

THIS WEEK

ANALYSIS

COVER STORY

1 Revving up glycolysis

A trio of papers has provided new hints on how best to use activators of PKM2, a target involved in cancer cell metabolism. Astex is using its findings to steer an early stage PKM2 program, whereas Agios is remaining mum on the direction of its PKM2 program.

TRANSLATIONAL NOTES

4 Mess with Texas

The disintegration of the Cancer Prevention & Research Institute of Texas' scientific board is a lesson in how not to manage perceived conflict between commercial and scientific interests at philanthropic research foundations.

6 From bedside to bench

The recently announced oncology R&D collaboration between Sanofi and Massachusetts General Hospital takes a different tack than most translational research partnerships by starting with insights gleaned from the bedside setting and working their way back to the bench.

TARGETS & MECHANISMS

7 Prime and pull against HSV-2

Yale researchers have mouse data showing that vaginal application of two chemokines recruits memory T cells into vaginal tissue and improves the protective effect of an HSV-2 vaccine. The team is now working to prolong the duration of the chemokines' effects and wants to extend the strategy to HIV prophylaxis.

THE DISTILLERY

9 This week in therapeutics

Treating pancreatic cancer with the water-soluble triptolide analog Minnelide; predicting the risk of doxorubicin-induced cardiomyopathy based on TOP2B expression; diagnosing MMPSI based on activating mutations in *KCNT1*; and more...

15 This week in techniques

Cell-penetrating, DNA-targeting SLE autoantibody for sensitizing cancers to DNA-damaging agents; mutations in fetal lncRNA as a diagnostic marker of HELLP syndrome; plasma levels of the CIZ1 truncated variant to diagnose early stage lung cancer; and more...

INDEXES

16 Company and institution index**16 Target and compound index**

Revving up glycolysis

By Joanne Kotz, Senior Editor

A trio of papers has provided new hints into how best to use small molecule activators of pyruvate kinase M2 isozyme, a cancer metabolism enzyme present nearly universally across tumor types. Based on that research, activating the enzyme might be most effective in tumors with low levels of serine or oxygen.¹⁻³

Pyruvate kinase occurs as two isoforms: *pyruvate kinase M1 isozyme (PKM1)* is expressed by most nonproliferative healthy tissues and *PKM2* is mainly expressed in cancer cells. Both enzymes catalyze the final step in the energy-producing process of glycolysis.

The major difference between PKM1 and PKM2 is that PKM1 is constitutively active, whereas PKM2 has low basal activity that can be fine-tuned up or down by other metabolic and signaling pathways. Although both enzymes convert phosphoenolpyruvate into ATP and pyruvate, the final product of glycolysis, PKM2 does so at a much slower rate than PKM1.

In cancer cells expressing primarily *PKM2*, this results in a bottleneck in the glycolytic pathway that leads to the buildup of intermediate metabolites of glycolysis, which are believed to feed alternative biosynthetic pathways that enhance tumor cell growth and proliferation.

Based on these observations, researchers at **Harvard Medical School** hypothesized that activating PKM2 in cancer could reduce tumor growth. Indeed, a 2008 paper in *Nature* showed that replacing PKM2 in cancer cells with the more active PKM1 decreased tumor formation in mice.⁴

The challenge has been identifying small molecule activators of PKM2.

Now, a team from **The Beatson Institute for Cancer Research** and **Astex Pharmaceuticals Inc.** has identified a previously undescribed allosteric site on PKM2 that binds serine to boost activity of the enzyme.¹ Independently, teams from the **Massachusetts Institute of Technology** and **Agios Pharmaceuticals Inc.** have each identified small molecule activators of PKM2 that bind a distinct allosteric site from the serine binding pocket and have shown that these molecules reduce cancer cell proliferation in combination with particular metabolic stresses.^{2,3}

Because activating PKM2 was only effective in blocking cancer cell growth under very specific metabolic conditions, the key next step will be identifying cancer subtypes or combination treatments that elicit a similar metabolic stress to sensitize tumors to the PKM2 activators.

Agios has a preclinical-stage program targeting PKM2 in cancer, and Astex has a discovery-stage program targeting PKM2 in cancer.

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SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

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The serine link

The Beatson-Astex team first knocked down both pyruvate kinase isoforms in colon cancer cells to see which metabolic biosynthesis pathways were affected. In cancer cells with reduced glycolysis, flux through the serine biosynthetic pathway was increased.

The team next asked if there was pathway feedback from serine biosynthesis back to glycolysis. Growing the cancer cells in serine-depleted media, which causes the cells to upregulate serine biosynthesis, decreased glycolytic activity compared with growing cells in serine-rich media.

Finally the team looked to see whether serine might directly connect the two pathways. Indeed, serine bound to PKM2 *in vitro* and activated enzyme activity. Crystallographic experiments showed that serine bound at a previously undescribed pocket.

Thus, serine is a direct connection between the two pathways. When serine levels are low, PKM2 activity is low and metabolites are shunted into the serine biosynthesis pathway. When serine levels are high, the metabolite activates PKM2, which increases glycolysis and decreases serine biosynthesis.

The results identify a site that can be targeted to activate PKM2 and also suggest that activating PKM2 when serine levels are low might short-circuit an adaptive tumor response.

Results were reported in *Nature*.

Activation energy

Teams led by Agios and MIT researchers started with a small molecule activator of PKM2 and looked for metabolic conditions in which the activating molecule lowered cancer cell proliferation.

The Agios team, led by Senior Director of Biochemistry Lenny Dang, ran a high throughput screen and medicinal chemistry optimization to identify a small molecule activator of PKM2.

In a lung cancer cell line, the PKM2 activator reduced production of serine, suggesting that flow through the glycolysis and serine biosynthesis pathways were linked.

Thus, the Agios team looked directly at the impact of amino acid availability on the anticancer activity of its PKM2 activator. The molecule decreased cancer cell proliferation when the cells were grown in media lacking serine but not when the cells were grown in serine-replete media.

An MIT team led by Matthew Vander Heiden also explored the conditions under which boosting PKM2 activity affected cancer cell growth. To do this, the team turned to TEPP-46, a small molecule activator of PKM2 it identified in 2010.⁵ Vander Heiden is an assistant professor of biology at MIT.

Similar to what Agios found, the effects of the MIT team's PKM2 activator depended on cell growth conditions. TEPP-46 decreased cancer cell proliferation under hypoxic conditions but not under aerobic conditions.

The Agios and MIT molecules both activated PKM2 by binding at the subunit interface—a different site from where serine binds.

Finally, the MIT team asked if the PKM2 activator would reduce tumor growth *in vivo*. In a xenograft mouse model of lung cancer, TEPP-46 increased tumor latency and decreased tumor size compared with vehicle.

The MIT results were published in *Nature Chemical Biology*. Agios reported its findings in *Chemistry & Biology*.

“My take-home from this is that the degree of PKM2 activity can set a cancer cell in an ATP-producing state that is not conducive to growth. When PKM2 activity is high, cells do not engage in growth-promoting metabolism, and this state is tumor suppressive,” said Vander Heiden, who sits on Agios’ scientific advisory board.

He cautioned that tumor suppression is distinct from shrinking existing tumors.

Vander Heiden added that “in cancer metabolism, we are still trying to understand the critical metabolic nodes that cancer cells depend on.

These studies suggest PKM2 may be a key controller in some cases, but we still do not know which tumors will be more sensitive. The emerging connection to serine may be one avenue for figuring out which patients might respond.”

