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THIS WEEK

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Finding the repurpose

By Tracey Baas, Senior Editor

A **Stanford University** team has used a computational approach to analyze publicly available gene expression profiles and identified two drug repurposing opportunities.[1,2] The researchers found that the anticonvulsant topiramate could have use in inflammatory bowel disease and that the generic ulcer drug cimetidine could help treat lung adenocarcinoma.

The computational method is exclusively licensed to **NuMedii Inc.**, a bioinformatics spinout from Stanford that is using the technology to evaluate molecular data to repurpose drugs.

The Stanford group used previously published gene expression data from 100 diseases and 164 drugs to confirm already known therapeutic uses and to predict the potential of the drugs to treat new indications (*see* **Figure 1, "Schematic workflow of drug-disease pairing using gene expression profile similarity"**).

The computational technique showed that topiramate had a stronger therapeutic score for IBD than prednisolone and that cimetidine had a stronger therapeutic score for lung adenocarcinoma than **AstraZeneca plc**'s Iressa gefitinib.

Topiramate, a sulfamate-substituted monosaccharide that acts as a sodium channel blocker, γ-aminobutyric acid receptor (GABAR) agonist and AMPAR antagonist, is marketed to treat epilepsy, seizures and migraines. The drug is available as a generic and is marketed as Topamax by **Johnson & Johnson**.

Iressa, an epidermal growth factor receptor (EGFR) inhibitor, is marketed in the EU to treat non–small cell lung cancer (NSCLC).

In a second *in silico* study, the researchers specifically focused on IBD. Using only the gene expression data from IBD patient samples and those of the 164 drug compounds, they again confirmed that topiramate had a stronger IBD therapeutic score than prednisolone.

The IBD and lung cancer results also were borne out in placebo-controlled animal studies. In a rat model of IBD, topiramate lowered the incidence of diarrhea and IBD-related colitis compared with saline. In mice with human lung adenocarcinoma cells, cimetidine decreased tumor growth compared with saline control.

The corresponding author of the study, Atul Butte, is chief of the Division of Systems Medicine and an associate professor in medicine and pediatrics at the **Stanford University School of Medicine**. He is a cofounder and chairman of the scientific advisory board at NuMedii.

Data were published in *Science Translational Medicine*.

"Drug repurposing using gene expression information is not new," according to Guanghui Hu, associate director of informatics and analysis

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at **Merck & Co. Inc.** However, he added, "this work makes two major contributions: Butte and coworkers manually generated 100 high-quality disease signatures, many of which had been missed in previous studies that mostly relied on automatic data processing, and by far the most important contribution was to validate some of the findings *in vivo*."

Oscar Puig, also associate director of informatics and analysis at Merck, added that "it is fairly quick to use these types of computational approaches to generate many potential new indications—the bottleneck is experimental validation, including both *in vitro* and *in vivo* testing. The lack of large-scale, cost-effective systems to speed up the validation process is a problem."

Jeremy Jenkins, a senior investigator in chemical biology informatics at **Novartis AG**'s **Novartis Institutes for BioMedical Research**, added that "typically, transcriptional profiles have been used to correlate compounds to one another to predict mechanism. In Butte's case, compound profiles are compared directly to disease signatures, bypassing the difficult requirement of compound-target and even compound-mechanism elucidation."

Beyond expression

Butte thinks that with the wide range of publicly available data repositories, his team's computational method can provide a systematic approach for repositioning established drugs to treat a wide range of diseases.

"Although we have shown proof of concept that our method works using microarray gene expression data available through public repositories such as the **National Center for Biotechnology Information** (NCBI)'s Gene Expression Omnibus and the **Broad Institute of MIT and Harvard**'s Connectivity Map, any type of experimentally obtained molecular signature data could be computationally analyzed and mined for possible drug repurposing," he said.

"I'm tremendously excited by Butte's effort, which represents leading-edge thinking in this important area," said David Shaywitz. "Today, most medical research is fundamentally reductionist in nature, trying to cure disease by breaking it down into the component parts. There's an urgent need—and opportunity—for complementary efforts that take a far more empirical approach and seek to capture and leverage the vast quantities of existing data and use this information to refine clinical treatment and improve patient health."

Shaywitz is director of strategic and commercial planning at **Theravance Inc.** He also is cofounder of the Harvard PASTEUR program, a translational research initiative at **Harvard Medical School**, and a founding advisor of **Sage Bionetworks**, a not-for-profit medical research initiative focused on open innovation.

According to Butte, the computational analysis technique could be applied to datasets beyond gene expression information. "Multiple publically accessible data repositories exist and hold different forms of high throughput data based on systems chemical biology information," he said. "One example of such a data repository is NCBI's PubChem Bioassay, where hundreds of different bioactivity readouts are stored for millions of different chemical molecules. Just as we evaluated a compound's therapeutic potential by mining gene expression data, we can do a similar thing by mining bioassay readout data. And that is only one example."

Jenkins would like to see other data integrated into future computational analyses to further elucidate an emerging axis of drug targets presented in Butte's manuscript but not fully evaluated.

"Their drug-disease matrix contains an implicit third axis of drug targets," he said. "Effective mapping of compounds to targets through

