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Killer targets in metastasis

By Amy Donner, Senior Editor

An international team has found a new pathway in NK cells that leads to the rejection of metastatic tumors.¹ It is still unclear which components of the pathway will make the best targets.

The pathway centers around an E3 ubiquitin ligase called casitas B cell lymphoma-b (CBL-B) that is known to negatively regulate T cells.² In 2007, a group led by Josef Penninger showed that *Cbl-b* knockout resulted in CD8⁺ T cell-mediated tumor rejection in several mouse models.³

In the following years, the group pursued strategies to target Cbl-b in T cells and understand the mechanism of Cbl-b activity in T cells. In a new study, an international team led by Penninger observed a curious result—*Cbl-b* knockouts that lacked T cells also rejected tumors. Penninger is senior scientist and scientific director of the **Institute of Molecular Biotechnology of the Austrian Academy of Sciences**.

That finding prompted Penninger to hypothesize that Cbl-b also must be operational elsewhere in the immune system and led his group to uncover NK cells as the mysterious other cell type in a CBL-B-dependent pathway that suppresses activity (see **Figure 1, “Strategies to activate antitumor NK cells”**).

“Since NK cells are known to be involved in rejection of metastasis, we asked whether CBL-B is a brake in NK cells, limiting their ability to kill metastatic tumors,” said Penninger.

In cultured mouse and human NK cells, knockout of *CBL-B* or RNAi against the target increased tumor cell killing compared with no treatment.

In a mouse xenograft model of melanoma, *Cbl-b* knockout or expression of an inactive *Cbl-b* variant in place of the wild-type enzyme increased survival compared with wild-type *Cbl-b* expression. Immunodepletion of NK cells reduced survival, indicating that Cbl-b negatively regulates the antitumor activity of NK cells.

In mouse models of metastatic melanoma and breast cancer, *Cbl-b* knockout decreased lung metastasis compared with wild-type *Cbl-b* expression. Transplantation of *Cbl-b* knockout NK cells into wild-type mice decreased lung metastasis compared with transplantation of wild-type NK cells or no treatment, demonstrating that the *Cbl-b* knockout NK cells were responsible for the antimetastatic effect.

The authors next set out to identify substrates for CBL-B. “We screened more than 9,000 proteins to find targets for the E3 ligase activity of CBL-B,” said Penninger. “We found TAM receptors.”

TAM receptors are a small family of receptor tyrosine kinases that include TYRO3 protein tyrosine kinase (TYRO3; SKY), AXL receptor tyrosine kinase (AXL; UFO) and c-Mer proto-oncogene tyrosine kinase (MERTK).

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PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798United Kingdom
T: +44 (0)18 6551 2184Washington, DC
2008 Q Street, NW, Suite 100
Washington, DC 20009
T: +1 202 462 9582**Nature Publishing Group**New York
75 Varick Street, 9th Floor
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The Macmillan Building
4 Crinan Street
London N1 9XW
United Kingdom
T: +44 (0)20 7833 4000Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
Shinjuku-ku, Tokyo 162-0843
Japan
T: +81 3 3267 8751

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In vitro assays showed that CBL-B added ubiquitin modifications to all three TAM family proteins. In cultured human cells, stimulation of the TAM receptors led to the recruitment of CBL-B and ubiquitination of AXL.

“TAM receptors can act as negative regulators in other cell types, so we asked whether TAM receptors can also inhibit NK activity,” Penninger said. In cultured mouse NK cells, stimulation of the TAM receptors suppressed the activation of NK cells. In the cells, *Cbl-b* knockout restored activation.

The data collectively indicate that CBL-B works with TAM receptor kinases in a pathway to suppress the activation of NK cells.

The final step was testing whether pharmacological inhibition of the TAM receptor kinases could block the suppression of NK cells and elicit antimetastatic effects. To do this, Penninger teamed up with scientists from the **Max Planck Institute of Biochemistry** and **Lead Discovery Center GmbH** (LDC) who developed a potent and selective pan-TAM receptor kinase inhibitor called LDC1267 (see Box 1, “The development and validation of LDC1267”).

In a mouse model of metastatic melanoma, transfer of LDC1267-treated, wild-type NK cells led to antitumor responses that were comparable to those seen with transfer of *Cbl-b* knockout NK cells. Intraperitoneal injection of LDC1267 also decreased the number of metastatic lung tumors compared with vehicle injection.

Injected and oral LDC1267 yielded comparable results in mouse models of metastatic breast and liver cancer.

Results were published in *Nature*. The team also included scientists from **Medical University Innsbruck**, **Brown University**, **The University of Western Australia** and **University Hospital Bonn**.

The series of molecules described in the paper, including LDC1267,

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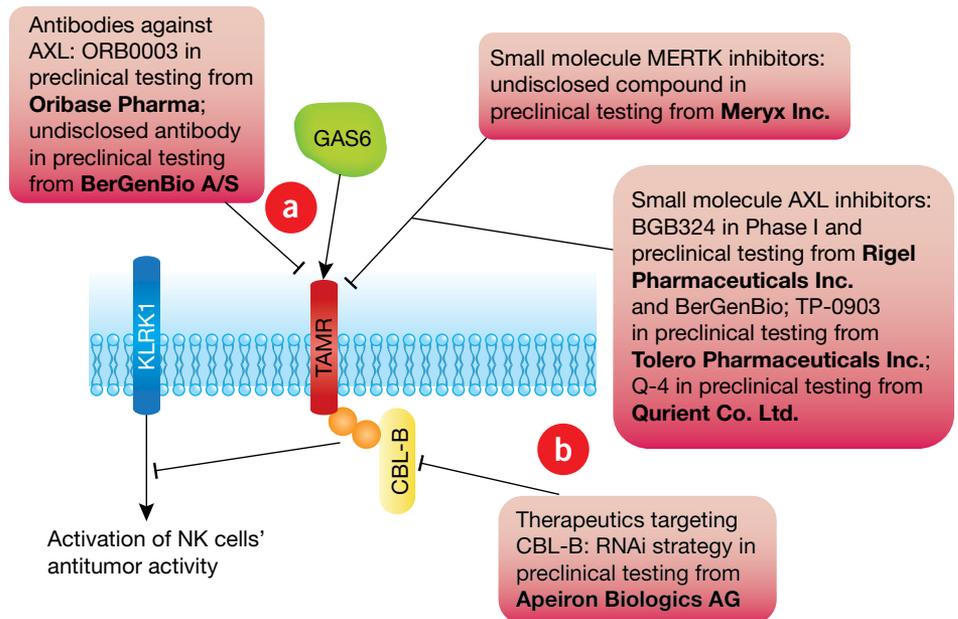
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Figure 1. Strategies to activate anti-tumor NK cells. NK activation occurs downstream of killer cell lectin-like receptor subfamily K member 1 (KLRK1; CD314; NKG2D). In *Nature*, scientists showed that a casitas B cell lymphoma-b (CBL-B)–TAM receptor (TAMR) pathway suppresses the activation of NK cells.¹

[a] TAMR kinases, including TYRO3 protein tyrosine kinase (TYRO3; SKY), AXL receptor tyrosine kinase (AXL; UFO) and c-Mer proto-oncogene tyrosine kinase (MERTK), are activated by an extracellular ligand, such as growth arrest–specific 6 (GAS6).

[b] Binding by GAS6 leads to the recruitment of CBL-B to TAMR and receptor ubiquitination (orange circles). Activation of this pathway inhibits NK cell antitumor activity.

A number of companies are developing therapeutics that activate antitumor immunity by interfering with this pathway.



is licensed to **Quriert Co. Ltd.** from LDC and the Max Planck Institute of Biochemistry.

With these compounds, “we have achieved pharmacological validation for certain types of drug-resistant cancers, and we have seen prominent activity in some leukemias,” said Bert Klebl, managing director and CSO of LDC.

Tackling the targets

Researchers had mixed views on whether CBL-B itself or the TAM receptors are better targets. Some companies have a head start on the latter family with programs against AXL.

That target is expressed in primary tumors and is an established driver of drug resistance in *epidermal growth factor receptor (EGFR)*-mutant lung cancer^{4,5} and progression of breast cancer.^{6,7}

Nevertheless, Penninger said that the company he founded, **Apeiron**

AG, wants to tackle CBL-B via RNAi. The company hopes to start Phase I testing in cancer this year.

Apeiron plans to collect white blood cells from patients, use RNAi *ex vivo* to knock down *CBL-B* and then return the cells to patients.