“The big challenge with cancer metabolism targets to date is that none have had a sufficiently dramatic effect in preclinical models to be exciting enough to take forward—and that’s the case with PKM2. There are effects, but they are small. This is likely because there are homeostatic mechanisms to guard against just this kind of pathway perturbation,” said Neil Thompson, SVP of biology at Astex.

Thus, Thompson thinks treating cancer with small molecules that modulate metabolic pathways will likely require either a tumor genetic alteration or combination treatment that overrides these homeostatic mechanisms.

Putting PKM2 into context

Vander Heiden’s group is now testing the effects of PKM2 activators in genetically engineered mouse cancer models and asking if the molecules are effective against existing tumors and if there is differential sensitivity across different tumor models.

Eyal Gottlieb, who was co-lead of the *Nature* study, suggested that combining PKM2 activators with serine uptake blockers might be the way to go. Gottlieb is a group leader in apoptosis and tumor metabolism at Beatson.

“The good news is that you don’t need to deplete serine completely; it is enough to partially deplete it, and there is one high-affinity serine receptor that could be targeted by a small molecule or an antibody,” said Gottlieb.

Thompson told *SciBX* that “ideally, a genetic selection strategy” would be the way to go for patient stratification, adding that “the best-characterized genetic alterations that confer serine deficiency are in breast cancer.”

Alternatively, he said a combination strategy that compromises serine biosynthesis might be an option.

Astex has found activators that bind at several distinct sites, but

Thompson said the serine site is particularly interesting.

The company has also identified inhibitors of PKM2. “In our thinking we’ve always felt that inhibitors could be as good as activators but would require targeting tumors with a different metabolic footprint—tumors that have a high dependence on the glycolytic pathway,” he added.

TEPP-46 was discovered under a collaboration between MIT and the NIH. The NIH holds issued composition-of-matter patents covering this molecule and an additional PKM2 activator series. The IP is available for licensing.

“In cancer metabolism, we are still trying to understand the critical metabolic nodes that cancer cells depend on. These studies suggest PKM2 may be a key controller in some cases, but we still do not know which tumors will be more sensitive.”

—Matthew Vander Heiden,
Massachusetts Institute of Technology

Agios declined to discuss its PKM2 program, but Dang did say that “PKM2 is still important in our cancer metabolism research portfolio.”

Agios’ lead programs target isocitrate dehydrogenase 1 (IDH1) and IDH2, which are mutated in various cancers and lead to increased production of the oncogenic metabolite 2-hydroxyglutarate

Dynamix Pharmaceuticals Ltd. has a small molecule PKM2 activator, DNX-3000, in preclinical development for cancer.

Kotz, J. *SciBX* 5(43); doi:10.1038/scibx.2012.1127
Published online Nov. 1, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

Agios Pharmaceuticals Inc., Cambridge, Mass.
Astex Pharmaceuticals Inc., Dublin, Calif.
The Beatson Institute for Cancer Research, Glasgow, U.K.
Dynamix Pharmaceuticals Ltd., Rehovot, Israel
Harvard Medical School, Boston, Mass.
Massachusetts Institute of Technology, Cambridge, Mass.
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Mess with Texas

By Lev Osherovich, Senior Writer

The public spat between the scientific board and management of the **Cancer Prevention & Research Institute of Texas** is a case study in how commercial and scientific interests can clash when the two sides are not on the same page about how grants are distributed. The lesson is that academic grant reviewers need to be aware of a foundation's commercial development priorities in any proposal-vetting process.

The Cancer Prevention & Research Institute of Texas (CPRIT) is a publicly funded agency tasked with financing basic and translational cancer research and cancer prevention initiatives in the state of Texas.¹ According to its charter, the organization has a broad remit to spend \$3 billion over 10 years “to develop therapies, protocols, medical pharmaceuticals or procedures for the cure or substantial mitigation of all types of cancer.”

Since 2009, CPRIT has spent about \$760 million on 427 grants to Texas academics, community health organizations and companies, the latter of which received 11 of these grants (see Table 1, “CPRIT’s commercial portfolio”).

According to CPRIT’s rules, proposals are separated into three tracks—research, prevention and commercialization—with separate review councils that evaluate them according to distinct criteria.

Each review council selects projects to recommend for approval by CPRIT’s governing board of 11 political appointees, who can in principle veto recommendations with a supermajority vote.

The Commercialization Review Councilors can informally consult their counterparts on the Scientific Review Council but have the ultimate say about which proposals to recommend for approval to CPRIT’s governing board.

In May, CSO Alfred Gilman announced his intention to resign from CPRIT and publicly complained to the general media that CPRIT’s

management was interfering in the scientific review process.² Gilman, emeritus professor of pharmacology at **The University of Texas Southwestern Medical Center**, helped build CPRIT’s Scientific Review Council and its network of academic peer reviewers who evaluate research-track proposals.

At issue was a \$20 million commercialization-track grant to the Houston-Area Translational Research Consortium (HATRC), a biotech incubator at **Rice University** and **The University of Texas MD Anderson Cancer Center**’s Institute for Applied Cancer Science. Gilman said CPRIT’s management fast-tracked HATRC despite the science panel’s reservations about the incubator’s scientific merits.

Gilman also said that CPRIT retaliated against its own scientific advisors by delaying the funding of some academic grants to UT Southwestern researchers.

In response to Gilman’s concerns, MD Anderson withdrew its application for HATRC’s funding.

Gilman and CPRIT’s management initially agreed to work together to address his concerns. Last month, however, Gilman resigned his post, as did all 8 members of CPRIT’s Scientific Review Council and 29 of about 140 peer reviewers.

Out with a bang

In an October op-ed piece in the *Houston Chronicle*, Gilman and former CPRIT Scientific Review Council chairman Phillip Sharp called for an investigation into what they said were conflicts of interest of CPRIT’s administrators.³

Sharp is an institute professor in the Koch Institute for Integrative Cancer Research at the

Massachusetts Institute of Technology.

CPRIT executive director Bill Gimson said the agency acted according to its charter.

He told *SciBX* that commercialization-track proposals like HATRC are evaluated according to different criteria than research-track grants to academic researchers and that weighing the commercial potential of HATRC independently of its scientific merit was in line with CPRIT’s policy.

“There is a natural tension between the academic and commercial world, at least in some quarters. The majority of our scientific reviewers are steeped in the NIH review process, and they’re not used to a commercial due diligence process.”

—Bill Gimson,
Cancer Prevention & Research
Institute of Texas

Table 1. CPRIT’s commercial portfolio. The Cancer Prevention & Research Institute of Texas (CPRIT) has issued about \$760 million in funding to academic researchers, community health organizations and 11 companies in the state of Texas. Listed below are the company grants.

Recipient	Program	Funding (\$M)
Cell Medica Ltd.	Company relocation and recruitment	15.6
Caliber Biotherapeutics LLC	Biobetter cancer mAbs	12.8
Peloton Therapeutics Inc.	Company formation, recruitment and relocation	11.0
Molecular Templates Inc.	Engineered Toxin Bodies (ETBs) as cancer therapeutics	10.6
Mirna Therapeutics Inc.	Cancer treatment including drug discovery, development and clinical trials	10.3
Kalon Biotherapeutics LLC	Formation of the Texas Cancer Therapeutics Process Development Lab	7.9
Pulmotect Inc.	Expanding the market and success rates for myeloablative cancer treatments using PUL-042, an innate immune stimulant	7.1
Asuragen Inc.	Mutation profiling for cancer personalized medicine using next-generation sequencing	6.8
Bellicum Pharmaceuticals Inc.	Clinical development of CaspaCIDE cell therapy	5.7
Apollo Endosurgery Inc.	Medical devices to treat cancerous lesions in the gastrointestinal tract	5.0
Rules-Based Medicine Inc.	Cancer biology and genetics research using genomics and proteomics	3.0

The problem with the HATRC proposal arose because “Dr. Gilman thought that it should have had a science review on the academic side of the house,” said Gimson.