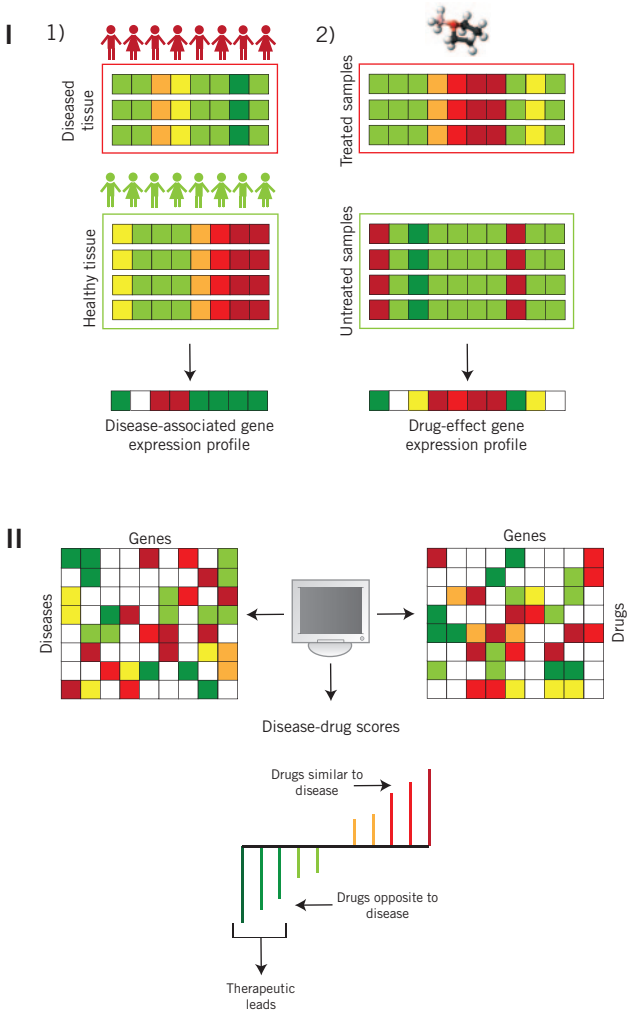

Figure 1. Schematic workflow of drug-disease pairing using gene expression profile similarity. Two types of gene expression collections are used to computationally evaluate a compound's therapeutic potential. (**I**) Disease-associated gene expression collections contain data that compare genes up- and downregulated in diseased tissue with genes in healthy tissue (**I.1**). Drug-effect gene expression collections contain data that compare genes up- and downregulated in drug-treated tissue with genes in untreated tissue (**I.2**).

(**II**) Using disease-associated and drug-effect gene expression collections, a modified Connectivity Map computational method[4] is used to query disease profiles against the drug-effect profiles and assign a disease-drug score to each comparison based on profile similarity. A drug that causes opposite gene expression changes from a specific disease (that is, the drug-effect and disease-associated profiles have a negative similarity score) is hypothesized to potentially have a therapeutic effect on that disease. (Figure based on Figure 1 in ref. 1.)

integrated bioassay data would allow a deeper understanding of how compound-target-disease transcriptional responses can be exploited."

Puig and Hu agreed. They noted that high throughput–based results such as *in vitro* screening, text mining or structural similarity data can be integrated for orthogonal profile analysis to further narrow down the best compounds for experimental validation.

Regardless of data type, Butte said NuMedii is interested in using computational analysis to find similarities between molecular signatures of orphan diseases and diseases with available therapeutics, as well as new first uses for compounds in development.

Work published last week in the *Public Library of Science Genetics* provided the basis for **Personalis Inc.**, another company cofounded by Butte. Using publically accessible databases, a group of Stanford University scientists published a computational analysis of genetic disease risk and drug responses from whole-genome sequencing data in a family of four.[3]

The study, led by Euan Ashley, assistant professor in cardiovascular medicine at Stanford, and coauthored by Butte, estimated risk factors for multiple diseases but focused in particular on the family history of pulmonary embolism and bleeding risk when using therapeutic blood thinners.

Personalis was founded in August of this year by Ashley; Butte; Russ Altman, chairman of the bioengineering department at Stanford; Michael Snyder, chairman in the genetics department at Stanford; and John West, previously CEO of Solexa Ltd., which was acquired by **Illumina Inc.** Personalis plans to use genome sequencing technology and computational analysis to provide genome interpretation for use in academic studies and clinical medicine.

Stanford and NuMedii have filed for patents covering topiramate to treat IBD and cimetidine to treat lung cancer. The IP is available for licensing from NuMedii.

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REFERENCES

1. Sirota, M. *et al. Sci. Transl. Med.*; published online Aug. 17, 2011; doi:10.1126/scitranslmed.3001318
Contact: Atul J. Butte, Stanford University School of Medicine, Stanford, Calif.
e-mail: abutte@stanford.edu
2. Dudley, J.T. *et al. Sci. Transl. Med.*; published online Aug. 17, 2011; doi:10.1126/scitranslmed.3002648
Contact: Atul J. Butte, Stanford University School of Medicine, Stanford, Calif.
e-mail: abutte@stanford.edu
3. Dewey, F.E. *et al. PLoS Genet.*; published online Sept. 15, 2011; doi:10.1371/journal.pgen.1002280
Contact: Euan A. Ashley, Stanford University, Stanford, Calif.
e-mail: euan@stanford.edu
4. Lamb, J. *et al. Science* **313**, 1929–1935 (2006)

COMPANIES AND INSTITUTIONS MENTIONED

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Theravance Inc. (NASDAQ:THRX), South San Francisco, Calif.

Optimism about oxytocin

By Lev Osherovich, Senior Writer

University of California, Los Angeles researchers have evidence of a link between psychological disposition and a receptor for the neuroactive hormone oxytocin.[1] A new company—**Pastorus Pharma LLC**—thinks the findings provide additional proof of concept for targeting the oxytocin receptor in behavioral and psychiatric indications.

A team led by Shelley Taylor, professor of psychology at UCLA, was looking for genetic factors that underlie variation in three psychological traits that influence an individual's ability to cope with stress: optimism, self-esteem and sense of mastery.

"We know that these factors affect response to stressful life events, which have a major role in the development of psychiatric disorders, including major depression, anxiety disorder and post-traumatic stress disorder," said René Hurlemann, associate faculty member in the Department of Psychiatry at the **University of Bonn**.

Other researchers had previously found that genetic variation in the oxytocin receptor (OXTR) affected self-assessed psychological well-being.[2] Taylor's team examined the relationship between OXTR genotype and measurable characteristics such as dispositional optimism and depressive symptoms.

Among 326 healthy volunteers, heterozygous and homozygous carriers of the A allele of OXTR were rated lower on scales of optimism (p=0.031), mastery (p=0.043) and self-esteem (p=0.004) than individuals homozygous for the G allele. About two-thirds of the subjects were A allele heterozygotes or homozygotes.

Taylor's study is among the first to identify "a specific marker for these personality traits," said Pastorus CEO and principal Glenn Cornett.

The results were reported in the *Proceedings of the National Academy of Sciences*.

The connection between OXTR variation and coping with stress could open a new therapeutic opportunity for modulating oxytocin signaling, which is better known as a regulator of interpersonal trust and maternal bonding. Indeed, a generic injectable form of oxytocin is used to induce delivery and promote lactation.