“We have long-term experience with *Cbl-b*-mutant mice. They are quite healthy, unlike *Ctla-4*-mutant mice. Thus, the potential side effects of blocking *CBL-B* might be less than blocking CTLA-4,” said Penninger.

Similar to CBL-B, CTLA-4 (CD152) negatively regulates T cells. CTLA-4 is the target of Yervoy ipilimumab, a human mAb from **Bristol-Myers Squibb Co.** that is marketed to treat metastatic melanoma. The drug’s label includes a warning of severe immune-mediated adverse events due to T cell activation and proliferation.

Stephen Frye told *SciBX* that it might be better to go after the TAM receptor kinases.

Box 1. The development and validation of LDC1267.

In 2008, Axel Ullrich and co-workers published evidence that the TAM receptor family protein AXL receptor tyrosine kinase (AXL; UFO) promotes metastatic behavior of cancer cells in culture. The group also showed that inhibition of AXL abrogated the behavior.⁶

Ullrich is director and a professor of molecular biology at the **Max Planck Institute of Biochemistry**.

Bert Klebl, managing director and CSO of **Lead Discovery Center GmbH (LDC)**, said that the findings were the starting point for a collaboration to optimize tyrosine kinase inhibitors against the TAM receptors.

Profiling and cellular characterization of the inhibitors were done in an iterative process with LDC and Max Planck scientists. “LDC optimized not only the selectivity and potency but also the physicochemical and pharmaceutical properties to yield bioavailable TAM receptor kinase inhibitor leads, which have shown proof of concept in a couple of animal models for cancer,” said Klebl.

LDC1267 was rationally designed using a pharmacophore-based approach and was selected from hundreds of compounds based on activity in cell-based AXL autophosphorylation assays.

LDC1267 binds the target kinases with nanomolar affinity *in vitro*. It is selective for the TAM receptor kinases from a panel of 456 kinases tested both through cell-free KINOMEScan assays and, in cells, through quantitative proteomic assays. —AD

“I consider the paper to be a very significant contribution to target validation for TAMs in the function of the innate immune system in oncology,” he said. Frye is director of the Center for Integrative Chemical Biology and Drug Discovery at **The University of North Carolina at Chapel Hill Eshelman School of Pharmacy**. He also is cofounder of **Meryx Inc.**, which is developing MERTK inhibitors for multiple indications, including cancer and viral infection.

Penninger countered that “TAM receptor inhibitors probably need more preclinical studies to establish the safety profile.”

Richard Godfrey said that the safety of TAM receptor inhibitors will hinge on specificity. “It is important to distinguish between compounds that inhibit specific TAM receptors and compounds that are pan-TAM kinase inhibitors. Multikinase inhibitors will be associated with more toxicity. Triple-TAM

family knockout mice exhibit postnatal degenerative syndromes, while mice carrying specific TAM receptor mutations are largely normal. Selective TAM inhibitors will not have the same effects as pan-TAM inhibitors.”

Godfrey is CEO of **BerGenBio A/S**, which is developing small molecules and antibodies against AXL. Lead compound BGB324, a small molecule that was in-licensed from **Rigel Pharmaceuticals Inc.**, has completed a Phase I study. Clinical trials in acute myelogenous leukemia (AML) and lung cancer are planned for this year.

Quriient CEO Kiyean Nam said that the company is developing AXL inhibitors for drug-resistant cancers. The goal is to establish clinical proof of concept before looking for a partner.

Other companies with AXL inhibitors in preclinical development for cancer include **Tolero Pharmaceuticals Inc.** and **Oribase Pharma**.

Regardless of target choice, Penninger noted that “for many cancers, metastases are what kill people. If we can indeed use CBL-B inhibition or TAM receptor inhibition to—at least in part—control metastases, this would be tremendous.”

Establishing clinical evidence for the antimetastatic activity of a therapeutic, however, is challenging because establishing that metastasis

has not occurred is nearly impossible.⁸

“We could monitor NK cell activity as a surrogate marker for drug action against metastasis. This is the first step for TAM receptors to become a viable target for metastasis,” said Nam.

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Contact: Josef M. Penninger, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria
e-mail: josef.penninger@imba.oeaw.ac.at
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COMPANIES AND INSTITUTIONS MENTIONED

Apeiron Biologics AG, Vienna, Austria
BerGenBio A/S, Bergen, Norway
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
Brown University, Providence, R.I.
Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria
Lead Discovery Center GmbH, Dortmund, Germany
Max Planck Institute of Biochemistry, Martinsried, Germany
Medical University Innsbruck, Innsbruck, Austria
Meryx Inc., Chapel Hill, N.C.
Oribase Pharma, Montpellier, France
Quriient Co. Ltd., Seongnam, South Korea
Rigel Pharmaceuticals Inc. (NASDAQ:RIGL), South San Francisco, Calif.
Tolero Pharmaceuticals Inc., Lehi, Utah
University Hospital Bonn, Bonn, Germany
The University of North Carolina at Chapel Hill Eshelman School of Pharmacy, Chapel Hill, N.C.
The University of Western Australia, Perth, Western Australia, Australia

“I consider the paper to be a very significant contribution to target validation for TAMs in the function of the innate immune system in oncology.”

—**Stephen Frye,**
Meryx Inc.

Repairing reproducibility

By C. Simone Fishburn, Senior Editor

Although the NIH is taking preliminary steps to improve the reliability of preclinical data, many researchers are not waiting for reproducibility guidelines and are taking up the mantle to raise standards at their own institutions.

Francis Collins and Lawrence Tabak recently outlined a series of measures they are planning to implement at the NIH to combat poor reproducibility in preclinical research.¹ The crux of the problem, they said, appears to be rooted in practices, policies and attitudes at academic centers, scientific publishers and funding agencies.

Collins is director and Tabak is principal deputy director of the NIH.

“Reports of challenges in reproducibility have been around for several years, but over the last couple of years they have increased in prevalence. We decided the agency needed to articulate a way forward,” Tabak told *SciBX*.

Indeed, industry researchers highlighted the frequent irreproducibility of preclinical data in two analyses published in 2011 and 2012. In the earlier article, **Bayer AG** scientists managed to reproduce published data in only about 25% of 67 projects.² The next year, scientists from **Amgen Inc.** and **The University of Texas MD Anderson Cancer Center** reported that the scientific findings of 53 landmark oncology studies were upheld in only 6 cases (11%).³

Since then, privately and publicly funded groups have launched initiatives to address the problem. The Reproducibility Initiative, a joint venture by **Science Exchange**, **PLOS** and **figshare**, was launched in 2012 to allow academic researchers to have their work replicated by a third party.⁴

The **Global Biological Standards Institute** was founded that same year to develop biological standards for basic and translational research. This year, the institute set up task forces to create standards for tools such as cell lines, antibodies and next-generation genome sequencing.⁵

Now, the NIH has decided to take a leadership position in trying to drive change, focusing first on better training for scientists and improving the rigor of the institute’s grant review teams.

Home testing

The NIH is starting by testing ideas and introducing new procedures for its own intramural scientists and grant review teams. The aim is to develop recommendations for use by other institutions.

For example, the NIH is developing a training module for postdocs, graduates and other students to teach good experimental design and record keeping. The module is focused on increasing the reproducibility and transparency of research findings and will become part of the mandatory training at the NIH. It will be made publicly available by the end of 2014.

Tabak said that the emphasis is on recommendations rather than rules, and he does not expect punitive actions for failure to comply. “We prefer to use the bully pulpit to convince people to do the right thing and make it obligatory when there’s no alternative. Some of the recommendations could become a best practice that we expect people to adhere to,” he said.

The NIH already has two types of pilot studies under way related to funding for clinical trials based on preclinical studies.

In one, the NIH is performing after-the-fact studies, Tabak told *SciBX*, in which the institute is replicating select experiments in published papers on which applications for clinical trials are based. Tabak said that the pilot program could provide an indication of what proportion of studies are reproducible and give a metric that can be followed over time to monitor improvement.

In the second type of pilot study, grant review panels will have an additional focus on evaluating the scientific premise of applications, including the statistical basis of preclinical experiments. If proposed clinical studies are based on underpowered preclinical experiments, that could affect the decision of whether to fund or not, Tabak said.

The pilot studies involve multiple NIH institutes, and the NIH plans to assess the outcomes and decide on what practices to adopt by year end.

Tabak said that he could not yet estimate what it would cost the scientific establishment in terms of time and money to replicate

selected experiments.

In addition, the NIH is aiming to increase transparency through PubMed Commons, an online discussion forum about published articles that was launched last December, and a planned Data Discovery Index to house primary data on which published manuscripts are based.