However, Gimson maintained that because the HATRC proposal came in on the commercialization track, the advice of the Scientific Review Board was nonbinding. The apparent unwillingness of both parties to budge from these positions led to Gilman’s resignation.

Gilman declined to discuss the matter with *SciBX*.

Texas hold ‘em

Several CPRIT scientific reviewers stated in resignation letters that CPRIT’s administration had pressed for re-evaluation of proposals rejected by the scientific reviewers but championed by commercial reviewers. Such a practice created the impression of favoritism, according to the former scientific reviewers.

Gimson said re-evaluation of commercialization-track proposals in light of new data and disclosures by companies was a normal part of CPRIT’s review process. He said requests by commercial reviewers for scientific reviewers to re-evaluate proposals arose because of the back-and-forth dialogue between industry applicants and CPRIT’s commercialization review board that is part of CPRIT’s due diligence.

“New information was sent back to the researchers for reassessment. We did that in good faith to make sure that all the peer reviewers were looking at all the same information,” said Gimson.

Gimson said the vetting of commercial projects is more rigorous than that of academic projects. He thinks misunderstandings by scientific reviewers of CPRIT’s commercialization-track vetting process were due in part to differences in the culture of academic peer review and business due diligence.

He said scientific reviewers expected commercialization-track grant proposals to be structured like NIH grant proposals, in which all data are disclosed and reviewed up front. In contrast, the due diligence process used by industry dealmakers involves gradual disclosure of information through dialogue.

“There is a natural tension between the academic and commercial world, at least in some quarters,” said Gimson. “The majority of our scientific reviewers are steeped in the NIH review process, and they’re not used to a commercial due diligence process.”

As CPRIT rebuilds its scientific board in the coming year, Gimson plans to bring new reviewers up to speed on the agency’s back-and-forth process with commercial applicants.

“If I could do things differently in the case of the [HATRC] incubator, we would have brought the academic and commercial reviewers together at an earlier point. This would potentially have avoided the questions raised by our CSO about whether this was a commercial or purely scientific process,” he said.

Gimson said that HATRC plans to resubmit its proposal, once again on the commercialization track, later this year.

California dreaming

At least one other taxpayer-funded agency—the **California Institute for Regenerative Medicine** (CIRM)—sees the CPRIT saga as a cautionary tale in avoiding conflicting interests.

CIRM, which was created by a statewide bond measure in 2004, aims to distribute \$3 billion over 10 years to California academic researchers and companies to develop stem cell technologies and therapies.

“I think that whenever public funding is involved you have to be extremely sensitive to anything you do that might in any way be perceived as a conflict of interest or as playing favorites,” said Jonathan Thomas, CIRM’s governing board chair.

Thomas said that in CIRM’s review process, grant proposals first are vetted by internal scientific staff, then evaluated by an independent panel of scientific experts from outside of California and finally approved by CIRM’s Independent Citizen’s Oversight Committee, a 27-member panel of industry experts, academics and patient advocates.

Unlike CPRIT, CIRM has a common track for evaluating commercial and academic proposals, and all components of the evaluation process are open to the public under California’s sunshine laws, which require CIRM’s committee meetings to be held in public. In evaluating commercially oriented proposals, “the emphasis is on the strength of the science,” said Thomas.

Thus, he thinks the internal conflict behind CPRIT’s schism is unlikely to happen at CIRM.

Last week, CIRM awarded \$10.1 million to **ViaCyte Inc.** for preclinical development of VC-01, a cell-based therapy for type 1 diabetes. The grant adds to the \$20 million that ViaCyte received from CIRM in 2009.

Also last week, **bluebird bio Inc.** received \$9.3 million from CIRM for a Phase I/II trial of LentiGlobin gene therapy for β -thalassemia.

Osherovich, L. *SciBX* 5(43); doi:10.1038/scibx.2012.1128
Published online Nov. 1, 2012

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COMPANIES AND INSTITUTIONS MENTIONED

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California Institute for Regenerative Medicine, San Francisco, Calif.
Cancer Prevention & Research Institute of Texas, Austin, Texas
Massachusetts Institute of Technology, Cambridge, Mass.
Rice University, Houston, Texas
The University of Texas MD Anderson Cancer Center, Houston, Texas
The University of Texas Southwestern Medical Center, Dallas, Texas
ViaCyte Inc., San Diego, Calif.

From bedside to bench

By Kai-Jye Lou, Staff Writer

The recently announced oncology R&D collaboration between **Sanofi** and **Massachusetts General Hospital** takes a different tack than most translational research partnerships, as the two parties are starting with insights gleaned from the bedside setting and are working their way back to the bench. The partners have formed teams to take on joint projects that will help formulate and test new hypotheses on how to best position the pharma's cancer therapeutics and design the associated clinical programs.

Under the deal, Sanofi and three labs at the **Massachusetts General Hospital Cancer Center** will work together for at least two years on joint projects. The partners will share scientific expertise, R&D capabilities and resources. Financial details are undisclosed.

"We've set up joint teams cochaired by lead scientists from Sanofi and MGH that will work together on projects to define what the translational roadmap should be for Sanofi's early stage candidates," said Donald Bergstrom, head of global translational and experimental medicine at Sanofi.

The pharma initially is bringing two molecules that have come out of its discovery labs along with some preliminary data suggesting the molecules could have utility for treating advanced tumors, including those that are intrinsically resistant or refractory to current drugs. The molecules go after new, undisclosed targets.

Bergstrom said the two compounds have key unaddressed translational questions, such as the ideal patient population to target and whether the therapeutics will be able to show clear evidence of benefit in the targeted population.

To address these questions and others, Sanofi needed preclinical models that faithfully recapitulated clinical scenarios in which the compounds could be applied. Bergstrom said this is where MGH comes in.

"What MGH scientists bring to this collaboration are their clinical insights and their expertise in translating such insights into preclinical models," Bergstrom told *SciBX*. "We chose to collaborate with MGH

because we saw that the scientists were not only taking their work from bench to bedside but also taking information from the bedside back to the bench by developing preclinical models to recapitulate the issues they see in the clinic."

Such models, he said, include those that recapitulate drug resistance and refractory tumors seen in patients.

Insights and opportunities

Bergstrom noted that the first goal of the R&D collaboration is to obtain better insights on how to position and develop Sanofi's early stage candidates. The other goal, he said, is to have the collaboration itself serve as a foundation for future translational partnerships with other parties.

In terms of milestones, the pharma wants to have data by next year that will either support or refute the case for developing an early stage candidate in a particular clinical setting.

Bergstrom said the preclinical translational models being developed at MGH will be used to both define and test hypotheses on how to develop a candidate.

"The teams will meet every two weeks to review project data and, if needed, modify current R&D roadmaps to better fit the new data," he added. "We will also constantly look at the project data for information on whether to continue developing a compound under an existing hypothesis or to develop it under a new hypothesis."