"We knew there was a pathway [involved in stress coping], but we didn't know what it was," said Taylor. "It was a bit of a surprise that it turned out to be oxytocin, which has previously been thought of as being involved in social or interpersonal pathways."

"We knew there was a pathway [involved in stress coping], but we didn't know what it was. It was a bit of a surprise that it turned out to be oxytocin, which has previously been thought of as being involved in social or interpersonal pathways."

—Shelley Taylor, University of California, Los Angeles

On the bright side

Uncovering the molecular basis for Taylor's findings will be tricky, as the effects of oxytocin signaling in humans are complex, subtle and difficult to tackle experimentally.

One possibility is that the A version of OXTR has a lower level of function and thus is less responsive to normal levels of oxytocin compared with the G allele. An opposite scenario—in which the A allele responds more strongly to the hormone than the G allele—also is possible. Because levels of OXTR expression can fluctuate in response to the hormone, Taylor thinks it is too soon to guess how the receptor variants affect the protein's function.

"We really don't know if the A allele is a gain or loss of function," said Hurlemann.

He thinks that to conclusively link Taylor's findings to disease, it will be necessary to screen for OXTR polymorphisms in patients with clinically defined psychiatric disorders.

"This study was done in healthy volunteers," said Hurlemann. "You would have to investigate the oxytocin receptor polymorphism in patients" with depression, anxiety or PTSD.

Hurlemann, Cornett and Taylor noted that previous studies have examined the relationship between plasma levels of oxytocin and psychiatric disorders, but results of those studies have been mixed and are difficult to interpret because of the hormone's short half-life in the blood.

If the A allele of OXTR turns out to decrease the receptor's signaling ability, there could be a case for giving oxytocin to depressed patients.

Hurlemann said oxytocin already has been tried as an adjunct to psychological counseling in small-scale, investigator-initiated studies in autism, schizophrenia and social anxiety. He is running a study of oxytocin to alleviate symptoms of opiate withdrawal.

"Oxytocin has been considered for everything from psychiatric disorders to sleep apnea," said Daniel Jacobs, founder, chairman and CEO of **Trigemina Inc.**, which is developing oxytocin therapeutics for pain.

Although some prior studies hinted at improvements in mood and affect from intranasal oxytocin, none was sufficiently powered to allow strong conclusions.[3]

Hurlemann said oxytocin therapy appears to alleviate delusional ideation in schizophrenia and reduce amygdala activation in patients with social anxiety, "but the results for depression haven't been so successful."

If the two OXTR alleles vary in their response to the hormone, it also may be useful to stratify patients in oxytocin trials by their OXTR allele.

Cornett noted that small-scale studies suggest oxytocin can alleviate social anxiety in some patients but not others. Taylor's findings could potentially account for differences in response.

"I would be very interested in genotyping responders and nonresponders" to oxytocin, said Cornett.

He added: "There could be a decent amount of overlap" between the three psychological traits measured by Taylor and the psychological risk factors in autism and schizophrenia, for which Pastorus is developing an intranasal formulation of oxytocin.

Cornett said Pastorus has a formulation and delivery technology that improves the bioavailability of nasal oxytocin.

"In comparison to the currently marketed delivery system, our technology increases bioavailability significantly. Based on results thus far, dosage consistency seems to be enhanced materially as well," said Cornett. "Our dry-powder technology involves mixing the active ingredient into cellulose particles, which then adhere to the nasal mucosa longer than do the saline drops administered in the current nasal-spray technology."

(Continues on p. 5)

STK33 strikes out

By Lev Osherovich, Senior Writer

Two years ago, Boston researchers reported that serine/threonine kinase 33 could be a target in tumors driven by activating mutations in *K-Ras*. The reports prompted at least one company—**Amgen Inc.**—to set about developing inhibitors of the kinase. Now, Amgen has reported that the original data cannot be reproduced, and the company has dropped the project.[1]

The original study, published in *Cell* by a team led by D. Gary Gilliland and William Hahn, predicted that inhibiting serine/threonine kinase 33 (STK33) could prevent the growth of tumors driven by mutant *K-Ras*.[2] The researchers showed that in 10 of 12 tumor lines with *K-Ras* mutations, small hairpin RNA knockdown of *STK33* prevented growth compared with no treatment. *STK33* knockdown did not significantly slow the growth of 12 tumor lines that had wild-type *K-Ras*.

Hahn is deputy CSO, chief of the Division of Molecular and Cellular Oncology and director of the Center for Cancer Genome Discovery at the **Dana-Farber Cancer Institute**. Gilliland, who at the time was professor of medicine at **Brigham and Women's Hospital**, is now SVP and franchise head of oncology at **Merck & Co. Inc.**

At the time of the original publication in 2009, Gilliland told *SciBX* that multiple pharmas were developing STK33 inhibitors.[3] Since then, the only preclinical program targeting STK33 to be publicly disclosed is Amgen's.

A team led by Isabelle Dussault, director of oncology research at Amgen, set out to expand Hahn and Gilliland's cell culture RNAi knockdown experiments. The Amgen group started by examining the growth-related effects of knocking down *STK33* in 33 tumor cell lines, including the 12 *K-Ras* mutant lines used in the *Cell* study.

Surprisingly, in all cell lines, the Amgen group found no difference in growth between cells with markedly decreased expression of STK33 due to small interfering RNA knockdown and control cells that received scrambled sequence siRNA.

In contrast, siRNA knockdown of *K-Ras* prevented the growth of *K-Ras* mutation–driven tumor cell lines compared with no knockdown.

Concurrently, Amgen also screened for small molecule STK33 inhibitors and found 1,043 hits with dose-dependent responses. However, none of the 145 most potent compounds—including those that had IC_{50} values of less than 10 nM—inhibited the growth of *K-Ras*-dependent tumor cell lines.

The results were published in *Cancer Research*.

Potential explanations for the discrepancy between the original *Cell* report and the Amgen study could include differences between the shRNA-based knockdown strategy employed by the Boston researchers and the transgenic siRNA used by the Amgen team, as well as other subtle differences in assay conditions.

Regardless of the reason, Amgen's negative findings with multiple therapeutic modalities—siRNA and small molecule inhibitors—and multiple cell lines suggest STK33 has lost its luster as a cancer target.

Amgen spokesperson Mary Klem told *SciBX* the company has discontinued its STK33 program.

