer. In cell culture, a Chk1 inhibitor plus the broad-spectrum HDAC inhibitor Zolinza vorinostat caused abnormal mitosis and apoptosis in both normal and transformed cell lines, whereas either compound alone killed transformed cells but not normal cells. In mice, combined treatment with Chk1 and HDAC inhibitors caused weight loss and abnormal chromosome morphology compared with either agent alone. Next steps include identifying compounds that synergize with HDAC inhibitors.  Partners Merck & Co. Inc. and Otsuka Pharmaceutical Co. Ltd. market Zolinza to treat cutaneous T cell lymphoma (CTCL). Celgene Corp's Istodax romidepsin is an HDAC inhibitor marketed for CTCL and lymphoma.  At least 20 more companies have HDAC inhibitors in development for cancer.  At least six companies have Chk1 inhibitors in various stages of development for cancer.  <b>SciBX 5(1); doi:10.1038/scibx.2012.10</b> <b>Published online Jan. 5, 2012</b>	Unpatented; licensing status not applicable	Lee, J.-H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 21, 2011; doi:10.1073/pnas.1117544108 <b>Contact:</b> Paul A. Marks, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:marksp@mskcc.org">marksp@mskcc.org</a>
Cancer	Thioredoxin; thioredoxin reductases	Mouse studies identified peptidomimetic inhibitors of the thioredoxin reductase pathway that could help treat cancer. In a mouse model of mammary carcinoma, the lead peptidomimetic inhibitor decreased tumor growth compared with vehicle. Next steps could include optimizing the lead inhibitor to improve its potency and pharmacokinetics.  <b>SciBX 5(1); doi:10.1038/scibx.2012.11</b> <b>Published online Jan. 5, 2012</b>	Patent and licensing status unavailable	Kłossowski, S. <i>et al. J. Med. Chem.</i> ; published online Dec. 1, 2011; doi:10.1021/jm201359d <b>Contact:</b> Ryszard Ostaszewski, Medical University of Warsaw, Warsaw, Poland e-mail: <a href="mailto:rysza@icho.edu.pl">rysza@icho.edu.pl</a>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Chronic myeloid leukemia (CML)	MEK; BCR-ABL tyrosine kinase	Cell culture and mouse studies suggest combining Tasigna nilotinib with MEK inhibitors could help treat drug-resistant CML. In cultured leukemia cells, the BCR-ABL inhibitors Tasigna, Gleevec imatinib or Sprycel dasatinib induced MEK pathway activation compared with vehicle control. In a mouse model of drug-resistant CML, Tasigna plus a MEK inhibitor lowered tumor volume compared with either inhibitor alone. Next steps include testing the combination in a clinical trial and identifying the mechanisms behind the effect. Novartis AG markets Gleevec and Tasigna for CML. Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel for CML. At least 10 companies have small molecule MEK inhibitors in Phase III or earlier for cancer.	Unpatented; licensing status not applicable	Packer, L.M. <i>et al. Cancer Cell</i> ; published online Dec. 6, 2011; doi:10.1016/j.ccr.2011.11.004 <b>Contact:</b> Richard Marais, The Institute of Cancer Research, London, U.K. e-mail: <a href="mailto:richard.marais@icr.ac.uk">richard.marais@icr.ac.uk</a>
Prostate cancer	Bone morphogenetic protein 7 (BMP7; OP-1)	Mouse studies suggest BMP7 could help prevent bone metastasis in prostate cancer. In a mouse model of metastatic prostate cancer, BMP7 reduced bone metastasis compared with vehicle. Next steps include planning a clinical trial of BMP7 in prostate cancer patients with bone metastasis and screening for BMP7 mimics. Stryker Corp. markets BMP7 products for long bone nonunion fractures and lumbar spine fusion.	Unpatented; licensing status not applicable	Kobayashi, A. <i>et al. J. Exp. Med.</i> ; published online Nov. 28, 2011; doi:10.1084/jem.20110840 <b>Contact:</b> Kounosuke Watabe, Southern Illinois University School of Medicine, Springfield, Ill. e-mail: <a href="mailto:kwatabe@siu.edu">kwatabe@siu.edu</a>