Bergstrom said the key criteria that will determine whether the collaboration gets extended are if Sanofi sees the collaboration as productive and whether the collaboration generates additional questions and hypotheses that need to be followed up on.

"I do think that there will be hypotheses that emerge from the projects that lead to extensions of existing research projections as well as to new research directions," he told *SciBX*.

Bergstrom said both Sanofi and MGH are incented to generate new IP under the collaboration. He declined to provide details.

Lou, K.-J. *SciBX* 5(43); doi:10.1038/scibx.2012.1129
Published online Nov. 1, 2012

COMPANIES AND INSTITUTIONS MENTIONED

Massachusetts General Hospital, Boston, Mass.

Massachusetts General Hospital Cancer Center, Boston, Mass.

Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

"We chose to collaborate with MGH because we saw that the scientists were not only taking their work from bench to bedside, but also taking information from the bedside back to the bench by developing preclinical models to recapitulate the issues they see in the clinic."

**—Donald Bergstrom,
Sanofi**

Prime and pull against HSV-2

By Michael J. Haas, Senior Writer

Yale School of Medicine researchers have mouse data showing that vaginal application of two chemokines recruits memory T cells into vaginal tissue and improves the protective effect of an HSV-2 vaccine.¹ The team is now working to prolong the duration of the chemokines' effects and wants to extend the strategy to HIV prophylaxis.

Memory T cells circulate freely throughout many organs of the body but cannot enter vaginal mucosae—and certain other tissues such as skin and lung airways—until recruited by chemokines in response to inflammation or infection. This mechanism restricts the ability of memory T cells induced by vaccines to reach and protect vaginal tissues prior to viral infection, thus blunting efficacy.

In 2009, a group of Yale researchers led by Akiko Iwasaki uncovered a potential way around the tissue entry roadblock. They showed in mice that vaginal infection with herpes simplex virus-2 (HSV-2) induced local expression of two chemokines—chemokine CXC motif ligand 9 (Cxcl9; Mig) and Cxcl10 (Ip-10). Those two chemokines recruited T cells expressing CXC chemokine receptor 3 (Cxcr3) into vaginal tissue.²

These findings led the researchers to hypothesize that they could improve the prophylactic effects of an HSV-2 vaccine by harnessing signaling between CXCL9 or CXCL10 and CXCR3.

In the new study, the group first looked at whether CXCL9 and CXCL10 could recruit virus-specific T cells to the vagina in the absence of infection. The team injected mice with HSV-2-specific human CD8⁺ T cells and inoculated the animals with a subcutaneous HSV-2 vaccine to induce expansion of those T cells.

Indeed, topical application of CXCL9 and CXCL10 to the vaginal tract increased levels of the virus-specific T cells compared with no chemokine treatment. The effect lasted for at least 12 weeks.

Next, the team investigated whether inoculation with an HSV-2 vaccine followed by topical application of the two chemokines to the vaginal tract—a strategy they dubbed prime and pull—would protect mice from HSV-2 infection. Mice receiving lethal vaginal challenge with the virus at 4 or 12 weeks after prime and pull had fewer symptoms of infection, lower viral titers in peripheral dorsal root ganglia and longer survival than mice given the vaccine alone.

Lastly, the team showed that topical application of CXCL9 and CXCL10 to the vaginal tract did not recruit other immune cells to the tissue or induce a local or systemic inflammatory response.

Iwasaki is professor of immunology and of molecular, cellular and developmental biology at the Yale School of Medicine. She conducted the study with Haina Shin, a postdoctoral fellow in her immunology research group.

Data were reported in *Nature*.

“The concept of giving chemokines or cytokines to develop and strengthen the immune response to vaccines is not new, but systemic administration of the molecules leads to unacceptable side effects such as pain, inflammation and cell damage,” said Gregory Stoloff, founder and CEO of **Seek Ltd.** “The Yale researchers have taken a different route

by applying the chemokines topically—thereby avoiding or reducing side effects—and showing that the molecules can penetrate the skin and vaginal wall to call T cells to the site.”

He added that the study “reinforces the idea that stimulating T cells and getting them into vaginal tissues before infection is possible and has a greater protective effect” than vaccination alone.

Seek's HIV-v, a T and B cell vaccine targeting the Nef, Rev, Vif and Vpr noncapsid HIV proteins, has completed Phase Ib/II testing to treat HIV.

Jessica Baker Flechtner, VP of research at **Genocea Biosciences Inc.**, agreed. “This is an innovative strategy to efficiently target the right cells to the right place at the right time,” she said.

Genocea's GEN-003, a vaccine consisting of the infected cell polypeptide 4 (ICP4) and gD2 antigens from HSV-2 combined with the saponin-derivative adjuvant Matrix M, is in Phase I/IIa testing to treat patients with moderate to severe HSV-2 infection who are otherwise healthy.

Past strategies aimed at achieving the same objective included intravaginal—rather than intramuscular—vaccination and applying a chemical pull signal to the genital mucosa without an initial prime vaccination. “Neither approach appears to have been as successful as that proposed by these authors,” she said.

As examples, she cited imiquimod and the related compound resiquimod, “which likely have no direct antiviral effect but instead promote antigen-specific T helper type 1 immunity when administered topically.”

Meda AB and **Medicis Pharmaceutical Corp.** market Aldara imiquimod, a 5% imiquimod cream that agonizes toll-like receptor 7 (TLR7), to treat genital warts, actinic keratosis and basal cell carcinoma (BCC).

In 2003, **3M Co.** and **Eli Lilly and Co.** suspended three Phase III trials of resiquimod—an immune response modifier that agonizes TLR7 and TLR8—to treat genital herpes after preliminary data showed that the doses used would not achieve adequate efficacy.

Pushing limits

Both Flechtner and Stoloff said the prime and pull strategy faces several logistical obstacles that could limit its clinical application.

For example, Flechtner said the two-part immunization regimen would require two clinic visits within a precise window of time to be effective and thus could run into compliance issues.

Both she and Stoloff said specialized training might be needed to ensure proper administration of the chemokine pull. The team “might benefit from discussing the strategy with primary care physicians to determine how something like this may be implemented in practice,” Flechtner said.

“Another problem is that the T cells won't remain in the restricted tissues for more than a few months,” Stoloff told *SciBX*. “So you couldn't apply a topical formulation of the chemokines and expect the effects to last four or five years. To keep the memory T cells in the vaginal tissues, you would have to apply the chemokines every six months or so, and unfortunately this is not practical.”

Lisa Wei, head of HSV research at **GenVec Inc.**, agreed. The team's study “demonstrates the potential for a single vaccination with a chemokine pull to confer about three months of protection,” but further

studies will have to determine whether prime and pull can boost vaginal mucosal immunity in humans and if so, for how long, she said.

GenVec's HSV-2, a vaccine to prevent and treat HSV-2 infection, is in preclinical testing.

Iwasaki acknowledged that it was not clear yet how long human vaginal tissues would retain T cells recruited by the chemokines. "But even if we assume long-term T cell residency is not sustained in humans, we have ways to deliver chemokines locally over a long period," such as the vaginal rings that are already being used to deliver contraceptives, she said.

"We hope to extend the strategy to males in the future because—in principle—topical application of chemokines could establish memory T cells in the male genital tract."

—Akiko Iwasaki,
Yale School of Medicine

Iwasaki also said her group is developing techniques to help retain memory T cells in vaginal tissue for a very long time "or perhaps even for the lifetime of the animal or human." Details on the techniques are undisclosed.