Lee Ellis told *SciBX* that the ability to comment on papers in PubMed Commons is a big step forward.

According to the Collins and Tabak paper, so far PubMed Commons has had about 2,000 people sign up and has received about 700 comments.

Ellis said, “These numbers are relatively low, but hopefully as more people become aware of this they’ll be more willing to comment on papers.” Although it will take some time to see the full effects of such comments, he said that the ability to stimulate discussion about published papers is healthy for the field.

Ellis is a professor of surgery and molecular and cellular oncology at MD Anderson and vice chair of the cancer research cooperative group **SWOG**. He was coauthor on the 2012 paper on reproducibility in oncology studies.

It takes a village

According to Tabak, the NIH initiative is not a reaction to political pressure and instead is part of a community-wide response to a problem that involves many stakeholders.

“NIH alone can’t solve this, but in partnering with journals, investigators and others we can make headway,” he said.

“Reports of challenges in reproducibility have been around for several years, but over the last couple of years they have increased in prevalence. We decided the agency needed to articulate a way forward.”

—Lawrence Tabak,
National Institutes of Health

The NIH is calling on other stakeholders to help tackle the problem, including journal editors and reviewers, and university promotion and tenure committees. According to Collins and Tabak, the pressures for rapid publication and the ties of high-impact publications to academic career progression have contributed to the poor rates of reproducibility.

“It’s not NIH’s problem to fix this alone. The first burden is also on us academics,” said Daria Mochly-Rosen, who is a professor of translational medicine in the Department of Chemical Systems and Biology at the **Stanford University School of Medicine**. She also was cofounder and CEO of Kai Pharmaceuticals Inc., which was acquired by Amgen in 2012, and is cofounder of **Aldea Pharmaceuticals Inc.**

Although the proposed NIH training module is expected to launch at year end, Mochly-Rosen and others at Stanford have already started implementing procedures for better training of lab scientists who are conducting experiments.

Often, she said, lack of reproducibility arises when experiments have confounding factors that are not perceived as important.

For example, cell lines might have guidelines for use between specific passage numbers. Those guidelines can often inadvertently get lost as the cells are used by different laboratory researchers, leading to contradictory results between labs.

In other situations, one lab might perform animal experiments at one time of day and a second lab might work at a different time of day. If circadian rhythms influence the system under investigation, the data may not be replicated in the repeat experiment.

Mochly-Rosen said that reproducibility problems can be partly mitigated by better recording of experimental conditions. She does not require the fully detailed forms used in industry but does encourage her lab members to record information on experimental conditions, reagent source and lot numbers and any deviations from the core protocol.

To ensure blinding and maintain objectivity, results are analyzed independently by another lab member who is blinded to the experimental conditions.

“This costs a lot of goodwill—you’re asking someone to give a day of their time to do something that they get no credit for. But out of a sense of community people will do this,” she said.

Prior to submitting a publication, Mochly-Rosen requests that some experiments be repeated by an independent scientist based only on the information included in the manuscript to ensure that sufficient detail is provided to reproduce the data.

Mochly-Rosen said that journals and reviewers also have a responsibility to maintain scientific standards. “It’s unacceptable to allow data to be published without including both positive and negative controls,” she said.

Indeed, the NIH is calling on journals to help raise standards and wants widespread adoption of practices already followed by **Nature Publishing Group** and the journals of the **American Association for the**

Advancement of Science. These include an expanded online methods section of supplementary material and checklists for editors and reviewers to ensure critical experimental design features are included.

Collins and Tabak also recommend that journals devote more space to reporting negative findings and corrections to earlier work.

Ellis told *SciBX* that publishing negative findings is particularly important and could help researchers avoid wasting resources and time on pursuing fruitless avenues already explored by others.

He outlined three types of negative data that should be published more widely: studies on hypotheses that prove to be incorrect; studies that try but fail to reproduce work published by someone else; and some of the scientist’s own studies that did not work in the context of a larger study that was consistent with the principal investigator’s hypothesis.

For example, he said, if an experiment did not work in 10% serum but did work in 1% serum, that information should be included.

“Reviewers only want the perfect story, but we should be able to publish all the relevant information, both positive and negative,” he said.

Mochly-Rosen said that many researchers are introducing better practices for ensuring reproducibility in their labs. However, she said, talking directly with students and colleagues can be difficult. Researchers sometimes react negatively to the issue as they think it impugns their scientific ability or integrity.

“The topic has been taboo, but we need to address it. This is not about improving the robustness of our published work for industry. We should do it because it’s the right thing to do,” she said.

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- Aldea Pharmaceuticals Inc.**, Redwood City, Calif.
- American Association for the Advancement of Science**, Washington, D.C.
- Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.
- Bayer AG** (Xetra:BAYN), Leverkusen, Germany
- figshare**, London, U.K.
- Global Biological Standards Institute**, Washington, D.C.
- National Institutes of Health**, Bethesda, Md.
- Nature Publishing Group**, London, U.K.
- PLOS**, San Francisco, Calif.
- Science Exchange**, Palo Alto, Calif.
- Stanford University School of Medicine**, Stanford, Calif.
- SWOG**, Portland, Ore.
- The University of Texas MD Anderson Cancer Center**, Houston, Texas

Zinc-ing about diabetes

By Kai-Jye Lou, Senior Writer

ZNT8 burst onto the scene in 2007 as a promising target for type 2 diabetes, and follow-up studies suggested that stimulating the zinc transporter protein could have therapeutic benefit.^{1,2} But a new study suggests that the preferred approach might be to inhibit the target.³

Because of the conflicting data, researchers say that more studies are needed to flesh out the functional consequences of expression of ZNT8 (solute carrier family 30 zinc transporter member 8; SLC30A8) and its variants before embarking on drug discovery efforts.

Pfizer Inc. is spearheading a collaborative effort to get such studies under way through its membership in the recently launched Accelerating Medicines Partnership (AMP), which is a public-private partnership to identify and validate disease targets in four disease areas including type 2 diabetes.⁴

ZNT8 is selectively expressed in islet β cells.⁵ Interest in the transporter protein as a type 2 diabetes target emerged when four separate genomewide association studies suggested that a SNP variant in the gene resulted in a missense mutation in ZNT8 that was associated with increased risk for the disease.⁶⁻⁹

Additional studies suggested that the missense mutation caused a loss of function, although it was never conclusively shown because nobody ever carried out the necessary experiments to fully characterize how the mutation affects ZNT8's function.

Nevertheless, the studies associated the variant with impaired insulin and glucose regulation,¹⁰⁻¹² and the collective body of data on the functional consequences of the ZNT8 missense variant have generally supported the case for stimulating the zinc transporter's activity to treat type 2 diabetes.

The new genetic study from a group of industry and academic researchers suggests a set of newly identified truncating mutations in ZNT8 that cause a loss of function that protects against diabetes rather than increasing the risk.

Thus, the new data suggest that inhibiting rather than stimulating ZNT8 could help treat type 2 diabetes.

Truncated

The team's genotype analysis of about 150,000 individuals across multiple population cohorts identified 12 different ZNT8 variants that encoded a truncated version of the ZNT8 protein.

As a group, carriers of these protein-truncating mutations had 65% decreased risk of type 2 diabetes compared with noncarriers ($p=1.7 \times 10^{-6}$).

Moreover, a cohort of Icelandic individuals showed that carriers of one of the mutations had lower nonfasting glucose levels than noncarriers

($p=4.6 \times 10^{-4}$). That finding suggested that the mutant ZNT8 is associated with improved glucose tolerance.

Cell line studies suggested that the two most commonly identified protective mutations resulted in the expression of an unstable variant of the transporter protein, which in turn suggests that decreased ZNT8 activity is associated with lower diabetes risk.

Results were published in *Nature Genetics*. The study was led by researchers at the **Broad Institute of MIT and Harvard, Massachusetts**

"The question we have been trying to answer in our studies is what genetic factors protect or make us susceptible to diabetes."

—Kári Stefánsson,
Amgen Inc.

General Hospital, Lund University and Pfizer. deCode genetics ehf (now part of **Amgen Inc.**), the Genetics of Type 2 Diabetes (GoT2D) consortium and the Type 2 Diabetes Genetic Exploration by Next-Generation Sequencing in Multi-Ethnic Samples (T2D-GENES) consortium also contributed to the study.

"The question we have been trying to answer in our studies is what genetic factors protect or make us susceptible to diabetes,"

said Kári Stefánsson, the co-corresponding author on the study and chairman and CEO of Amgen's deCode unit. He said that such information could be used by drug developers to better understand how to treat the disease.