<b>Cardiovascular disease</b>				
Atherosclerosis	G protein-coupled bile acid receptor 1 (GPBAR1; TGR5)	Mouse studies suggest agonizing TGR5 could help prevent atherosclerosis. In a mouse model of atherosclerosis, the TGR5 agonist INT-777 decreased plaque size and expression of proinflammatory cytokines compared with vehicle control. Next steps could include testing the effect of TGR5 agonists on cardiac function in models of metabolic disease. INT-777, a TGR5 agonist from Intercept Pharmaceuticals Inc., is in preclinical development for metabolic syndrome and diabetes.	Composition-of-matter patents for TGR5-agonizing compounds filed by Intercept Pharmaceuticals; licensing status unavailable	Pols, T.W.H. <i>et al. Cell Metab.</i> ; published online Dec. 7, 2011; doi:10.1016/j.cmet.2011.11.006 <b>Contact:</b> Kristina Schoonjans, Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland e-mail: <a href="mailto:kristina.schoonjans@epfl.ch">kristina.schoonjans@epfl.ch</a>
Atherosclerosis	Rho kinase	<i>In vitro</i> and mouse studies suggest inhibiting rho kinase could help prevent atherosclerosis progression. Hydrogels that modeled the low vessel elasticity of aged individuals had greater vessel permeability than hydrogels that modeled the higher vessel elasticity of younger individuals. In bovine aortic endothelial cells or mouse aortas, pharmacological or small interfering RNA inhibition of rho kinase led to more rho-dependent elasticity and less vessel permeability than no rho kinase inhibition. Next steps include developing an inhibitor of rho kinase and a targeted delivery method. At least nine companies have rho kinase inhibitors in development stages ranging from preclinical to marketed to treat various conditions including aneurysm and glaucoma.	Findings unpatented; unavailable for licensing	Huynh, J. <i>et al. Sci. Transl. Med.</i> ; published online Dec. 7, 2011; doi:10.1126/scitranslmed.3002761 <b>Contact:</b> Cynthia A. Reinhart-King, Cornell University, Ithaca, N.Y. e-mail: <a href="mailto:cak57@cornell.edu">cak57@cornell.edu</a>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Dermatology</b>				
Scars/wrinkles	Focal adhesion kinase (FAK)	<p>Mouse studies suggest topical FAK inhibitors could help prevent dermal scarring. In a mouse model of cutaneous scarring, a topical FAK inhibitor decreased scar formation compared with vehicle. Next steps include identifying new FAK inhibitors and developing drug-eluting dermal hydrogels.</p> <p>CureFAKtor Pharmaceuticals LLC's FAK and VEGF receptor 3 (FLT4; VEGFR-3) inhibitor, CFAK-C4, is in preclinical development for pancreatic cancer.</p> <p>Teva Pharmaceutical Industries Ltd's anaplastic lymphoma kinase (ALK) and FAK inhibitor, CEP-37440, is in preclinical development for multiple cancers.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.16</b> Published online Jan. 5, 2012</p>	Patent application filed; available for licensing	<p>Wong, V.W. <i>et al. Nat. Med.</i>; published online Dec. 11, 2011; doi:10.1038/nm.2574</p> <p><b>Contact:</b> Geoffrey C. Gurtner, Stanford University, Stanford, Calif. e-mail: <a href="mailto:ggurtner@stanford.edu">ggurtner@stanford.edu</a></p>
<b>Endocrine/metabolic disease</b>				