Gilliland declined to comment on the Amgen study, and Hahn did not respond to e-mail seeking comment.

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REFERENCES

1. Babij, C. *et al. Cancer Res.*; published online July 8, 2011; doi:10.1158/0008-5472.CAN-11-0778
   Contact: Isabelle Dussault, Amgen Inc., Thousand Oaks, Calif. e-mail: idussaul@amgen.com
2. Scholl, C. *et al. Cell* **137**, 821–834 (2009)
3. Osherovich, L. *SciBX* **2**(23); doi:10.1038/scibx.2009.929

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Brigham and Women's Hospital, Boston, Mass.
Dana-Farber Cancer Institute, Boston, Mass.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.

(Continued from "**Optimism about oxytocin**," p. 4)

The company plans to run a dose-ranging Phase I study in "a couple hundred patients" and then a Phase IIb study in autism and schizophrenia, Cornett said. Pastorus is raising money and does not have a timeline for starting the trials.

Cornett and an undisclosed partner are the investors in Pastorus. The company is seeking additional seed funding from individual investors. Cornett said he is open to seeking venture capital financing in the future.

Trigemina has completed a 40-patient Phase II trial of TI-001, an intranasal formulation of oxytocin for chronic headache. In that trial, 50% of patients receiving oxytocin reported a decrease in headache 4 hours postdosing compared with 12% of placebo patients. However, in a subsequent 20-patient dose-escalation study, 70% of patients receiving placebo also reported reduced pain.

Jacobs attributed the high placebo response rate to the environment in which dosing was conducted. "Whose headache doesn't go away when you're in a nice, quiet, dimly lit room?" he said.

The company plans to run a second Phase II trial next year using an improved protocol with a different dosing environment and quantitative pain endpoints.

Taylor did not patent her discoveries.

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REFERENCES

1. Saphire-Bernstein, S. *et al. Proc. Natl. Acad. Sci. USA*; published online Sept. 6, 2011; doi:10.1073/pnas.1113137108
   Contact: Shelley E. Taylor, University of California, Los Angeles, Calif. e-mail: taylors@psych.ucla.edu
2. Lucht, M.J. *et al. Prog. Neuropsychopharmacol. Biol. Psychiatry* **33**, 860–866 (2009)
3. MacDonald, K. & MacDonald T.M. *Harv. Rev. Psychiatry* **18**, 1–21 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

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University of California, Los Angeles, Calif.

Smegmatis meets *tuberculosis*

By Kai-Jye Lou, Staff Writer

Researchers at the **Albert Einstein College of Medicine of Yeshiva University** have created an attenuated strain of *Mycobacterium smegmatis* containing *M. tuberculosis* genes. The vector conferred better protection against tuberculosis than the standard bacillus Calmette-Guérin (BCG) vaccine in mice.[1] The not-for-profit **Aeras** has licensed the technology and is now working with the researchers to determine an optimal combination of genes to use in *M. smegmatis*.

The only prophylactic for TB is the BCG vaccine, which is prepared from a live, attenuated bacterial strain closely related to *M. tuberculosis* called *M. bovis*. In BCG, deletion of the *region of difference 1* locus is responsible for its attenuation and loss of virulence.[2]

Although the vaccine protects infants from pulmonary TB, it is not effective at protecting adults, nor can it prevent transmission or clear latent infections.

Albert Einstein College of Medicine's new vaccine originated from research on *Mycobacterium* secretion systems and their role in helping the bacteria evade the host immune system.

M. tuberculosis employs multiple strategies to do this, including a specialized secretion system encoded by genes in the bacterium's *esx-1* locus. The *M. tuberculosis* genome contains four additional *esx* loci—*esx-2* through *esx-5*—that may encode secretion systems, but their functions are poorly understood.

The researchers were exploring the role of the *esx-3* locus in immune evasion because it is the only *esx* locus conserved across all strains of *Mycobacterium*.[3,4] The locus is essential for the growth of *M. tuberculosis* and the attenuated *M. bovis* strain used in BCG.[5]

The team found that unlike *M. tuberculosis* and BCG, the more distant relative *M. smegmatis* could grow normally when *esx-3* was deleted, and thus they selected the strain to study the locus' role.

In mouse models of *M. smegmatis* infection, an *esx-3*-deleted strain was unable to evade the host innate immune system, whereas wild-type and *esx-1*-deleted strains did not elicit a strong innate immune response. Moreover, the *esx-3*-deleted strain had attenuated virulence.

Next, the researchers inserted a set of 26 *M. tuberculosis* genes including all 11 *esx-3* genes into the attenuated *M. smegmatis* strain. Despite the addition of *esx-3* genes, the strain still was not virulent and could not evade the immune system.

At this point, the researchers began to think they had the makings of a vaccine vector in hand.

In proof-of-concept studies in mouse models of lethal *M. tuberculosis* infection, i.v. or subcutaneous immunization with the recombinant attenuated *M. smegmatis* strain increased survival and resulted in greater decreases in tissue bacterial load compared with immunization using the BCG vaccine. Several of the mice receiving the recombinant *M. smegmatis* vaccine had tissue bacterial load reductions that were over 1,000-fold greater than those for mice given BCG.

Results were published in *Nature Medicine*.

"This is the first time we have seen a vaccine that can produce over three-log reductions in tissue bacterial burdens over BCG and a bactericidal immune response that causes a sustained decline in bacterial load," said William Jacobs Jr., corresponding author on the paper and a professor in the Department of Microbiology and Immunology and the Department of Genetics at Albert Einstein College of Medicine.

"What we've been seeing with TB vaccine candidates up until now are around one-log reductions in bacterial loads over BCG and immune responses that result in growth inhibition," he added.

Jacobs, who also is an investigator at the **Howard Hughes Medical Institute**, said the recombinant *M. smegmatis* vaccine vector is easy to modify because the genes in the cosmid insert could be swapped out with those encoding antigens from *M. tuberculosis* that are known to elicit an adaptive immune response.

> **"This is the first time we have seen a vaccine that can produce over three-log reductions in tissue bacterial burdens over BCG and a bactericidal immune response that causes a sustained decline in bacterial load."**
>
> ***—William Jacobs Jr., Albert Einstein College of Medicine of Yeshiva University***

Cosmids are plasmid-type DNA vectors that can be used to deliver recombinant genes.