The team also is testing the prime and pull strategy to prevent HIV infection in nonhuman primates.

"We also wish to understand whether prime and pull can be used to treat reactivation of HSV-2" and thus prevent recurrence of the disease in the genital tissues, she said. "We hope to extend the strategy to males in the future because—in principle—topical application of chemokines could establish memory T cells in the male genital tract."

Yale University has filed a provisional patent covering the findings, and the IP is available for licensing.

Haas, M.J. *SciBX* 5(43); doi:10.1038/scibx.2012.1130
Published online Nov. 1, 2012

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1. Shin, H. & Iwasaki, A. *Nature*; published online Oct. 17, 2012; doi:10.1038/nature11522
Contact: Akiko Iwasaki, Yale School of Medicine, New Haven, Conn.
2. Nakanishi, Y. *et al. Nature* **462**, 510–513 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

3M Co. (NYSE:MMM), St. Paul, Minn.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Genocea Biosciences Inc., Cambridge, Mass.
GenVec Inc. (NASDAQ:GNVC), Gaithersburg, Md.
Meda AB (SSE:MEDAA), Solna, Sweden
Medicis Pharmaceutical Corp. (NYSE:MRX), Scottsdale, Ariz.
Seek Ltd., London, U.K.
Yale School of Medicine, New Haven, Conn.
Yale University, New Haven, Conn.

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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
Autoimmune disease				
Psoriasis	IL-1 receptor-like 2 (IL1RL2; IL-36R)	<p>Mouse studies suggest antagonizing IL-36R could help treat psoriasis. In a mouse model of psoriasis, knocking out <i>Il-36r</i> protected mice from psoriasis symptoms and decreased recruitment of inflammatory macrophages and neutrophils compared with what was seen in wild-type controls. Knocking out the <i>Il-36 receptor antagonist</i> (<i>IL36RN</i>; <i>IL-1F5</i>) led to a more severe disease phenotype. Next steps could include developing IL-36R antagonists.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1131 Published online Nov. 1, 2012</p>	Patent and licensing status unavailable	<p>Tortola, L. <i>et al. J. Clin. Invest.</i>; published online Oct. 15, 2012; doi:10.1172/JCI63451 Contact: Manfred Kopf, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: manfred.kopf@ethz.ch</p>
Cancer				
Acute myelogenous leukemia (AML)	FMS-like tyrosine kinase 3 (FLT3; CD135); aurora kinases	<p><i>In vitro</i> and mouse studies identified inhibitors of aurora kinases and FLT3 that could help treat AML. In enzymatic assays, an optimized imidazole[4,5-<i>b</i>]pyridine-based compound inhibited activity of aurora kinases and FLT3 with nanomolar K_d values. In mice with mutant <i>FLT3</i>-expressing human AML xenografts, oral treatment with the inhibitor blocked tumor growth and caused tumor regression, whereas vehicle treatment did not. Ongoing work includes additional preclinical formulation and toxicology studies.</p> <p>At least nine companies have FLT3 inhibitors in clinical and preclinical testing to treat cancers.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1132 Published online Nov. 1, 2012</p>	Covered by issued and filed patent applications; unavailable for licensing	<p>Bavetsias, V. <i>et al. J. Med. Chem.</i>; published online Oct. 8, 2012; doi:10.1021/jm300952s Contact: Julian Blagg, The Institute of Cancer Research, London, U.K. e-mail: julian.blagg@icr.ac.uk</p>
Cancer	Checkpoint kinase 1 (Chk1)	<p>Mouse studies identified a Chk1 inhibitor that could help treat cancer. In a transgenic mouse model of neuroblastoma, oral treatment with the lead Chk1 inhibitor, CCT244747, decreased tumor burden compared with vehicle. In a mouse xenograft model of human colon cancer, CCT244747 plus chemotherapy decreased tumor growth better than chemotherapy alone. Next steps could include optimization of the lead Chk1 inhibitor and IND-enabling studies.</p> <p>At least four companies have Chk1 inhibitors in preclinical or clinical development to treat cancer.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1133 Published online Nov. 1, 2012</p>	Patent and licensing status undisclosed	<p>Lainchbury, M. <i>et al. J. Med. Chem.</i>; published online Oct. 19, 2012; doi:10.1021/jm3012933 Contact: Ian Collins, The Institute of Cancer Research, Sutton, U.K. e-mail: ian.collins@icr.ac.uk</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Pyruvate kinase M2 isozyme (PKM2)	<p><i>In vitro</i> and cell culture studies identified a serine-binding, allosteric activation site on PKM2 that could be targeted to help inhibit tumor growth. Activating PKM2 has previously been shown to reduce tumor growth in mice, and serine deprivation has been linked to glycolysis, which is a hallmark metabolic pathway in cancer cells. In serine-starved colon cancer cells, adding serine increased PKM2 activity and increased glycolysis. <i>In vitro</i>, serine bound a previously undescribed pocket on PKM2 and enhanced the enzyme's activity. Next steps could include designing drug-like small molecule activators that bind the allosteric site.</p> <p>Astex Pharmaceuticals Inc. has a discovery-stage program targeting PKM2.</p> <p>Agios Pharmaceuticals Inc. has a preclinical-stage program targeting PKM2 in cancer.</p> <p>Dynamix Pharmaceuticals Ltd.'s PKM2 activator, DNX-3000, is in preclinical development to treat cancer (<i>see Revving up glycolysis, page 1</i>).</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1134 Published online Nov. 1, 2012</p>	Unpatented; licensing status not applicable	<p>Chaneton, B. <i>et al. Nature</i>; published online Oct. 14, 2012; doi:10.1038/nature11540</p> <p>Contact: Eyal Gottlieb, Cancer Research UK and The Beatson Institute for Cancer Research, Glasgow, U.K. e-mail: e.gottlieb@beatson.gla.ac.uk</p> <p>Contact: Marc O'Reilly, Astex Pharmaceuticals Inc., Cambridge, U.K. e-mail: marc.oreilly@astx.com</p>
Melanoma	IL-9	<p>Mouse studies suggest IL-9-producing T helper type 9 (Th9) cells could help treat melanoma. In a mouse model of melanoma, an IL-9-neutralizing antibody increased susceptibility to developing lung metastasis compared with IgG control. In the mouse melanoma model, adoptive transfer of Th9 cells led to smaller tumors than transfer of Th1 cells or vehicle. Next steps could include evaluating the adoptive transfer of Th9 cells in additional cancer models.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1135 Published online Nov. 1, 2012</p>	Patent and licensing status unavailable	<p>Lu, Y. <i>et al. J. Clin. Invest.</i>; published online Oct. 15, 2012; doi:10.1172/JCI65459</p> <p>Contact: Qing Yi, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: qyi@mdanderson.org</p>
Pancreatic cancer	Unknown	<p>Mouse studies identified a water-soluble triptolide analog that could help treat pancreatic cancer. Triptolide is a plant-derived compound with anticancer effects that has limited clinical utility due to its poor water solubility. In mouse xenograft models of pancreatic cancer, oral treatment with the water-soluble triptolide analog, dubbed Minnelide, decreased tumor volumes and increased survival with an effect comparable to that of triptolide. In a mouse xenograft model of pancreatic cancer, Minnelide decreased tumor burden compared with Gemzar gemcitabine. Next steps include starting a Phase I trial to evaluate the Minnelide in pancreatic cancer.</p> <p>Eli Lilly and Co. markets the nucleoside analog Gemzar to treat pancreatic and other cancers.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1136 Published online Nov. 1, 2012</p>	Patent application filed; licensed to Minneamrita Therapeutics LLC	<p>Chugh, R. <i>et al. Sci. Transl. Med.</i>; published online Oct. 17, 2012; doi:10.1126/scitranslmed.3004334</p> <p>Contact: Ashok K. Saluja, University of Minnesota, Minneapolis, Minn. e-mail: asaluja@umn.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Small cell lung cancer (SCLC)	Aurora kinase B (AURKB; aurora-B); c-Myc (MYC)	<p>A cell screening study suggests aurora-B inhibitors could help treat SCLCs with <i>MYC</i> amplification. A screen of 267 small molecules across 44 SCLC cell lines identified genomic alterations that resulted in sensitivity to small molecule aurora-B inhibitors. In <i>MYC</i>-amplified SCLC cell lines, aurora-B inhibitors led to apoptosis, mitochondrial membrane potential collapse and cell-cycle arrest. In SCLC lines without <i>MYC</i> amplification, aurora-B inhibitors did not induce such effects. Next steps could include testing aurora-B inhibitors in patients with <i>MYC</i>-amplified SCLC.</p> <p>Corresponding author Roman Thomas has cofounded cancer genomics company Blackfield AG. At least four companies have aurora-B inhibitors in preclinical or clinical development to treat cancer.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1137 Published online Nov. 1, 2012</p>	Unpatented; licensing status not applicable	<p>Sos, M.L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 3, 2012; doi:10.1073/pnas.1207310109 Contact: Roman K. Thomas, University of Cologne, Cologne, Germany e-mail: roman.thomas@uni-koeln.de Contact: Martin L. Sos, University of California, San Francisco, Calif. e-mail: martin.sos@ucsf.edu</p>
Cardiovascular disease				
Atherosclerosis	MicroRNA-155 (miR-155)	<p><i>In vitro</i> and mouse studies suggest inhibiting miR-155 could help treat atherosclerosis. In an <i>apolipoprotein E (ApoE)</i>-deficient mouse model of atherosclerosis, <i>miR-155</i> knockout decreased plaque size and macrophage numbers in atherosclerotic lesions compared with <i>miR-155</i> expression. Next steps could include testing miR-155 inhibitors in additional models of atherosclerosis.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1138 Published online Nov. 1, 2012</p>	Patent and licensing status unavailable	<p>Nazari-Jahantigh, M. <i>et al. J. Clin. Invest.</i>; published online Oct. 8, 2012; doi:10.1172/JCI61716 Contact: Andreas Schober, Ludwig Maximilian University of Munich, Munich, Germany e-mail: aschober@med.lmu.de</p>
Cardiomyopathy	Topoisomerase II β (TOP2B)	<p>Mouse studies suggest TOP2B expression could help predict the risk of doxorubicin-induced cardiomyopathy. Cardiomyocytes from doxorubicin-treated mice with cardiac-specific <i>Top2b</i> deficiency showed lower DNA damage responses and apoptosis and greater mitochondrial biosynthesis and function than cardiomyocytes with normal <i>Top2b</i> expression. In mice with cardiac-specific <i>Top2b</i> deficiency, doxorubicin induced no change in left ventricular ejection fraction, a clinical measure of cardiomyopathy, whereas the drug decreased ejection fractions in wild-type controls. Ongoing work includes determining whether TOP2B expression correlates with cardiomyopathy in patients treated with doxorubicin.</p> <p>SciBX 5(43); doi:10.1038/scibx.2012.1139 Published online Nov. 1, 2012</p>	<p>Patented by The University of Texas MD Anderson Cancer Center; available for licensing Contact: Natalie Wright, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: nwright@mdanderson.org</p>	<p>Zhang, S. <i>et al. Nat. Med.</i>; published online Oct. 28, 2012; doi:10.1038/nm.2919 Contact: Edward T.H. Yeh, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: etyeh@mdanderson.org</p>