"The fact that we see truncated proteins resulting from these gene variants and proteins with decreased activity points us in a direction that loss-of-function mutations are protective in human subjects," added Ann-Marie Richard, a coauthor and principal scientist in Pfizer's Cardiovascular and Metabolic Diseases (CVMED) research unit.

Determining functional consequences

Stefánsson said that the results from the earlier studies and his new paper might not be in direct conflict. Instead, he said that the missense mutation found in the earlier studies could actually be a gain of function rather than a loss of function.

Under that scenario, the missense mutation's gain of function would logically produce results that are the opposite of the newly found loss-of-function truncating mutations.

At the end of the day, additional studies in human cell lines and subjects are needed to characterize the functional consequences of multiple ZNT8 variants.

Tim Rolph, VP and CSO of the CVMED research unit at Pfizer, said that AMP will take up the mantle of running such studies. The **NIH** launched AMP last month, and

Pfizer is one of the initiative's industry partners.

The type 2 diabetes arm of the partnership has a 5-year budget of \$58.4 million.

"Our goal now is to understand mechanistically the consequences of knocking down this gene," said Jeff Trimmer, executive director and group leader in Pfizer's CVMED research unit.

Rolph and Trimmer are both coauthors on the *Nature Genetics* study.

Richard said that it will be necessary to phenotypically characterize the metabolic differences between carriers and noncarriers of the identified ZNT8 variants, for example, by looking at circulating levels of insulin, proinsulin and glucagon.

"Our goal now is to understand mechanistically the consequences of knocking down this gene."

—Jeff Trimmer,
Pfizer Inc.

To help address some known inconsistencies between mouse and human data, Rolph said that researchers should generate and characterize heterozygous *Znt8* knockouts and see how the phenotype compares with that of human carriers of the protective *ZNT8* variants.

Homozygous *Znt8* knockout mice show a broad spectrum of phenotypes that vary according to gender and genetic backgrounds.^{13,14} These phenotypes range from having modest hyperglycemia and altered insulin secretion to having normal glucose and insulin regulation.

Guy Rutter, a professor and head of the section of cell biology at **Imperial College London**, added that it will be important to evaluate the effects of overexpressing various *ZNT8* variants in preclinical models. Those studies, he said, would help resolve the apparent discrepancy between the conclusions of the current study and those that preceded it.

Rutter also wanted to see additional sequencing studies around the area of the genome in which the identified mutations occur to determine if they also affect other genes.

Separately, Stefánsson said that deCode has been recruiting known carriers of *ZNT8* variants over the last few months to participate in studies to characterize the effects of the variants on glucose tolerance and insulin sensitivity.

Amgen spokesperson Kristen Davis said that at this time it is still too early to discuss the company's future research plans with *ZNT8*. Amgen currently has the fusion protein AMG 876 in Phase I testing to treat type 2 diabetes. Details of the compound and its target are undisclosed.

The findings reported in *Nature Genetics* are unpatented.

Lou, K.-J. *SciBX* 7(10); doi:10.1038/scibx.2014.276
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Contact: David Altshuler, Broad Institute of MIT and Harvard, Cambridge, Mass.
e-mail: altshuler@molbio.mgh.harvard.edu
Contact: Kári Stefánsson, deCode genetics ehf and Amgen Inc. Reykjavik, Iceland
e-mail: kstefans@decode.is
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Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Broad Institute of MIT and Harvard, Cambridge, Mass.
Imperial College London, London, U.K.
Lund University, Lund, Sweden
Massachusetts General Hospital, Boston, Mass.
National Institutes of Health, Bethesda, Md.
Pfizer Inc. (NYSE:PFE), New York, N.Y.

Hitchhiker's guide to the lymph node

By Benjamin Boettner, Associate Editor

A team at the **Massachusetts Institute of Technology** has figured out how to ferry cancer vaccines into lymph nodes—a location that orchestrates immune responses but has been hard to target directly. The key was tethering the vaccines to albumin to hitchhike on the carrier's normal transportation route.¹

In proof-of-concept studies, tumor antigens and adjuvants targeted to lymph nodes elicited strong immune responses and slowed or reduced tumor growth in mice. The team is now testing additional cancer vaccines in mice and is combining the approach with other immunomodulatory therapies.

Lymph nodes contain large populations of immune cells and are thus important reservoirs to target cancer vaccines that operate by harnessing the immune response.²

Previous strategies for concentrating vaccines in lymph nodes have focused on antibody-based targeting technologies, local delivery to lymphatic tissue and nanoparticle-based drug delivery. However, these approaches have been limited by dilution effects, tolerance to the antigens or the need for sophisticated surgical manipulation.

Darrell Irvine and coworkers at MIT have now found a way to streamline lymph node delivery based on their observation that dyes and other compounds that bind strongly to serum albumin are highly effective lymph node tracers.

Albumin binds to poorly soluble molecules in serum and carries them to the lymphatic system, where their cargo is released and taken up by various immune cells.

Irvine's team decided to test whether it could get tumor-targeting vaccines to hitchhike along with albumin to the lymph node by conjugating them to an albumin-binding lipid tail.

Irvine is a professor of materials science and engineering and of biological engineering at MIT.

Amphiphiles, adjuvants and antigens

The team started by constructing a series of model vaccines containing either peptide antigens or adjuvants conjugated to fatty acid tails that would bind albumin.

Whereas antigens stimulate the production of tumor-specific antibodies to destroy the tumor, adjuvants stimulate the immune system's response to the target antigen and reduce the chance of developing tolerance. Both are needed for effective tumor immunotherapy.

For the adjuvant vaccines, the team generated a series of amphiphilic compounds (amph-CpGs) composed of lipid tails of varying length and structure conjugated to a CpG DNA—an oligonucleotide that binds toll-like receptor 9 (TLR9) and is a potent adjuvant.

A lipophilic diacyl tail conjugated to CpG produced a conjugate that bound albumin with high affinity *in vitro* and accumulated in lymph nodes in mice to levels eightfold higher than those for unconjugated CpG.

In mice challenged with a test antigen, the optimized amph-CpG conjugates produced 32-fold higher antigen-specific T cell responses than unmodified CpG, demonstrating potent immunostimulatory effects of the lymph node-targeted adjuvant vaccine.

For the antigen-based vaccines, the team created amph-peptides containing an albumin-binding diacyl lipid tail conjugated to peptide from an HIV antigen, the melanoma-associated antigen Trp2 or the E7 transforming protein (human papillomavirus-16; HpV16gp2).

To increase solubility, the researchers introduced a polyethylene glycol (PEG) spacer with optimized length between the albumin-binding tail and the peptide antigen.

In mice, the amph-peptide vaccines efficiently drained with albumin into lymph nodes and, when injected together with the adjuvant amph-CpG vaccine, gave rise to antigen-specific cytokine-producing CD8⁺ T cells.

In mouse tumor models, coadministration of amph-CpG and E7 transforming protein amph-peptides caused regression of cervical tumors. Amph-CpG coadministered with Trp2 amph-peptides slowed melanoma growth compared with free CpG or tumor antigens.

Because side effects from systemic exposure are among the major drawbacks of adjuvant therapy, the team tested for signs of systemic inflammation.

Amph-CpG did not increase levels of serum cytokines or cause spleen enlargement in contrast to free CpG, suggesting that directly targeting the vaccines to the lymph nodes by albumin hitchhiking might reduce systemic exposure sufficiently to avoid immune-related toxicity.

Results were published in *Nature*.

“This approach could have great potential in cancer immunotherapy as, so far, conventional DNA and peptide vaccines against tumor antigens proved to be quite disappointing in larger controlled trials.”

—Sonia Quaratino,
Merck KGaA

Teaching tolerance

Sonia Quaratino, senior medical director and immunology advisor at **Merck KGaA**, told *SciBX* that the rapid accumulation in lymph

nodes and powerful T cell immune response in the absence of increased systemic toxicity was impressive.

“This approach could have great potential in cancer immunotherapy as, so far, conventional DNA and peptide vaccines against tumor antigens proved to be quite disappointing in larger controlled trials,” she said.

Adrian Bot, VP of translational medicine at **Kite Pharma Inc.**, told *SciBX* that this was an unexpected finding with several key advantages: the targeted protein—albumin—is ubiquitous; it uses an easily optimized chemistry with scale-up potential; and it may be applicable to three disease areas—infectious vaccines, cancer and autoimmunity.

Kite has several cancer immunotherapeutics in preclinical development.