"You may also be able to use this vector to create vaccines for other diseases by using the cosmid to insert genes encoding the antigens that are relevant to those diseases," added Jacobs.

"It is very interesting that they were able to use *M. smegmatis* as a vector to express TB genes because it is a much more distant relative to TB compared with BCG," said Peter Andersen, a professor of infectious disease and VP of vaccine R&D at the **State Serum Institute** (SSI).

He said the mouse data suggest that a vaccine using recombinant *M. smegmatis* could prime the immune system more strongly against *M. tuberculosis* antigens than BCG.

Thomas Evans, CSO at Aeras, said the organization licensed the technology for three reasons. First, *M. smegmatis* is fast and easy to grow, which suggests it could potentially be used to create vaccine candidates that would be cheap and easy to manufacture. Second, the organization has been looking to expand its portfolio of vaccine candidates to avoid having multiple "me too" approaches in development. Finally, Evans said Aeras is interested in vaccination strategies that can circumvent a pathogen's ability to evade the immune system.

Aeras has five clinical-stage TB vaccine candidates in development and expects to have a sixth enter clinical trials by year end. The two most advanced are MVA85A and AERAS-402/Crucell Ad35, both of which are in Phase IIb testing.

MVA85A is a recombinant modified vaccinia virus Ankara expressing *M. tuberculosis* antigen 85A. The vaccine is being developed with the Oxford-Emergent Tuberculosis Consortium Ltd., a joint venture between **Emergent BioSolutions Inc.** and the **University of Oxford**. AERAS-402/Crucell Ad35 is an adenovirus serotype 35 (Ad35) vector that expresses *M. tuberculosis* antigen 85B, 85A and the TB10.4 antigen. It is being developed with **Johnson & Johnson**'s Crucell N.V. unit.

Building the candidate

Both Jacobs and Evans noted that several aspects of their bacterial strain need to be optimized before it can be used to create an actual vaccine candidate.

For example, Jacobs said his group is working to improve the stability of the cosmid antigen expression system.

Also, Evans noted that Aeras and the group at Albert Einstein College of Medicine are working together to determine the minimum set of genes to delete from and insert into *M. smegmatis* to elicit a protective immune response against TB.

"We need to determine the optimal *M. smegmatis* backbone to use and figure out which exact genes in the *esx-3* locus to delete," Evans told *SciBX*. "Likewise, we need to narrow down the set of genes we insert by determining the key set of immunoprotective TB genes."

Andersen noted that the H4 TB subunit vaccine being developed by his group at SSI in partnership with **Sanofi** includes the TB10.4 antigen from *M. tuberculosis*, which is encoded by a gene in the *esx-3* locus.

He said the researchers also should consider evaluating the potential use of the recombinant *M. smegmatis* in a booster vaccine because the strain could be sufficiently different from BCG and *M. tuberculosis* to be used in such a setting.

Evans estimates that the organization is more than a year away from having a preclinical vaccine candidate that uses the recombinant *M. smegmatis* vector.

The Albert Einstein College of Medicine of Yeshiva University has a pending patent covering the vaccine platform described in the paper. Aeras has licensed the technology for use in TB. Applications to other indications are still available for licensing.

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REFERENCES

1. Sweeney, K.A. *et al. Nat. Med.*; published online Sept. 4, 2011; doi:10.1038/nm.2420
   Contact: William R. Jacobs Jr., Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.
   e-mail: jacobsw@hhmi.org
2. Pym, A.S. *et al. Mol. Microbiol.* **46**, 709–717 (2002)
3. Gey Van Pittius, N.C. *et al. Genome Biol.* **2**, RESEARCH0044 (2001)
4. Stinear, T.P. *et al. Genome Res.* **18**, 729–741 (2008)
5. Siegrist, M.S. *et al. Proc. Natl. Acad. Sci. USA* **106**, 18792–18797 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

Aeras, Rockville, Md.
Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.
Emergent BioSolutions Inc. (NYSE:EBS), Rockville, Md.
Howard Hughes Medical Institute, Chevy Chase, Md.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
State Serum Institute, Copenhagen, Denmark
University of Oxford, Oxford, U.K.