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Endoplasmic reticulum to nucleus signaling 1 (ERN1; IRE1)	An SAR study identified small molecule modulators of IRE1 that could be useful for treating type 2 diabetes. IRE1 has both kinase and endonuclease activities that are overactive in type 2 diabetes. <i>In vitro</i> and in cell culture, one class of IRE1 modulators decreased the protein's kinase activity but increased its endonuclease activity compared with vehicle control. A second class of compounds inhibited both the kinase and endonuclease activity of IRE1. Next steps include testing compounds from the two classes in cell culture and mouse models of type 2 diabetes and dyslipidemia. MannKind Corp. has compounds that inhibit IRE1 activity in preclinical development to treat multiple myeloma (MM). Ruga Corp. has an inhibitor of IRE1 activity in preclinical development for the same indication. SciBX 5(43); doi:10.1038/scibx.2012.1140 Published online Nov. 1, 2012	Patent pending; available for licensing	Wang, L. <i>et al. Nat. Chem. Biol.</i> ; published online Oct. 21, 2012; doi:10.1038/nchembio.1094 Contact: Dustin J. Maly, University of Washington, Seattle, Wash. e-mail: maly@chem.washington.edu Contact: Feroz R. Papa, University of California, San Francisco, Calif. e-mail: frpapa@medicine.ucsf.edu
Infectious disease				
HBV	B cell lymphoma 2 (BCL-2; BCL2); Bcl-x _L	Worm and cell culture studies suggest inhibiting BCL2-family proteins could help treat HBV infection. In the <i>Caenorhabditis elegans</i> roundworm, the HBV protein HBx was shown to interact with a BCL2 homolog and triggered both necrotic and apoptotic cell death. In human hepatocyte cells, HBx bound to BCL2 and Bcl-x _L and triggered cell death. In hepatocytes, small hairpin RNA against BCL2 or Bcl-x _L led to less HBV DNA replication than control shRNA. Next steps could include evaluating pharmacological inhibitors of BCL2-family proteins in models of HBV infection. At least 13 companies have compounds that target BCL2 family proteins in Phase II testing or earlier to treat various cancers. SciBX 5(43); doi:10.1038/scibx.2012.1141 Published online Nov. 1, 2012	Patent and licensing status unavailable for findings from both studies	Geng, X. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 22, 2012; doi:10.1073/pnas.1204668109 Contact: Ding Xue, University of Colorado at Boulder, Boulder, Colo. e-mail: ding.xue@colorado.edu Contact: Ning-Shao Xia, Xiamen University, Xiamen, China e-mail: nsxia@xmu.edu.cn Geng, X. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 22, 2012; doi:10.1073/pnas.1204652109 Contact: Ding Xue, University of Colorado at Boulder, Boulder, Colo. e-mail: ding.xue@colorado.edu
Neurology				
Alzheimer's disease (AD); schizophrenia	Nicotinic acetylcholine receptor $\alpha 7$ (CHRNA7)	Rodent studies identified a CHRNA7 agonist that could help treat cognitive impairment associated with AD and schizophrenia. In rats, the agonist decreased markers of schizophrenia compared with vehicle. In rats, the agonist also increased memory. Siena Biotech S.p.A. is not disclosing next steps, which could include testing the lead compound in additional rodent models of AD and schizophrenia. At least five companies have CHRNA7 agonists in Phase II testing or earlier to treat AD or schizophrenia. SciBX 5(43); doi:10.1038/scibx.2012.1142 Published online Nov. 1, 2012	Patented; available for licensing from Siena Biotech	Zanaletti, R. <i>et al. J. Med. Chem.</i> ; published online Oct. 19, 2012; doi:10.1021/jm3013568 Contact: Riccardo Zanaletti, Siena Biotech S.p.A, Siena, Italy e-mail: riccardozanaletti@hotmail.com