According to Bot, however, animal models have limited translational value for active immunotherapy. *In vitro* and *in vivo* modeling of the approach with human cells and humanized mouse models will be important and should ultimately be complemented by a primate model, he said.

Peter Emtage said that to understand the specific immune responses, the immuno-phenotype of the activated cells will have to be determined. “It would be important to find out what the effector and helper memory pools look like after single and multiple immunizations and if T cells are educated in an optimal fashion,” he said.

Emtage is VP of immune-mediated therapy at **AstraZeneca plc’s MedImmune LLC** unit.

Jeffrey Hubbell told *SciBX*, “The next challenge is to optimize the approach to achieve more profound tumor killing rather than slowing of tumor growth.” Hubbell is a professor and director of the Institute of Bioengineering at the **Swiss Federal Institute of Technology Lausanne**.

Bot, Quaratino and Hubbell all said that key to progressing the vaccines will be whether they can eventually help to break immune tolerance to tumor antigens.

Bot added that if this technology can overcome tolerance against self-antigens, it could be applied in many other areas and have a significant competitive advantage over other vaccine technologies.

To overcome self-tolerance, Hubbell and Quaratino suggested that the cancer vaccines could be combined with checkpoint blockade approaches.

These include inhibitory antibodies against programmed cell death 1 (PDCD1; PD-1; CD279) and CTLA-4 (CD152), two negative immune regulators expressed on T cells whose blockade can amplify tumor-directed immune responses.³

Several companies have antibodies against CTLA-4 and PD-1 on the market or in clinical testing for various cancers.

According to Bot, the vaccines could also be effective in infectious diseases such as influenza and hepatitis B. Irvine told *SciBX* that his lab

plans to test the HIV amph-peptide vaccine soon in nonhuman primates.

In addition, the antigen vaccines might be effective in autoimmune diseases if used without the adjuvant vaccines. “It would be intriguing if the amph-vaccine approach could be utilized for tolerization or desensitization in the absence of an adjuvant. If that is possible, it could open other paths of investigation and translation, doubling the value of the technology,” said Bot.

MIT has filed a patent application on the lymph node-targeting strategy including the chemical structure and design of the lymph node-targeting materials. The IP is available for licensing through the MIT Technology Licensing Office.

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AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Kite Pharma Inc., Los Angeles, Calif.

Massachusetts Institute of Technology, Cambridge, Mass.

MedImmune LLC, Gaithersburg, Md.

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland

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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
Cancer				
Acute myelogenous leukemia (AML)	DNA (cytosine-5-)-methyltransferase 3α (DNMT3A)	<i>In vitro</i> and mouse studies suggest eliminating DNMT3A-mutant preleukemia cells could help prevent AML. Sequencing of peripheral blood samples from patients at diagnosis showed a common leukemia-associated mutation in DNMT3A. The mutation was present in leukemia blast cells and in T cells and hematopoietic progenitor cells that lack other cancer-associated mutations. In cell samples from five patients treated with chemotherapy, DNMT3A-mutant cells persisted through remission and relapse. In mouse xenograft repopulation assays, transplanted DNMT3A-mutant hematopoietic progenitors from patients had a competitive advantage over nonmutant cells. Next steps could include determining the effects of eliminating DNMT3A-mutant cells on AML outcomes.	Patent and licensing status unavailable	Shlush, L.I. <i>et al. Nature</i> ; published online Feb. 12, 2014; doi:10.1038/nature13038 Contact: John E. Dick, University of Toronto, Toronto, Ontario, Canada e-mail: jdick@uhnresearch.ca
		SciBX 7(10); doi:10.1038/scibx.2014.278 Published online March 13, 2014		
Acute myelogenous leukemia (AML); acute lymphoblastic leukemia (ALL)	Myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX); multiple endocrine neoplasia I (MEN1; menin)	SAR studies suggest compounds that disrupt the interaction between MLL and menin could be useful for treating some forms of AML and ALL. About 5% of AML and ALL cases are caused by activating mutations and translocations in MLL. <i>In vitro</i> , hydroxy- and aminomethylpiperidine compounds inhibited MLLs interaction with its cofactor menin. In cultured leukemia cells, the best of these compounds inhibited proliferation with an IC ₅₀ of about 56 nM and led to expression of myeloid differentiation markers. Next steps include pharmacokinetic optimization and selection of lead candidates.	Patent pending; available for licensing	He, S. <i>J. Med. Chem.</i> ; published online Jan. 28, 2014; doi:10.1021/jm401868d Contact: Jolanta Grembecka, University of Michigan, Ann Arbor, Mich. e-mail: jolantag@umich.edu
		SciBX 7(10); doi:10.1038/scibx.2014.279 Published online March 13, 2014		
Brain cancer	V-rel reticuloendotheliosis viral oncogene homolog A (RELA; p65); chromosome 11 open reading frame 95 (C11orf95)	Patient sample and cell culture studies suggest targeting a C11orf95-RELA fusion protein could help treat supratentorial ependymomas. Genetic analyses of patient brain tumor samples identified an oncogenic fusion between RELA and C11orf95 in about 70% of supratentorial ependymomas and in no cases of posterior fossa ependymomas. In nude mice, implants of neural stem cells expressing the C11orf95-RELA fusion protein induced brain tumor formation and resulted in decreased survival compared with implants of cells expressing C11orf95 or RELA alone. Next steps include determining the mechanism by which the fusion protein transforms neural stem cells into malignant cells and using the mouse models to screen for therapeutics targeting the fusion protein.	Unpatented; licensing status not applicable	Parker, M. <i>et al. Nature</i> ; published online Feb. 19, 2014; doi:10.1038/nature13109 Contact: Richard J. Gilbertson, St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project, Memphis, Tenn. e-mail: richard.gilbertson@stjude.org Contact: David W. Ellison, same affiliation as above e-mail: david.ellison@stjude.org Contact: Jinghui Zhang, same affiliation as above e-mail: jinghui.zhang@stjude.org
		SciBX 7(10); doi:10.1038/scibx.2014.280 Published online March 13, 2014		