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				
Breast cancer	Heat shock protein 90 (Hsp90); Hsp70	*In vitro* studies identified an Hsp90 inhibitor that could help treat breast cancer. Hsp90 inhibitors that work by blocking the Hsp90 ATP-binding site can promote cancer cell survival through increased expression of Hsp70. In triple-negative breast cancer cells, a compound that blocked Hsp90's interaction with a cochaperone lowered Hsp70 expression, whereas a compound that blocked the Hsp90 ATP-binding site increased Hsp70 expression. The interaction inhibitor also increased cell-cycle arrest and apoptosis and decreased cell migration compared with a compound that blocked the Hsp90 ATP-binding site. Next steps could include testing the interaction inhibitor in mouse models of cancer. At least 13 companies have Hsp90 inhibitors in clinical and preclinical testing to treat cancer. ***SciBX* 4(37); doi:10.1038/scibx.2011.1034** **Published online Sept. 22, 2011**	Findings unpatented; unavailable for licensing	Pimienta, G. *et al. Mol. Pharm.*; published online Sept. 1, 2011; doi:10.1021/mp200346y **Contact:** Genaro Pimienta, Yale University, New Haven, Conn. e-mail: genaro.pimienta-rosales@yale.edu
Cancer	Glutathione S-transferase ω1 (GSTO1)	*In vitro* studies identified GSTO1 inhibitors that could help treat cancer. In a human breast cancer cell line, a lead α-chloroacetamide–based compound selectively inhibited GSTO1 with an IC_{50} of 35 nM. In the same cells, the GSTO1 inhibitor plus cisplatin increased cytotoxicity compared with cisplatin alone. Next steps include determining whether the compound selectivity inhibits GSTO1 *in vivo* and whether inhibiting GSTO1 alone or in combination with chemotherapy impairs tumor growth in xenograft mouse models. ***SciBX* 4(37); doi:10.1038/scibx.2011.1035** **Published online Sept. 22, 2011**	Unpatented; licensing status not applicable	Tsuboi, K. *et al. J. Am. Chem. Soc.*; published online Sept. 7, 2011; doi:10.1021/ja2066972 **Contact:** Benjamin F. Cravatt, The Scripps Research Institute, La Jolla, Calif. e-mail: cravatt@scripps.edu
Cancer	HER2 (EGFR2; ERBB2; neu); neuregulin 1 (NRG1)	*In vitro*, mouse and patient studies suggest HER2 inhibitors could help treat EGFR inhibitor–resistant cancer. In primary and metastatic colorectal cancer patients, greater levels of HER2 or NRG1 in tumors were associated with resistance to Erbitux cetuximab and correlated with poor survival. In a panel of Erbitux-resistant human cancer cell lines, HER2 and NRG1 levels were higher than those in Erbitux-sensitive cell lines. In xenograft mice with Erbitux-resistant cancer cells, Erbitux plus Tykerb lapatinib or pertuzumab decreased tumor growth compared with Erbitux alone. Ongoing work includes additional studies in xenograft models and primary tumors. Eli Lilly and Co., Bristol-Myers Squibb Co. and Merck KGaA market Erbitux, a mAb targeting EGFR, to treat colorectal cancer and head and neck cancer. GlaxoSmithKline plc markets Tykerb/Tyverb, an inhibitor of HER2 and epidermal growth factor receptor 1 (EGFR1; HER1; ERBB1) to treat breast cancer. Pertuzumab (2C4; R1273; RG1273), a mAb HER dimerization inhibitor that prevents HER2 from binding to HER1, HER3 (EGFR3; ERBB3) and HER4 (EGFR4; ERBB4) from Roche's Genentech Inc. unit and Chugai Pharmaceutical Co. Ltd., is in Phase III testing to treat breast cancer, Phase II testing to treat non–small cell lung cancer (NSCLC) and Phase I testing to treat ovarian cancer. ***SciBX* 4(37); doi:10.1038/scibx.2011.1036** **Published online Sept. 22, 2011**	Patent and licensing status for findings in first study unavailable Findings in second study unpatented; available for partnering	Yonesaka, K. *et al. Sci. Transl. Med.*; published online Sept. 7, 2011; doi:10.1126/scitranslmed.3002442 **Contact:** Kazuhiko Nakagawa, Kinki University School of Medicine, Osaka, Japan e-mail: nakagawa@med.kindai.ac.jp **Contact:** Pasi A. Jänne, Dana-Farber Cancer Institute, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. e-mail: pjanne@partners.org Bertotti, A. *et al. Cancer Discov.*; published online Sept. 2, 2011; doi:10.1158/2159-8290.CD-11-0109 **Contact:** Livio Trusolino, Institute for Cancer Research and Treatment, Torino, Italy e-mail: livio.trusolino@ircc.it