Gaucher's disease	Histone deacetylase (HDAC); glucocerebrosidase (GBA; GCase)	<p><i>In vitro</i> studies suggest HDAC inhibitors could help treat Gaucher's disease. In fibroblasts from patients with Gaucher's disease, the HDAC inhibitor Zolinza vorinostat increased levels of functional GCCase enzyme compared with no treatment. Future studies could include testing HDAC inhibitors in animal models of the disease.</p> <p>Merck &amp; Co. Inc. and Otsuka Pharmaceutical Co. Ltd. market Zolinza to treat cutaneous T cell lymphoma (CTCL).</p> <p>Istodax romidepsin, an HDAC inhibitor from Celgene Corp., is marketed to treat CTCL and lymphoma.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.17</b> Published online Jan. 5, 2012</p>	Patent and licensing status unavailable	<p>Lu, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 12, 2011; doi:10.1073/pnas.1119181109</p> <p><b>Contact:</b> Zhengping Zhuang, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:zhuangp@ninds.nih.gov">zhuangp@ninds.nih.gov</a></p> <p><b>Contact:</b> Roscoe O. Brady, same affiliation as above e-mail: <a href="mailto:bradyr@ninds.nih.gov">bradyr@ninds.nih.gov</a></p>
<b>Infectious disease</b>				
Malaria	PD-1 receptor (PDCD1; PD-1; CD279); programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1); lymphocyte-activation gene 3 (LAG3; CD223)	<p>Patient sample and mouse studies suggest inhibiting PD-L1 and LAG3 could help treat malaria. In mouse models of malaria infection, blocking LAG3 and the PD-1 ligand PD-L1 restored host T cell function and cleared infection compared with blocking each separately. Next steps could include testing the strategy in additional animal models.</p> <p>Immutep S.A.'s anti-LAG3 antibody ImmuTune IMP701 is in preclinical testing for cancer. Immutep and GlaxoSmithKline plc have the anti-LAG3 antibody ImmuTune IMP731 in preclinical testing for transplant.</p> <p>Bristol-Myers Squibb Co. has an anti-PD-1 antibody in Phase I testing to treat solid tumors.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.18</b> Published online Jan. 5, 2012</p>	Patent and licensing status unavailable	<p>Butler, N.S. <i>et al. Nat. Immunol.</i>; published online Dec. 11, 2011; doi:10.1038/ni.2180</p> <p><b>Contact:</b> John T. Harty, The University of Iowa, Iowa City, Iowa e-mail: <a href="mailto:john-harty@uiowa.edu">john-harty@uiowa.edu</a></p>
Malaria; <i>Salmonella</i>	Heme oxygenase decycling 1 (HMOX1; HO-1; Hsp32)	<p>Mouse studies suggest inhibiting HO-1 could protect against <i>Salmonella</i> infection in patients exposed to malaria. In a mouse model of <i>Salmonella</i> infection, animals previously exposed to malaria had greater bacteremia and lower survival than unexposed mice. In previously exposed mice, an HO-1 inhibitor given prior to <i>Salmonella</i> infection decreased bacteremia and increased survival compared with no treatment. Next steps include evaluating an HO-1 inhibitor in additional models of malaria-<i>Salmonella</i> co-infection.</p> <p>OB-24, an HO-1 inhibitor from Osta Biotechnologies Inc., is in preclinical development for prostate cancer.</p> <p>SyB-0702, a polyethylene glycol-conjugated zinc protoporphyrin (PEG-ZnPP) that targets HO-1 from SymBio Pharmaceuticals Ltd., is in preclinical development for solid tumors.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.19</b> Published online Jan. 5, 2012</p>	Unpatented; unavailable for licensing	<p>Cunnington, A.J. <i>et al. Nat. Med.</i>; published online Dec. 18, 2011; doi:10.1038/nm.2601</p> <p><b>Contact:</b> Eleanor M. Riley, London School of Hygiene &amp; Tropical Medicine, London, U.K. e-mail: <a href="mailto:eleanor.riley@lshtm.ac.uk">eleanor.riley@lshtm.ac.uk</a></p>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Musculoskeletal disease</b>				
Muscular atrophy	Guanine nucleotide binding protein (G protein) $\alpha$ -inhibiting activity polypeptide 2 (GNAI2)	<p>Mouse and tissue culture studies suggest increasing GNAI2 signaling could help promote muscle repair and regeneration. In mice, a vector expressing <i>Gnai2</i> increased muscle fiber size and abundance compared with a control vector. In human skeletal muscle myotubules, a vector expressing GNAI2 prevented tumor necrosis factor-<math>\alpha</math> (TNF-<math>\alpha</math>)-induced muscle atrophy, whereas a control vector did not. Next steps could include identifying compounds that could increase GNAI2 signaling and evaluating their effects in animal models of muscular atrophy.