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Casitas B cell lymphoma-b (CBL-B); TYRO3 protein tyrosine kinase (TYRO3; SKY); AXL receptor tyrosine kinase (AXL; UFO); c-Mer proto-oncogene tyrosine kinase (MERTK)	<p>In vitro and mouse studies suggest TYRO3, AXL and MERTK receptor (TAM receptor) inhibitors could help prevent metastasis by activating NK cells. In mice, deletion of Cbl-b increased NK cell antitumor activity compared with no deletion. In vitro assays identified the TAM receptors as substrates for CBL-B's E3 ubiquitin ligase activity. In multiple mouse models of metastasis, a small molecule inhibitor of the TAM receptors decreased metastasis compared with vehicle. Next steps include developing an siRNA-based clinical candidate to target CBL-B.</p> <p>Rigel Pharmaceuticals Inc. and partner BerGenBio A/S have a small molecule inhibitor of AXL in Phase I or earlier testing to treat various cancers.</p> <p>Tolero Pharmaceuticals Inc. and partner Oribase Pharma have AXL inhibitors in preclinical development to treat cancer.</p> <p>Qurient Co. Ltd. has the AXL inhibitor Q-4 in preclinical development for cancer (see Killer targets in metastasis, page 1).</p> <p>SciBX 7(10); doi:10.1038/scibx.2014.281 Published online March 13, 2014</p>	Patent filed by Lead Discovery Center GmbH and Max Planck Institute of Biochemistry covering a chemical series of TAM receptor inhibitors; licensed to Qurient	<p>Paolino, M. <i>et al. Nature</i>; published online Feb. 19, 2014; doi:10.1038/nature12998</p> <p>Contact: Josef M. Penninger, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria e-mail: josef.penninger@imba.oeaw.ac.at</p>
Liver cancer	IL-17A	<p>Mouse studies suggest IL-17A inhibitors could help treat hepatocellular carcinoma (HCC). Elevated tumor levels of IL-17A are associated with poor prognosis in patients with HCC. In mice with HCC tumors, <i>Il-17a</i> deficiency decreased tumor growth compared with unmodified <i>Il-17a</i> expression. In mice with HCC, recombinant IL-17a recruited tumor-infiltrating, myeloid-derived suppressor cells that secreted proinflammatory cytokines, which in turn induced IL-17a production in $\gamma\delta$ T cells in a feed-forward loop that drove tumor growth. Future studies could include testing anti-IL-17A antibodies in the HCC models.</p> <p>Novartis AG's secukinumab (AIN457), a human IgG1 mAb targeting IL-17A, is under regulatory review to treat psoriasis. It also is in Phase III testing to treat rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis and in Phase II trials to treat multiple sclerosis (MS).</p> <p>Eli Lilly and Co.'s ixekizumab (LY2439821), a humanized mAb against IL-17A, is in Phase III testing to treat psoriasis and psoriatic arthritis and in Phase I trials to treat RA.</p> <p>Novimmune S.A., Roche and its Genentech Inc. unit have NI-1401 (MCAF5352A; RG7624), a human mAb that binds IL-17A and IL-17F, in Phase I testing to treat autoimmune disease.</p> <p>SciBX 7(10); doi:10.1038/scibx.2014.282 Published online March 13, 2014</p>	Patent and licensing status unavailable	<p>Ma, S. <i>et al. Cancer Res.</i>; published online Feb. 13, 2014; doi:10.1158/0008-5472.CAN-13-2534</p> <p>Contact: Haiyan Liu, Soochow University, Suzhou, China e-mail: hliu@suda.edu.cn</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	CREB binding protein (CREBBP; CBP); enhancer of zeste homolog 2 (EZH2); histone deacetylase (HDAC)	<i>In vitro</i> and mouse studies suggest HDAC or EZH2 inhibitors could help treat <i>PTEN</i> (<i>MMAC1</i> ; <i>TEP1</i>)-deficient prostate cancers lacking CBP. CBP mutations have previously been found in some prostate cancers. In mice with <i>Pten</i> depletion, <i>Cbp</i> knockout increased prostatic intraepithelial neoplasia compared with no <i>Cbp</i> alteration. In human or mouse prostate cancer cells, siRNA-mediated <i>PTEN</i> knockdown alone or in combination with <i>CBP</i> knockdown increased levels of the methyltransferase EZH2 compared with what was seen using control siRNA. In a <i>Pten^{+/-}/Cbp^{-/-}</i> mouse model of prostate cancer, the histone deacetylase inhibitor panobinostat caused tumor regression. Next steps include testing HDAC or EZH2 inhibitors in patients with CBP-low, PTEN-low and EZH2-high prostate cancers. Novartis AG's panobinostat is in Phase III testing to treat various hematological malignancies. Epizyme Inc. and Eisai Co. Ltd. have the EZH2 inhibitor E7438 in Phase I/II testing to treat lymphoma. Constellation Pharmaceuticals Inc., Novartis and GlaxoSmithKline plc each have EZH2 inhibitors in discovery to treat cancer. SciBX 7(10); doi:10.1038/scibx.2014.283 Published online March 13, 2014	Findings unpatented; unavailable for licensing	Ding, L. <i>et al. Cancer Res.</i> ; published online Feb. 3, 2014; doi:10.1158/0008-5472.CAN-13-1659 Contact: Haojie Huang, Mayo Clinic, Rochester, Minn. e-mail: huang.haojie@mayo.edu
Prostate cancer	E1A binding protein p300 (EP300; p300); <i>PTEN</i> (<i>MMAC1</i> ; <i>TEP1</i>)	<i>In vitro</i> and mouse studies suggest inhibiting p300 could help treat <i>PTEN</i> -deficient prostate cancers. In a mouse model of <i>Pten</i> -deficient prostate cancer, knockout of <i>p300</i> increased survival compared with no alteration and prevented development of invasive cancers. In human prostate cancer cells, combined knockdown of <i>PTEN</i> and <i>p300</i> increased androgen receptor polyubiquitination and decreased androgen receptor expression compared with knockdown of <i>PTEN</i> alone. Next steps could include developing a p300 inhibitor. SciBX 7(10); doi:10.1038/scibx.2014.284 Published online March 13, 2014	Unpatented; unavailable for licensing	Zhong, J. <i>et al. Cancer Res.</i> ; published online Jan. 30, 2014; doi:10.1158/0008-5472.CAN-13-2485 Contact: Haojie Huang, Mayo Clinic, Rochester, Minn. e-mail: huang.haojie@mayo.edu
Endocrine/metabolic disease				
Diabetes	Solute carrier family 30 zinc transporter member 8 (SLC30A8; ZNT8)	Human genetic studies suggest inhibiting SLC30A8 could help prevent or treat type 2 diabetes. Previous studies in mice had alternatively suggested that loss of SLC30A8 activity could increase the risk of developing type 2 diabetes. Genotyping and analysis of about 150,000 individuals showed that carriers of mutations in <i>SLC30A8</i> that result in the expression of a truncated protein had 65% decreased risk of developing type 2 diabetes compared with noncarriers ($p=1.7\times 10^{-6}$). The two most commonly identified protective mutations result in the expression of an unstable variant of the protein. Next steps include characterizing the biological effects of the truncating <i>SLC30A8</i> mutations in humans (see <i>Zinc-ing about diabetes</i> , page 7). SciBX 7(10); doi:10.1038/scibx.2014.285 Published online March 13, 2014	Unpatented; licensing status not applicable	Flannick, J. <i>et al. Nat. Genet.</i> ; published online March 2, 2014; doi:10.1038/ng.2915 Contact: David Altshuler, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: altshuler@molbio.mgh.harvard.edu Contact: Kari Stefansson, deCode genetics ehf and Amgen Inc., Reykjavik, Iceland e-mail: kstefans@decode.is

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Hematology				
Anemia	Activin receptor-like kinase 3 (ALK3)	Mouse studies suggest inhibiting the bone morphogenetic protein type I receptor ALK3 could help treat anemia. In mice, hepatocyte-specific <i>Alk3</i> knockout prevented decreases in serum iron levels, whereas hepatocyte-specific <i>Alk2 (Acvr1)</i> knockout did not. Next steps could include testing specific ALK3 antagonists in models of anemia of chronic conditions. Acceleron Pharma Inc.'s ALK3 antagonist ACE-661 is in preclinical testing for osteoporosis and bone repair. SciBX 7(10); doi:10.1038/scibx.2014.286 Published online March 13, 2014	Patent and licensing status unavailable	Mayeur, C. <i>et al. Blood</i> ; published online Feb. 5, 2014; doi:10.1182/blood-2013-02-480095 Contact: Andrea U. Steinbicker, University Hospital Muenster, Muenster, Germany e-mail: andrea.steinbicker@ukmuenster.de
Infectious disease				
Bacterial infection	Quinolone resistance protein (NorA)	<i>In vitro</i> studies suggest boronic acid derivatives that inhibit the NorA bacterial efflux pump could help prevent antibiotic resistance. In a screen of 150 boronic compounds, 24 increased potency of the antibiotic ciprofloxacin, with the best one raising antibiotic activity 4-fold against a NorA-expressing <i>Staphylococcus aureus</i> strain at low micromolar concentrations. The most potent inhibitors had low cytotoxicity against human cells and no antibacterial activity alone. Next steps could include improving the potency of the lead NorA boronic inhibitor. SciBX 7(10); doi:10.1038/scibx.2014.287 Published online March 13, 2014	Patent and licensing status unavailable	Fontaine, F. <i>et al. J. Med. Chem.</i> ; published online Feb. 5, 2014; doi:10.1021/jm401808n Contact: Anne-Sophie Voisin-Chiret, University of Caen Lower Normandy, Caen, France e-mail: anne-sophie.voisin@unicaen.fr
Musculoskeletal disease				
Osteoporosis	Sialic acid binding Ig-like lectin 15 (SIGLEC15)	Cell-based and mouse studies suggest inhibition of SIGLEC15 could help prevent osteoclast-mediated bone destruction in osteoporosis and other bone-loss disorders. <i>In vitro</i> , an anti-SIGLEC15 mAb decreased formation of osteoclasts from precursor cells compared with control antibody. In young mice, the anti-SIGLEC15 mAb increased bone mineral density and trabecular bone volume and decreased serum osteoclast marker activity compared with control antibody. Next steps include testing SIGLEC15 inhibitors in models of cancer-induced bone loss. SciBX 7(10); doi:10.1038/scibx.2014.288 Published online March 13, 2014	Patented by Alethia BioTherapeutics Inc.; unavailable for licensing	Stuible, M. <i>et al. J. Biol. Chem.</i> ; published online Jan. 20, 2014; doi:10.1074/jbc.M113.494542 Contact: Gilles B. Tremblay, Alethia BioTherapeutics Inc., Montreal, Quebec, Canada e-mail: gilles.tremblay@alethiabio.com
Neurology				
Pain	Neurotensin (NTS)	<i>In vitro</i> and rodent studies suggest a conjugate of NTS and the brain-penetrating peptide Angiopep could help treat pain. In a mouse <i>in situ</i> model of brain penetration, the conjugate, dubbed ANG2002, had more than 10-fold better brain uptake than unconjugated NTS. In mouse models of acute pain or rat models of persistent, neuropathic and bone cancer-associated pain, i.v. delivery of ANG2002 decreased pain behaviors more potently than delivery of NTS alone or vehicle control. Next steps include IND-enabling studies and clinical testing. Angiochem Inc.'s ANG2002 is in preclinical development to treat pain. SciBX 7(10); doi:10.1038/scibx.2014.289 Published online March 13, 2014	Angiopep and conjugates patented by Angiochem; patent application filed covering ANG2002; available for partnership	Demeule, M. <i>et al. J. Clin. Invest.</i> ; published online Feb. 17, 2014; doi:10.1172/JCI70647 Contact: Philippe Sarret, University of Sherbrooke, Sherbrooke, Quebec, Canada e-mail: philippe.sarret@usherbrooke.ca