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Not applicable	*In vitro* and mouse studies identified illudin M–based compounds that could help treat cancer. Ferrocene and ruthenocene diester derivatives of the cytotoxic fungal metabolite illudin M had low micromolar IC_{50} values in 8 human cancer cell lines and were about 5- to 50-fold more potent in these cells than in normal fibroblasts. In mice, both types of derivatives were well tolerated, whereas illudin M caused toxicity. Next steps include testing activity of the compounds in xenograft mouse models of cancer. ***SciBX* 4(37); doi:10.1038/scibx.2011.1037** **Published online Sept. 22, 2011**	Unpatented; unavailable for licensing	Schobert, R. *et al. J. Med. Chem.*; published online Aug. 18, 2011; doi:10.1021/jm200359n **Contact:** Thomas Mueller, Martin Luther University Halle-Wittenberg, Halle, Germany e-mail: thomas.mueller@medizin.uni-halle.de **Contact:** Rainer Schobert, University of Bayreuth, Bayreuth, Germany e-mail: Rainer.Schobert@unibayreuth.de
Cancer	Serine/threonine kinase 33 (STK33)	Cell culture studies suggest inhibiting STK33 may not help treat cancer. Previous work had suggested that small hairpin RNA knockdown of STK33 lowered growth of tumor cell lines driven by activating mutations in *K-Ras*. However, a team at Amgen Inc. found no effect from STK33 knockdown in 27 *K-Ras* wild-type and mutated tumor lines. In addition, small molecule inhibitors of STK33 did not decrease growth in *K-Ras* mutant tumors. Next steps include identifying other proteins that could be targeted to prevent growth of *K-Ras* mutant tumors. Amgen has discontinued development of its STK33 program (*see* **STK33 strikes out, page 5**). ***SciBX* 4(37); doi:10.1038/scibx.2011.1038** **Published online Sept. 22, 2011**	Patent and licensing status undisclosed	Babij, C. *et al. Cancer Res.*; published online July 8, 2011; doi:10.1158/0008-5472.CAN-11-0778 **Contact:** Isabelle Dussault, Amgen Inc., Thousand Oaks, Calif. e-mail: idussaul@amgen.com
Cancer	Tissue factor	Mouse studies suggest inhibiting the tissue factor–activated coagulation cascade could help treat cancer. In a mouse model of breast cancer, two doxorubicin prodrugs that targeted coagulation-associated serum proteases accumulated in the tumor, which decreased tumor growth and lung metastases and prolonged mouse survival compared with doxorubicin control. Next steps include selecting a lead compound. Eisai Co. Ltd.'s MORAb-066, a humanized mAb against tissue factor, is in preclinical testing to treat pancreatic cancer. Genmab A/S's HuMax-TF tissue factor mAb is in preclinical testing to treat cancer. Affinity Pharmaceuticals Inc. did not disclose their next steps. ***SciBX* 4(37); doi:10.1038/scibx.2011.1039** **Published online Sept. 22, 2011**	Patent application filed; licensed by Affinity Pharmaceuticals; available for licensing, collaboration and investment	Liu, Y. *et al. Cancer Res.*; published online Aug. 31, 2011; doi:10.1158/0008-5472.CAN-11-1145 **Contact:** Cheng Liu, The Scripps Research Institute, La Jolla, Calif. e-mail: chengliu@scripps.edu
Cardiovascular disease				
Heart failure	ATPase Ca^{++} transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A); SMT3 suppressor of mif two 3 homolog 1 (SUMO1)	Studies in mice and in patient samples suggest upregulating cardiac SUMO1 could help treat heart failure. In heart failure patient samples, levels of SUMO1 and SUMOylation levels of SERCA2A, a transporter implicated in heart failure, were lower in failing hearts than normal hearts. In a mouse model of heart failure, animals overexpressing SUMO1 had greater heart function and longer survival than wild-type mice. Next steps include testing the effects of *SUMO1* gene therapy in pig models of heart failure and screening for compounds that increase SUMOylation of SERCA2A. ***SciBX* 4(37); doi:10.1038/scibx.2011.1040** **Published online Sept. 22, 2011**	Patent application filed; available for licensing from Mount Sinai School of Medicine **Contact:** William Chiang, Mount Sinai School of Medicine, New York, N.Y. e-mail: william.chiang@exchange.mssm.edu	Kho, C. *et al. Nature*; published online Sept. 7, 2011; doi:10.1038/nature10407 **Contact:** Roger J. Hajjar, Mount Sinai School of Medicine, New York, N.Y. e-mail: roger.hajjar@mssm.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Hypertension	CXC chemokine receptor 2 (CXCR2; IL8RB)	*In vitro* and mouse studies suggest CXCR2 antagonists could help treat familial pulmonary arterial hypertension (PAH). In a mouse model of PAH, the CXCR2 antagonist SCH527123 decreased both leukocyte infiltration in the lungs and pulmonary vascular remodeling and increased cardiac output compared with vehicle. Future studies could include testing CXCR2 antagonists in animal models of nonfamilial PAH. Navarixin (SCH527123) from Ligand Pharmaceuticals Inc. and Merck & Co. Inc. is in Phase II testing to treat chronic obstructive pulmonary disease (COPD). SB-656933, a CXCR2 antagonist from GlaxoSmithKline plc, is in Phase II testing to treat cystic fibrosis (CF). AZD5069, a CXCR2 antagonist from AstraZeneca plc, is in Phase II testing to treat COPD. ***SciBX* 4(37); doi:10.1038/scibx.2011.1041** **Published online Sept. 22, 2011**	Patent and licensing status unavailable	Burton, V.J. *et al. Blood*; published online Sept. 7, 2011; doi:10.1182/blood-2011-05-347393 **Contact:** Victoria J. Burton, Novartis Institutes for BioMedical Research, Horsham, U.K. e-mail: victoria.burton@novartis.com
Endocrine disease				
Diabetes	β-Site APP-cleaving enzyme 2 (BACE2); BACE1; transmembrane protein 27 (TMEM27)	Cell culture and mouse studies suggest preventing TMEM27 cleavage by inhibiting BACE2 could help treat type 2 diabetes. TMEM27 promotes pancreatic β cell function but is negatively regulated by a previously unknown protease. In a mouse pancreatic β cell line, small interfering RNA knockdown of Bace2 decreased Tmem27 cleavage compared with knockdown of Bace1 or a panel of other proteases. In a mouse model of type 2 diabetes, a BACE2 inhibitor increased both β cell mass and glucose tolerance compared with vehicle. Roche, which coauthored the study, said that it has performed additional preclinical experiments to further explore the utility of the target but declined to disclose next steps. ***SciBX* 4(37); doi:10.1038/scibx.2011.1042** **Published online Sept. 22, 2011**	Patent applications filed by Roche covering assays relevant to the target; unavailable for licensing; patent and licensing status from the Swiss Federal Institute of Technology Zurich (ETHZ) unavailable	Esterházy, D. *et al. Cell Metab.*; published online Sept. 7, 2011; doi:10.1016/j.cmet.2011.06.018 **Contact:** Markus Stoffel, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: stoffel@imsb.biol.ethz.ch
Diabetes	p38 Mitogen-activated protein kinase (p38 MAPK; MAPK14); X-box binding protein 1 (XBP1)	Mouse studies suggest p38 MAPK activation in the liver could help treat type 2 diabetes. In obese mice, p38 Mapk activity and Xbp1 nuclear translocation were lower than those in lean mice. Also in the obese mice, adenovirus-mediated expression of MAP kinase kinase 6 (Map2k6) in the liver increased activation of p38 Mapk, Xbp1 nuclear translocation, insulin sensitivity and glucose tolerance compared with adenovirus-mediated expression of a control protein. Next steps include identifying compounds that activate p38 MAPK. ***SciBX* 4(37); doi:10.1038/scibx.2011.1043** **Published online Sept. 22, 2011**	Patent application ready to be filed; licensing status not applicable	Lee, J. *et al. Nat. Med.*; published online Sept. 4, 2011; doi:10.1038/nm.2449 **Contact:** Umut Ozcan, Harvard Medical School, Boston, Mass. e-mail: umut.ozcan@childrens.harvard.edu
Infectious disease				