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.20</b> Published online Jan. 5, 2012</p>	Patent and licensing status unavailable	<p>Minetti, G.C. <i>et al. Sci. Signal.</i>; published online Nov. 24, 2011; doi:10.1126/scisignal.2002038 <b>Contact:</b> Mara Fornaro, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: <a href="mailto:mara.fornaro@novartis.com">mara.fornaro@novartis.com</a> <b>Contact:</b> David J. Glass, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: <a href="mailto:david.glass@novartis.com">david.glass@novartis.com</a></p>
<b>Neurology</b>				
Alzheimer's disease (AD)	$\beta$ -Amyloid (A $\beta$ )	<p><i>In vitro</i> studies suggest grafted antibodies that recognize AD-associated A<math>\beta</math> fibrils could help treat AD. <i>In vitro</i>, antibodies grafted with amyloidogenic peptide segments of A<math>\beta</math> bound to A<math>\beta</math> fibrils but not to A<math>\beta</math> monomers. In rat neuronal cells treated with A<math>\beta</math> fibrils, the grafted antibodies prevented toxicity compared with no treatment. Next steps include testing whether the antibodies prevent A<math>\beta</math> toxicity in rats and designing and evaluating grafted antibodies against other disease-linked proteins.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.21</b> Published online Jan. 5, 2012</p>	Patent application filed; available for licensing	<p>Perchiacca, J.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 14, 2011; doi:10.1073/pnas.1111232108 <b>Contact:</b> Peter M. Tessier, Rensselaer Polytechnic Institute, Troy, N.Y. e-mail: <a href="mailto:tessier@rpi.edu">tessier@rpi.edu</a></p>
Attention deficit hyperactivity disorder (ADHD)	Metabotropic glutamate receptor subtype 5 (mGluR5; GRM5); mGluR7 (GRM7); mGluR8 (GRM8)	<p>A genomewide association study suggests agonizing mGluR5, mGluR7 or mGluR8 could be useful for treating ADHD. In a study of 2,493 patients with ADHD and 9,222 controls, <i>mGluR5</i> deletions were found in 10 patients and 1 control (<math>p=1.36\times 10^{-6}</math>). Deletions in <i>mGluR7</i> and <i>mGluR8</i> were found in six and eight cases, respectively, and zero controls (<math>p=3.52\times 10^{-6}</math> and <math>p=8.14\times 10^{-3}</math>). Next steps include testing an mGluR5 agonist in ADHD patients.</p> <p>Addex Pharmaceuticals Ltd.'s ADX63365, a positive allosteric modulator of mGluR5, is in preclinical development for cognitive dysfunction and schizophrenia. Seaside Therapeutics Inc. has mGluR5 agonists in discovery for various forms of autism spectrum disorder (ASD; <i>see Fine-tuning mGluRs</i>, page 5).</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.22</b> Published online Jan. 5, 2012</p>	Unpatented; licensing status not applicable	<p>Elia, J. <i>et al. Nat. Genet.</i>; published online Dec. 4, 2011; doi:10.1038/ng.1013 <b>Contact:</b> Hakon Hakonarson, The Children's Hospital of Philadelphia, Philadelphia, Pa. e-mail: <a href="mailto:hakonarson@email.chop.edu">hakonarson@email.chop.edu</a></p>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Autism spectrum disorder (ASD)	Metabotropic glutamate receptor subtype 5 (mGluR5; GRM5)	<p>Studies in mice suggest agonizing mGluR5 may help treat a hereditary form of ASD caused by tuberous sclerosis complex (TSC). In a mouse model of TSC, brain slices showed deficient mGluR5 signaling compared with brain slices from wild-type controls. Treatment with a positive allosteric modulator of mGluR5 increased electrophysiological functioning in brain slices and decreased ASD-like behavior compared with vehicle treatment. Next steps could include additional preclinical development of mGluR5 agonists in preparation for clinical trials in TSC patients.