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Other				
Adjuvant	Toll-like receptor 9 (TLR9)	<i>In vitro</i> , mouse and primate studies suggest a CpG DNA nanoparticle wrapped in the polysaccharide schizophyllan could be used as a vaccine adjuvant that activates B cells and plasmacytoid dendritic cells (pDCs). The K3-SPG nanoparticle incorporated CpG DNAs, which are TLR9 agonists that activate B cells, in complex with soluble β -glucan schizophyllan. In mice injected with antigen, co-injection with the K3-SPG adjuvant increased Tlr9-dependent pDC activation compared with co-injection with the CpG DNA without schizophyllan. In mice and cynomolgus monkeys immunized against influenza, the adjuvant increased antibody titers compared with CpG DNA without schizophyllan. Next steps include collaboration with a pharmaceutical company for preclinical and clinical development.	Patent application filed; unavailable for licensing	Kobiyama, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 10, 2014; doi:10.1073/pnas.1319268111 Contact: Ken J. Ishii, National Institute of Biomedical Innovation, Osaka, Japan e-mail: kenishii@biken.osaka-u.ac.jp
SciBX 7(10); doi:10.1038/scibx.2014.290 Published online March 13, 2014				
Pulmonary disease				
Acute lung injury	Thrombospondin-1 (TSP-1; THBS1)	<i>In vitro</i> and mouse studies suggest TSP-1 could help stimulate alveolar lung repair after injury. In cocultures of bronchioalveolar stem cells with lung endothelial cells, <i>Tsp-1</i> -deficient endothelial cells decreased differentiation of the stem cells into alveolar cells and increased differentiation to bronchiolar cells compared with wild-type endothelial cells. In a mouse lung injury model, conditioned medium from wild-type lung endothelial cells increased numbers of alveolar cells threefold over conditioned medium from <i>Tsp-1</i> -deficient endothelial cells. Next steps include testing delivery of factors that promote alveolar differentiation <i>in vivo</i> .	Findings unpatented; unavailable for licensing	Lee, J.-H. <i>et al. Cell</i> ; published online Jan. 30, 2014; doi:10.1016/j.cell.2013.12.039 Contact: Carla F. Kim, Boston Children's Hospital, Boston, Mass. e-mail: carla.kim@childrens.harvard.edu
SciBX 7(10); doi:10.1038/scibx.2014.291 Published online March 13, 2014				
Renal disease				
Renal disease	Adenosine A ₃ receptor (ADORA ₃)	<i>In vitro</i> and cell-based studies identified an ADORA ₃ partial agonist that could help treat kidney disease caused by renal fibrosis. <i>In vitro</i> , the compound bound ADORA ₃ with a K _i of about 5 nM and activated adenylate cyclase with an EC ₅₀ of about 46 nM. In a mouse cell-based model of kidney fibrosis, the compound inhibited transforming growth factor- β 1 (Tgfb1)-stimulated collagen I expression with an IC ₅₀ of about 0.83 μ M. Next steps could include testing the compound in animal models of chronic kidney disease. Acorn Biomedical Inc. and Domain Therapeutics S.A. have ADORA ₃ antagonists for glaucoma in preclinical development.	Patent and licensing status unavailable	Nayak, A. <i>et al. J. Med. Chem.</i> ; published online Jan. 24, 2014; doi:10.1021/jm4015313 Contact: Lak Shin Jeong, Seoul National University, Seoul, South Korea e-mail: lakjeong@snu.ac.kr
SciBX 7(10); doi:10.1038/scibx.2014.292 Published online March 13, 2014				

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Measurement of β -amyloid ($A\beta$) oligomers in cerebrospinal fluid (CSF) to diagnose and monitor the progression of Alzheimer's disease (AD)	An assay that measures $A\beta$ oligomers levels in CSF could help diagnose AD and monitor disease progression in patients. An ELISA using an anti- $A\beta$ oligomer mAb detected $A\beta$ oligomers in CSF at levels as low as 0.09 picograms/mL. In CSF from patients with AD, $A\beta$ oligomer levels were higher than those in CSF from healthy controls and patients with Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) or schizophrenia. In patients with AD, $A\beta$ oligomer levels correlated with disease severity as measured by mini-mental state examination (MMSE) scores. Next steps could include testing diagnostic applications of the assay in a larger cohort of patients with AD.	Patent and licensing status unavailable	Savage, M.J. <i>et al. J. Neurosci.</i> ; published online Feb. 19, 2014; doi:10.1523/JNEUROSCI.1675-13.2014 Contact: Mary J. Savage, Merck & Co. Inc., West Point, Pa. e-mail: mary_savage@merck.com
	SciBX 7(10); doi:10.1038/scibx.2014.293 Published online March 13, 2014		
Protein M, an IgG-binding protein with a new mode of antibody interaction	<i>In vitro</i> studies suggest Protein M, a broadly reactive, antibody-binding protein, could complement Proteins A and G as a reagent for large-scale antibody purification. Protein M from <i>Mycoplasma genitalium</i> bound all isotypes of human and nonhuman IgG through a binding mode distinct from other high-affinity IgG-binding proteins targeting a conserved region on the variable chain of IgG. In binding assays, pretreatment with recombinant Protein M blocked binding between antibody-antigen pairs including a monoclonal anti-influenza antibody-antigen pair and a mouse polyclonal lupus antibody-antigen pair. Ongoing studies could include purifying the agent for therapeutic and research purposes.	Patent application filed; licensing negotiations under way with three undisclosed companies; available for licensing	Grover, R.K. <i>et al. Science</i> ; published online Feb. 7, 2014; doi:10.1126/science.1246135 Contact: Richard A. Lerner, The Scripps Research Institute, La Jolla, Calif. e-mail: rlerner@scripps.edu
	SciBX 7(10); doi:10.1038/scibx.2014.294 Published online March 13, 2014		
Disease models			
Long-term, <i>Plasmodium cynomolgi</i> -infected primary hepatocyte culture to screen for malaria therapeutics	Long-term, <i>P. cynomolgi</i> -infected primary hepatocyte cultures could be used to identify therapeutics that prevent malaria relapse. Screening of compounds to eliminate quiescent <i>Plasmodium</i> hypnozoites currently relies on macaque models. <i>Macaca fascicularis</i> primary hepatocytes and a human hepatoma cell line were cocultured on a collagen layer and covered with a matrigel layer, resulting in long-term primary hepatocyte cultures that could support <i>P. cynomolgi</i> infection for about 40 days. In the <i>P. cynomolgi</i> -infected cocultures, the generic antimalarial atovaquone eliminated the parasitic hypnozoite-derived schizont form but spared the quiescent hypnozoite form, which could be activated at an increased rate by histone methyltransferase inhibitors. Next steps include using the assay to evaluate the efficacy of different drug combinations to both activate and kill the parasite.	Culturing system unpatented; licensing status not applicable; human hepatoma cell line used in study, HepaRG, patented by Institut National de la Santé et de la Recherche Médicale (INSERM); licensed by Biopredic International	Dembélé, L. <i>et al. Nat. Med.</i> ; published online Feb. 9, 2014; doi:10.1038/nm.3461 Contact: Georges Snounou, Pierre and Marie Curie University, Paris, France e-mail: georges.snounou@upmc.fr
	SciBX 7(10); doi:10.1038/scibx.2014.295 Published online March 13, 2014		