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Encephalopathy	Potassium channel subfamily T member 1 (KCNT1)	Genetic studies suggest activating mutations in <i>KCNT1</i> could help diagnose malignant migrating partial seizures of infancy (MMPSI). Exome sequencing studies of 12 patients with MMPSI, identified mutations in <i>KCNT1</i> in 6 patients but not in their unaffected parents or in 200 unaffected controls. In <i>Xenopus laevis</i> oocytes, rat <i>Kcnt1</i> with the disease-associated mutations was a constitutively active ion channel, whereas wild-type rat <i>Kcnt1</i> was not. Next steps could include studies in additional patients. SciBX 5(43); doi:10.1038/scibx.2012.1143 Published online Nov. 1, 2012	Patent and licensing status unavailable	Barcia, G. <i>et al. Nat. Genet.</i> ; published online Oct. 21, 2012; doi:10.1038/ng.2441 Contact: Rima Nabbout, Necker Hospital–Hospital for Sick Children, Paris, France e-mail: rimanabbout@yahoo.com
Parkinson's disease (PD)	Chemokine CX3C motif ligand 1 (CX3CL1; fractalkine)	Mouse studies suggest the soluble isoform of CX3CL1 could help treat PD. In a mouse model of chemical-induced PD, substantia nigra injection of an adeno-associated viral vector expressing soluble <i>Cx3cl1</i> decreased the loss of dopaminergic neurons and increased motor coordination compared with injection of a vector expressing the membrane-bound <i>Cx3cl1</i> isoform. Next steps could include testing soluble CX3CL1 in additional models of neuroinflammation and neurodegeneration. SciBX 5(43); doi:10.1038/scibx.2012.1144 Published online Nov. 1, 2012	Patent and licensing status unavailable	Morganti, J.M. <i>et al. J. Neurosci.</i> ; published online Oct. 17, 2012; doi:10.1523/JNEUROSCI.0539-12.2012 Contact: Paula C. Bickford, University of South Florida, Tampa, Fla. e-mail: pbickfor@health.usf.edu
Pulmonary disease				
Pulmonary fibrosis	Amphiregulin (AREG); epidermal growth factor receptor 1 (EGFR1; HER1; ErbB1); transforming growth factor- β 1 (TGFB1)	<i>In vitro</i> and mouse studies suggest inhibiting AREG-EGFR1 signaling could help treat idiopathic pulmonary fibrosis (IPF). In the lungs of patients with IPF, TGFB1 levels were greater than those in lungs of healthy individuals. In a mouse fibroblast cell line, human and mouse TGFB1 upregulated Areg, which activated Egfr1 and increased proliferation compared with vehicle. In a transgenic <i>TGFB1</i> -expressing mouse model of pulmonary fibrosis, <i>AREG</i> small interfering RNA or an EGFR1 inhibitor decreased collagen accumulation and pulmonary fibrosis compared with a scrambled siRNA or vehicle. Ongoing work includes investigating expression of AREG in serum and tissues from patients with IPF and other fibrotic diseases. At least 16 companies market inhibitors of EGFR or EGFR1 to treat various cancers. SciBX 5(43); doi:10.1038/scibx.2012.1145 Published online Nov. 1, 2012	Patented by Yale University and Bioneer Corp.; available for licensing	Zhou, Y. <i>et al. J. Biol. Chem.</i> ; published online Oct. 19, 2012; doi:10.1074/jbc.M112.356824 Contact: Chun Geun Lee, Yale School of Medicine, New Haven, Conn. e-mail: chungeun.lee@yale.edu
Renal disease				
Renal damage	Adenosine A ₂ receptor (ADORA ₂)	<i>In vitro</i> and mouse studies suggest ADORA ₂ agonist-treated dendritic cells (DCs) could help treat acute kidney injury. Mice with <i>Adora₂</i> ^{-/-} DCs showed greater susceptibility to kidney injury than mice with DCs deficient in other adenosine receptors. In wild-type mice, ADORA ₂ agonist-treated DCs given before or 1–6 hours after kidney injury protected kidney function, whereas untreated DCs did not. Next steps could include optimizing the cell-based therapy protocol. Addex Therapeutics Ltd.'s A2A PAM, a positive allosteric modulator of ADORA ₂ , is in discovery stages to treat psoriasis and osteoarthritis. SciBX 5(43); doi:10.1038/scibx.2012.1146 Published online Nov. 1, 2012	Patent and licensing status unavailable	Li, L. <i>et al. J. Clin. Invest.</i> ; published online Oct. 24, 2012; doi:10.1172/JCI63170 Contact: Li Li, University of Virginia, Charlottesville, Va. e-mail: ll3m@virginia.edu

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Various				
Autoimmune disease; inflammation; rheumatoid arthritis (RA)	CC chemokine receptor 1 (CCR1; CD191)	<i>In vitro</i> and mouse studies identified CCR1 antagonists that could help treat inflammation in RA and other diseases. Chemical synthesis, SAR and <i>in vitro</i> testing of 4-(4-chlorophenyl)piperidine analogs identified multiple compounds as selective nanomolar antagonists of CCR1. In a human monocyte chemotaxis assay, one of the lead compounds inhibited cell migration with a low nanomolar IC ₅₀ value. In mice, the compound showed good bioavailability and pharmacokinetics. Future studies could include testing the lead compound in animal models of RA. CCX354, a small molecule CCR1 antagonist from ChemoCentryx Inc. and GlaxoSmithKline plc, has completed Phase II testing to treat RA. <i>SciBX</i> 5(43); doi:10.1038/scibx.2012.1147 Published online Nov. 1, 2012	Patent and licensing status undisclosed	Cavallaro, C.L. <i>et al.</i> <i>J. Med. Chem.</i> ; published online Oct. 17, 2012; doi:10.1021/jm300896d Contact: Cullen L. Cavallaro, Bristol-Myers Squibb Co., Princeton, N.J. e-mail: cullen.cavallaro@bms.com