</p> <p>Addex Pharmaceuticals Ltd.'s ADX63365, a positive allosteric modulator of mGluR5, is in preclinical development for cognitive dysfunction and schizophrenia.</p> <p>Seaside Therapeutics Inc., which was cofounded by the corresponding author of this study, has mGluR5 agonists in discovery for various forms of ASD (<i>see Fine-tuning mGluRs</i>, page 5).</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.23</b> Published online Jan. 5, 2012</p>	Patent and licensing status unavailable	<p>Auerbach, B.D. <i>et al. Nature</i>; published online Nov. 23, 2011; doi:10.1038/nature10658</p> <p><b>Contact:</b> Mark F. Bear, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:mbear@mit.edu">mbear@mit.edu</a></p>
<b>Ophthalmic disease</b>				
Corneal wound	Vimentin (VIM)	<p>A study in mice suggests decreasing VIM expression could help reduce fibrosis resulting from corneal wounds. In mice with fibrotic corneal injuries, withaferin A, a small molecule that downregulates VIM, led to greater corneal transparency than vehicle. Next steps include medicinal chemistry optimization of withaferin A for localized and systemic delivery.</p> <p><b>SciBX 5(1); doi:10.1038/scibx.2012.24</b> Published online Jan. 5, 2012</p>	Patent applications filed; licensing status not applicable	<p>Bargagna-Mohan, P. <i>et al. J. Biol. Chem.</i>; published online Nov. 22, 2011; doi:10.1074/jbc.M111.297150</p> <p><b>Contact:</b> Royce Mohan, University of Connecticut Health Center, Farmington, Conn. e-mail: <a href="mailto:mohan@uchc.edu">mohan@uchc.edu</a></p>

## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
High throughput sequencing of tumor tissue to guide clinical trial enrollment	High throughput sequencing of tumor tissue from patients with advanced cancer could help guide clinical trial enrollment. In a patient with refractory metastatic melanoma, sequencing of frozen tumor samples identified 36 point mutations, 269 chromosome amplifications, 24 gene rearrangements and 4 gene fusions, including an activating mutation in <i>v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS)</i> not previously documented in melanoma. The sequencing results suggested the patient could be treated with a combination of MEK and phosphoinositide 3-kinase (PI3K) inhibitors. Next steps include adapting the sequencing approach to work on fixed samples and scaling up to conduct sequencing on 100 patients in 2012.	Unpatented; available for partnering	Roychowdhury, S. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 30, 2011; doi:10.1126/scitranslmed.3003161 <b>Contact:</b> Arul M. Chinnaiyan, University of Michigan, Ann Arbor, Mich. e-mail: <a href="mailto:arul@umich.edu">arul@umich.edu</a>
	<b>SciBX 5(1); doi:10.1038/scibx.2012.25</b> Published online Jan. 5, 2012		
Quantification of minimal residual disease in chronic lymphocytic leukemia (CLL) following hematopoietic stem cell transplant	High throughput measurement of minimal residual disease in CLL following hematopoietic stem cell transplant could improve early intervention to prevent disease relapse. In samples from patients with CLL, the approach showed higher sensitivity for minimal residual disease than a flow cytometry-based technique and did not require the use of patient-specific primers and probes. Next steps include demonstrating the applicability and sensitivity of the screening approach in an undisclosed setting.	Work unpatented; licensing status not applicable	Logan, A.C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 12, 2011; doi:10.1073/pnas.1118357109 <b>Contact:</b> David B. Miklos, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:dmiklos@stanford.edu">dmiklos@stanford.edu</a> <b>Contact:</b> Ronald W. Davis, same affiliation as above e-mail: <a href="mailto:dbowe@stanford.edu">dbowe@stanford.edu</a>