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Transcription activator-like effector nuclease (TALEN)-mediated genome editing to generate genetically modified monkeys	<p>Primate studies suggest TALENs could be used to generate genetically modified monkeys to model disease. In single-cell rhesus or cynomolgus monkey embryos, microinjection of three <i>methyl CpG binding protein 2 (MECP2; RTT)</i>-targeting TALEN plasmids plus a <i>RAD51 homolog (RAD51)</i> plasmid resulted in eight-cell-stage embryos with <i>MECP2</i> disruptions. Embryo transfer to female monkeys produced three aborted male fetuses and one live female infant. Sequencing analysis of tissues from the TALEN monkeys showed that the TALEN fetuses and infant had multiple point mutations across <i>MECP2</i> and no off-target mutational effects. Next steps include using the system to generate monkey models for neurological and metabolic diseases.</p> <p>SciBX 7(10); doi:10.1038/scibx.2014.296 Published online March 13, 2014</p>	Unpatented; licensing status not applicable	<p>Liu, H. <i>et al. Cell Stem Cell</i>; published online Feb. 13, 2014; doi:10.1016/j.stem.2014.01.018 Contact: Weizhi Ji, Yunnan Key Laboratory of Primate Biomedical Research, Kunming, China e-mail: wji@kbimed.com Contact: Yi Eve Sun, same affiliation as above e-mail: ysun@mednet.ucla.edu Contact: Siguang Li, Tongji University School of Medicine, Shanghai, China e-mail: siguangli@163.com</p>
Transgenic mouse models of Netherton syndrome expressing human <i>kallikrein-related peptidase 5 (KLK5)</i>	<p>Transgenic mice expressing human <i>KLK5</i> in the epidermis could be used to study the biology of Netherton syndrome and screen for drugs to treat the indication. Netherton syndrome is a severe form of ichthyosis caused by mutations in serine peptidase inhibitor Kazal type 5 (<i>SPINK5; LEKT1</i>), an inhibitor of <i>KLK5</i>. The transgenic mice survived longer than <i>Spink5</i>-deficient mice and recapitulated symptoms of Netherton syndrome including reddened, scaling skin; hyperkeratosis; detachment of the skin's outer epidermal layer from the underlying granular layer; and skin barrier and hair defects. The transgenic mice also had enlarged lymph nodes and increased levels of allergy-associated cells and T helper type 2 (Th2) proinflammatory molecules in the skin and increased serum levels of IgE compared with wild-type controls. Future studies could include evaluating potential Netherton syndrome therapies in the model.</p> <p>SciBX 7(10); doi:10.1038/scibx.2014.297 Published online March 13, 2014</p>	Patent and licensing status unavailable	<p>Furio, L. <i>et al. J. Exp. Med.</i>; published online Feb. 17, 2014; doi:10.1084/jem.20131797 Contact: Alain Hovnanian, University Paris Descartes–Sorbonne, Paris, France e-mail: alain.hovnanian@inserm.fr</p>
Drug delivery			
Drug-loaded, neutrophil-targeting nanoparticles to prevent inflammation-induced tissue damage	<p>Neutrophil-targeting nanoparticles could help prevent tissue damage involving vascular inflammation. In mice with vascular inflammation, bovine serum albumin nanoparticles were preferentially internalized by neutrophils adhering to the inflammation site. In these mice, albumin nanoparticles loaded with the spleen tyrosine kinase (SYK) inhibitor piceatannol decreased Syk pathway-induced vascular adhesion of neutrophils compared with unloaded nanoparticles. In mouse models of acute lung injury, piceatannol-loaded nanoparticles decreased neutrophil infiltration and lung inflammation compared with free piceatannol. Next steps include testing nanoparticles loaded with SYK inhibitors or other classes of neutrophil adhesion inhibitors in models of acute lung injury, sepsis and/or ischemia/reperfusion injury.</p> <p>Gilead Sciences Inc. has GS-9973, an oral SYK inhibitor, in Phase II trials to treat hematological malignancies. Rigel Pharmaceuticals Inc. has fostamatinib disodium (FosD), an oral SYK inhibitor, in Phase II testing to treat idiopathic thrombocytopenic purpura (ITP). ZaBeCor Pharmaceutical Co. has Excellair, an siRNA targeting SYK, in Phase II testing to treat asthma.</p> <p>SciBX 7(10); doi:10.1038/scibx.2014.298 Published online March 13, 2014</p>	Patented by the University of Illinois; available for licensing	<p>Wang, Z. <i>et al. Nat. Nanotechnol.</i>; published online Feb. 23, 2014; doi:10.1038/nnano.2014.17 Contact: Asrar B. Malik, University of Illinois at Chicago College of Medicine, Chicago, Ill. e-mail: abmalik@uic.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Gene catalog for differentiating human pluripotent stem cells (hPSCs) into mature, insulin-producing pancreatic β cells	<i>In vitro</i> and computational studies identified genes that could help develop strategies for β cell production from hPSCs. Antibody staining for insulin followed by cell sorting was used to isolate pure populations of insulin-producing cells derived from hPSCs. Subsequent gene expression and hierarchical clustering analyses demonstrated similarities between insulin-producing cells derived from different hPSCs. The analyses also found similarities between hPSC-derived cells and fetal insulin-producing cells and differences between hPSC-derived cells and adult insulin-producing cells. Further comparison between fetal and adult cells identified a catalog of genes responsible for β cell maturation and metabolic functionalization. Next steps include identifying the gene regulatory network associated with the catalog and potential drug targets.	Patent application filed covering method for analyzing RNA following intracellular sorting (MARIS); available for licensing	Hrvatín, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 10, 2014; doi:10.1073/pnas.1400709111 Contact: Douglas A. Melton, Harvard University, Cambridge, Mass. e-mail: dmelton@harvard.edu
	SciBX 7(10); doi:10.1038/scibx.2014.299 Published online March 13, 2014		
Lymph node–targeting cancer vaccines	Mouse studies suggest albumin-binding DNA and peptide vaccines could help stimulate antitumor immunity in lymph nodes to help treat cancer. SAR studies defined a set of design rules for vaccines consisting of toll-like receptor 9 (TLR9)-binding CpG oligonucleotides or polyethylene glycol (PEG)-linked immunogenic peptides and lymph node–targeting, lipophilic, albumin-binding tails. In mouse models of melanoma and cervical cancer, antigenic peptide conjugates in combination with albumin-targeting CpG increased antigen-specific CD8 ⁺ T cell numbers in sentinel lymph nodes and decreased tumor growth compared with unmodified CpG in combination with unconjugated antigenic peptides. Ongoing work includes testing potential vaccine formulations in genetically engineered mouse models of cancer and combining this vaccination strategy with other immunomodulatory therapies (<i>see Hitchhiker's guide to the lymph node, page 9</i>).	Patent application filed covering chemical structure and design of the lymph node–targeting materials; available for licensing	Liu, H. <i>et al. Nature</i> ; published online Feb. 16, 2014; doi:10.1038/nature12978 Contact: Darrell J. Irvine, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: djirvine@mit.edu
	SciBX 7(10); doi:10.1038/scibx.2014.300 Published online March 13, 2014		
Markers			
Injectable, synthetic markers for paper-based detection of disease in urine samples	Mouse studies suggest nanoparticles coated with protease-sensitive peptides that release biomarkers into urine can be used with paper-based assays to diagnose colorectal cancer and thrombosis. In mouse models of thrombosis or colorectal cancer, i.v. infused thrombin- or matrix metalloprotease–sensitive nanoparticles coated with reporter peptides underwent cleavage in blood clots or tumors, respectively, to release the reporter molecules, which were concentrated in urine. The reporters were detectable in urine samples with ELISA and a paper-based lateral flow assay. In mice, the paper-based assay distinguished between thrombotic and control animals with 92% accuracy and between animals with and without subcutaneous colorectal tumors with 90% accuracy. Next steps include developing similar systems for detection of prostate cancer and for early detection of liver cancer metastasis.	Patent applications filed covering material formulation of synthetic biomarkers, urinary analysis and companion paper tests; unavailable for licensing	Warren, A.D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 24, 2014; doi:10.1073/pnas.1314651111 Contact: Sangeeta N. Bhatia, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: sbhatia@mit.edu
	SciBX 7(10); doi:10.1038/scibx.2014.301 Published online March 13, 2014		

Erratum: Analysis: Cover Story

Fishburn, C.S. *SciBX* 7(8); doi:10.1038/scibx.2014.215
Published online Feb. 27, 2014

The Analysis item “AMplifying targets” mischaracterized the scope and purpose of the European Innovative Medicines Initiative (IMI) in a paraphrased quote from David Wholley. IMI is a public-private partnership involving government and academic organizations that is much larger in scale than the Accelerating Medicines Partnership and also aims to spur the development of new companies and provide a regional economic stimulus.

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