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This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Cell-penetrating, DNA-targeting systemic lupus erythematosus (SLE) autoantibody 3E10 for sensitizing cancers to DNA-damaging agents	<i>In vitro</i> and mouse studies suggest lupus autoantibodies targeting DNA could help sensitize tumors to DNA-damaging agents. In human breast cancer and glioma cells and in a mouse xenograft model of human glioma, the DNA-targeting SLE autoantibody 3E10 plus ionizing radiation or doxorubicin increased cell death and tumor suppression compared with radiation or doxorubicin alone. In DNA binding assays, 3E10 bound single-stranded DNA and inhibited DNA repair. In cancer cells with <i>breast cancer 2 early onset (BRCA2)</i> mutations that impair DNA-damage responses, 3E10 alone showed cytotoxicity. Next steps include identifying tumor types most sensitive to the autoantibody. SciBX 5(43); doi:10.1038/scibx.2012.1148 Published online Nov. 1, 2012	Patent application filed covering use of cell-penetrating autoantibodies to treat cancer; available for licensing	Hansen, J.E. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 24, 2012; doi:10.1126/scitranslmed.3004385 Contact: Peter M. Glazer, Yale School of Medicine, New Haven, Conn. e-mail: peter.glazer@yale.edu
Markers			
Mutations in fetal long noncoding RNA (lncRNA) as a diagnostic marker of hemolysis, liver enzymes and low platelets (HELLP) syndrome	Human and <i>in vitro</i> studies suggest fetal lncRNA mutations could help diagnose HELLP syndrome in pregnant women. Genomic analysis of patients with HELLP syndrome and unaffected family members identified associations between the syndrome in the mother and multiple SNPs on an lncRNA on fetal chromosome 12q23.2. In a human trophoblast cell line expressing wild-type lncRNA, antisense against lncRNA sites corresponding to several of the SNPs decreased the cells' invasive capacity, mimicking a clinical feature of HELLP syndrome, compared with inactive control antisense. Ongoing work includes investigating whether fetal lncRNA is detectable in maternal plasma. SciBX 5(43); doi:10.1038/scibx.2012.1149 Published online Nov. 1, 2012	Unpatented; available for partnering	van Dijk, M. <i>et al. J. Clin. Invest.</i> ; published online Oct. 24, 2012; doi:10.1172/JCI65171 Contact: Cees B.M. Oudejans, VU University Medical Center, Amsterdam, the Netherlands e-mail: cbm.oudejans@vumc.nl
Plasma levels of the CDKN1A interacting zinc finger protein 1 (CIZ1) truncated variant to diagnose early stage lung cancer	Patient sample and mouse studies suggest plasma levels of truncated CIZ1 could help diagnose early stage lung cancer. In plasma samples from 40 patients with stage 1 lung cancer and 120 controls, an antibody targeting truncated CIZ1 identified the cancers with 95% accuracy and up to 74% specificity. In mouse xenograft models of human lung cancer, small hairpin RNA targeting the truncated CIZ1 decreased tumor cell proliferation compared with control shRNA. Next steps include developing a high throughput quantitative immunoassay. SciBX 5(43); doi:10.1038/scibx.2012.1150 Published online Nov. 1, 2012	Findings patented by Cizzle Biotechnology Ltd.; available for licensing	Higgins, G. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 16, 2012; doi:10.1073/pnas.1210107109 Contact: Dawn Coverley, The University of York, Yorkshire, U.K. e-mail: dawn.coverley@york.ac.uk

Company and institution index

3M Co.	7	N	National Institutes of Health	3	CCR1	14	IL-36R	9
A		P			CCT244747	9	<i>IL-36 receptor antagonist</i>	9
Addex Therapeutics Ltd.	13	Peloton Therapeutics Inc.	4	CD8	7	<i>IL36RN</i>	9	
Agios Pharmaceuticals Inc.	1,10	Pulmotect Inc.	4	CD135	9	Imidazole[4,5- <i>b</i>]pyridine	9	
Apollo Endosurgery Inc.	4	R		CD191	14	Imiquimod	7	
Astex Pharmaceuticals Inc.	1,10	Rice University	4	CDKN1A interacting zinc		Infected cell polypeptide 4	7	
Asuragen Inc.	4	Ruga Corp.	12	finger protein 1	15	Ip-10	7	
B		Rules-Based Medicine Inc.	4	Checkpoint kinase 1	9	IRE1	12	
Beatson Institute for		S		Chemokine CX3C motif		Isocitrate dehydrogenase 1	3	
Cancer Research	1	Sanofi	6	ligand 1	13	K		
Bellicum Pharmaceuticals Inc.	4	Seek Ltd.	7	Chemokine CXC motif		KCNT1	13	
Bioneer Corp.	13	Siena Biotech S.p.A.	12	ligand 9	7	L		
Blackfield AG	11	U		Chk1	9	LentiGlobin	5	
bluebird bio Inc.	5	University of Texas MD		CHRNA7	12	M		
C		Anderson Cancer Center	4,11	CIZ1	15	Matrix M	7	
Caliber Biotherapeutics LLC	4	University of Texas		c-Myc	11	MicroRNA-155	11	
California Institute for		Southwestern Medical Center	4	CX3CL1	13	Mig	7	
Regenerative Medicine	5	V		CXC chemokine receptor 3	7	Minnelide	10	
Cancer Prevention & Research		ViaCyte Inc.	5	Cxcl9	7	miR-155	11	
Institute of Texas	4	Y		Cxcl10	7	MYC	11	
Cell Medica Ltd.	4	Yale School of Medicine	7	Cxcr3	7	N		
ChemoCentryx Inc.	14	Yale University	8,13	D		Nef	7	
Cizzle Biotechnology Ltd.	15		DNX-3000	3,10	Nicotinic acetylcholine		
D		Target and compound index		Doxorubicin	11,15	receptor $\alpha 7$	12	
Dynamix Pharmaceuticals		2-Hydroxyglutarate	3	E		P		
Ltd.	3,10	3E10	15	EGFR	13	Phosphoenolpyruvate	1	
E		4-(4-Chlorophenyl)piperidine	14	EGFR1	13	PKM1	1	
Eli Lilly and Co.	7,10	A		Endoplasmic reticulum to		PKM2	1,10	
G		A2A PAM	13	nucleus signaling 1	12	Potassium channel		
Genocea Biosciences Inc.	7	Adenosine A ₂ receptor	13	Epidermal growth factor		subfamily T member 1	13	
GenVec Inc.	7	ADORA ₂	13	receptor 1	13	PUL-042	4	
GlaxoSmithKline plc	14	Aldara	7	ErbB1	13	Pyruvate	1	
H		Amphiregulin	13	ERN1	12	Pyruvate kinase M1 isozyme	1	
Harvard Medical School	1	<i>ApoE</i>	11	F		Pyruvate kinase M2 isozyme	1,10	
K		<i>Apolipoprotein E</i>	11	FLT3	9	R		
Kalon Biotherapeutics LLC	4	AREG	13	FMS-like tyrosine kinase 3	9	Resiquimod	7	
M		ATP	1	Fractalkine	13	Rev	7	
MannKind Corp.	12	AURKB	11	G		S		
Massachusetts General		Aurora-B	11	gD2	7	Serine	1,10	
Hospital	6	Aurora kinase	9	Gemcitabine	10	T		
Massachusetts General		Aurora kinase B	11	Gemzar	10	TEPP-46	2	
Hospital Cancer Center	6	B		GEN-003	7	TGFB1	13	
Massachusetts Institute of		B cell lymphoma 2	12	H		TLR7	7	
Technology	1,4	BCL-2	12	HBx	12	TLR8	7	
Meda AB	7	BCL2	12	HER1	13	Toll-like receptor 7	7	
Medicis Pharmaceutical Corp.	7	Bcl-x _L	12	HIV-v	7	TOP2B	11	
Minneamrita Therapeutics		<i>BRCA2</i>	15	HSV-2	8	Topoisomerase II β	11	
LLC	10	<i>Breast cancer 2 early onset</i>	15	I		Transforming growth		
Mirna Therapeutics Inc.	4	C		ICP4	7	factor- $\beta 1$	13	
Molecular Templates Inc.	4	CaspaCIDE	4	IDH1	3	Triptolide	10	
		CC chemokine receptor 1	14	IDH2	3	V		
				<i>IL-1F5</i>	9	VC-01	5	
				IL-1 receptor-like 2	9	Vif	7	
				IL1RL2	9	Vpr	7	
				IL-9	10			