	<b>SciBX 5(1); doi:10.1038/scibx.2012.26</b> Published online Jan. 5, 2012		
Real-time classification of glioma tumors with mass spectrometry-based lipid profiling	A mass spectrometry-based method for profiling lipids in glioma tissue samples could enable classification of brain tumors during surgery. In 36 human glioma samples, mass spectrometry-derived lipid profiles enabled real-time classification by tumor type, tumor grade and tumor cell concentration. Across the tumor sample panel, individual classifications were in 80% agreement with expert histopathological analyses. Ongoing work includes adapting the method for real-time analysis of tumor cell concentrations in surgical tissue samples to help define tumor margins during surgery.	Patent and licensing information available from Partners HealthCare <b>Contact:</b> Sheri Mennillo, Partners HealthCare Research Ventures & Licensing, Boston, Mass. e-mail: <a href="mailto:smennillo@partners.org">smennillo@partners.org</a>	Eberlin, L.S. <i>et al. Cancer Res.</i> ; published online Dec. 2, 2011; doi:10.1158/0008-5472.CAN-11-2465 <b>Contact:</b> Nathalie Y.R. Agar, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:nagar@bwh.harvard.edu">nagar@bwh.harvard.edu</a>
	<b>SciBX 5(1); doi:10.1038/scibx.2012.27</b> Published online Jan. 5, 2012		
<b>Chemistry</b>			
Selective arylation of imidazoles to synthesize Tasigna nilotinib and its analogs	N <sup>1</sup> -selective palladium-catalyzed arylation of imidazoles could be used to synthesize Tasigna nilotinib and its analogs. Synthesis using a preactivated palladium catalyst resulted in more efficient and more selective arylation of imidazoles at the N <sup>1</sup> position than synthesis without preactivation. The method was used to synthesize Tasigna, with each N-arylated precursor and Tasigna itself obtained as a single, site-selective product. Next steps could include using the method to synthesize analogs of Tasigna and other imidazole-based drugs. Tasigna, a BCR-ABL tyrosine kinase inhibitor from Novartis AG, is marketed to treat chronic myelogenous leukemia (CML).	Unpatented; licensing status not applicable	Ueda, S. <i>et al. J. Am. Chem. Soc.</i> ; published online Nov. 29, 2011; doi:10.1021/ja2102373 <b>Contact:</b> Stephen L. Buchwald, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:sbuchwal@mit.edu">sbuchwal@mit.edu</a>
	<b>SciBX 5(1); doi:10.1038/scibx.2012.28</b> Published online Jan. 5, 2012		

## This week in techniques

Approach	Summary	Licensing status	Publication and contact information
<b>Drug platforms</b>			
Prophylactic vaccination with antibody-expressing adenoviral transgenes	An adenoviral vector encoding pathogen-neutralizing antibodies could help prevent viral infections. In a humanized mouse model of HIV infection, prophylactic vaccination with adenoviral gene vectors expressing HIV-neutralizing antibodies prevented CD4 <sup>+</sup> cell depletion compared with vaccination using a control vector. Next steps include planning Phase I trials to examine antibody production levels and safety.  <i>SciBX</i> 5(1); doi:10.1038/scibx.2012.29 Published online Jan. 5, 2012	Patent application filed; available for licensing	Balazas, A.B. <i>et al. Nature</i> ; published online Nov. 30, 2011; doi:10.1038/nature10660 <b>Contact:</b> David Baltimore, California Institute of Technology, Pasadena, Calif. e-mail: <a href="mailto:baltimo@caltech.edu">baltimo@caltech.edu</a>

## CORRIGENDA AND ERRATA

**Erratum: Analysis: Tools**

Baas, T. *SciBX* 4(48); doi:10.1038/scibx.2011.1342  
Published online Dec. 15, 2011

The Analysis item “Picturing pathology” omitted a title for Michael Becich. In addition to being chair of biomedical informatics at the University of Pittsburgh, Becich is also a scientific board member of Omnyx LLC.

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