HIV/AIDS	Lysine-specific histone demethylase 1 (KDM1A; LSD1)	*In vitro* studies suggest inhibiting LSD1 could prevent reactivation of latent HIV. In T cells with latent HIV infection, small hairpin RNA knockdown or small molecule inhibition of LSD1 prevented activation of HIV transcription compared with what was seen using shRNA or vehicle controls. Next steps could include developing more specific LSD1 inhibitors. ***SciBX* 4(37); doi:10.1038/scibx.2011.1044** **Published online Sept. 22, 2011**	Patent and licensing status unavailable	Sakane, N. *et al. PLoS Pathog.*; published online Aug. 18, 2011; doi:10.1371/journal.ppat.1002184 **Contact:** Melanie Ott, University of California, San Francisco, Calif. e-mail: mott@gladstone.ucsf.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pneumonia; staphylococcus	ADAM10	Mouse studies suggest inhibiting the α-hemolysin receptor ADAM10 could help treat staphylococcal pneumonia. In mice, α-hemolysin-deficient *Staphylococcus aureus* caused less pulmonary histopathology than a wild-type *S. aureus* strain. In a model of lethal *S. aureus* pneumonia, Adam10 knockout mice had decreased lung histopathology compared with wild-type littermates. Next steps include identifying additional targets that could help treat or prevent *S. aureus* α-hemolysin-mediated disease. ***SciBX* 4(37); doi:10.1038/scibx.2011.1045** **Published online Sept. 22, 2011**	Patent applications filed covering targeting of α-hemolysin-mediated processes; available for licensing from The University of Chicago Office of Technology and Intellectual Property	Inoshima, I. *et al. Nat. Med.*; published online Sept. 18, 2011; doi:10.1038/nm.2451 **Contact:** Juliane Bubeck Wardenburg, The University of Chicago, Chicago, Ill. e-mail: jbubeckw@peds.bsd.uchicago.edu
Viral infection	DNA-damage-inducible transcript 4 (DDIT4; RTP801; REDD1)	*In vitro* and cell culture studies suggest inducing REDD1 expression could help treat viral infection. A screen of 200,000 compounds identified naphthalimide-based compounds that inhibited replication of influenza virus and vesicular stomatitis virus. In wild-type cells infected with influenza virus, the lead compound induced the expression of REDD1 and increased cell survival compared with vehicle. The compound did not increase the survival of infected REDD1-deficient cells. Next steps include developing additional compounds identified in the high throughput screen. ***SciBX* 4(37); doi:10.1038/scibx.2011.1046** **Published online Sept. 22, 2011**	Patent and licensing status undisclosed	Mata, M.A. *et al. Nat. Chem. Biol.*; published online Sept. 11, 2011; doi:10.1038/nchembio.645 **Contact:** Beatriz M.A. Fontoura, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas e-mail: beatriz.fontoura@utsouthwestern.edu
Neurology				
Addiction	Protein kinase Cε (PKCE)	Mouse studies suggest PKCE inhibition could help treat both alcohol and nicotine addiction. Previous studies showed Pkce knockout mice had lower alcohol self-administration than wild-type controls. In a new study using these knockout mice, nicotine self-administration also was lower than that for wild-type controls. Next steps include developing a small molecule PKCE inhibitor that penetrates the CNS. ***SciBX* 4(37); doi:10.1038/scibx.2011.1047** **Published online Sept. 22, 2011**	Unpatented; available for licensing	Lee, A.M. & Messing, R.O. *Proc. Natl. Acad. Sci. USA*; Sept. 12, 2011; doi:10.1073/pnas.1106277108 **Contact:** Robert O. Messing, University of California, San Francisco, Calif. e-mail: romes@gallo.ucsf.edu
Depression	Oxytocin receptor (OXTR)	A study in humans suggests modulating OXTR could be useful for treating mood disorders including depression. In a psychological assessment of 326 subjects, carriers of the A allele of *OXTR* had lower optimism and self-esteem than individuals homozygous for the more common G allele (p=0.031 and p=0.004, respectively). Next steps include determining the functional differences between the G and A alleles of *OXTR* and testing whether pharmacological modulation of OXTR can affect psychological characteristics. Trigemina Inc. has nasally delivered oxytocin in Phase IIa testing for chronic headache. Pastorus Pharma LLC has nasally delivered oxytocin in preclinical development for autism spectrum disorder (ASD) and schizophrenia (*see* **Optimism about oxytocin, page 4**). ***SciBX* 4(37); doi:10.1038/scibx.2011.1048** **Published online Sept. 22, 2011**	Unpatented; licensing status not applicable	Saphire-Bernstein, S. *et al. Proc. Natl. Acad. Sci. USA*; published online Sept. 6, 2011; doi:10.1073/pnas.1113137108 **Contact:** Shelley E. Taylor, University of California, Los Angeles, Calif. e-mail: taylors@psych.ucla.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology	Lysophosphatidic acid receptor 1 (LPAR1; EDG2; LPA1)	A study in mice suggests LPAR1 antagonists may help prevent or treat hemorrhage-associated fetal hydrocephalus (FH). In mouse embryos given lysophosphatidic acid to induce FH, pretreatment with an LPAR1 antagonist decreased disease-associated histological changes in the brain compared with vehicle. Next steps include studying different chemical scaffolds of LPAR1 antagonists and dosing the molecules at different points during FH disease progression. AM152, an LPA1 antagonist from Bristol-Myers Squibb Co., has completed Phase I testing for pulmonary fibrosis. ***SciBX* 4(37); doi:10.1038/scibx.2011.1049** **Published online Sept. 22, 2011**	Unpatented; licensing status not applicable	Yung, Y.C. *et al. Sci. Transl. Med.*; published online Sept. 7, 2011; doi:10.1126/scitranslmed.3002095 **Contact:** Jerold Chun, The Scripps Research Institute, La Jolla, Calif. e-mail: jchun@scripps.edu
Seizures	Solute carrier family 7 member 11 cystine glutamate transporter (SLC7A11; xCT)	Mouse studies suggest the xCT blocker Azulfidine sulfasalazine could help reduce seizures associated with glioma. In mice implanted with human gliomas, glutamate release from tumor cells triggered epileptic events. Animals receiving Azulfidine at concentrations similar to those used in the clinic for other indications had decreased epileptic events compared with untreated controls. Next steps could include testing Azulfidine in additional mouse models. Pfizer Inc. markets Azulfidine to treat inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). ***SciBX* 4(37); doi:10.1038/scibx.2011.1050** **Published online Sept. 22, 2011**	Patent and licensing status unavailable	Buckingham, S.C. *et al. Nat. Med.*; published online Sept. 11, 2011; doi:10.1038/nm.2453 **Contact:** Harald Sontheimer, The University of Alabama at Birmingham, Birmingham, Ala. e-mail: sontheimer@uab.edu

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
Disease models			
Modeling HIV infection with transgenic cats	Transgenic cats expressing antiviral host factors could be used as models to develop new treatments for HIV infection. Cats are naturally infected with the HIV-related feline immunodeficiency virus (FIV). Transgenic cats were generated by injecting a lentiviral transgene vector into oocytes prior to *in vitro* fertilization. In cats expressing a primate antiviral protein, FIV replication was lower than that in wild-type controls. Next steps include studying additional antiviral host factors in the model. ***SciBX* 4(37); doi:10.1038/scibx.2011.1051** **Published online Sept. 22, 2011**	Unpatented; unavailable for licensing	Wongsrikeao, P. *et al. Nat. Methods*; published online Sept. 11, 2011; doi:10.1038/nmeth.1703 **Contact:** Eric Poeschla, Mayo Clinic, Rochester, Minn. e-mail: emp@mayo.edu
Mouse model of hypokalemic periodic paralysis	A mouse model of hypokalemic periodic paralysis could aid the development of new treatments for the dise ase. Hypokalemic periodic paralysis is an inherited genetic disease that can be caused by mutations in *sodium channel voltage-gated type IV α-subunit* (*SCN4A*). Mice carrying mutations in the murine homolog of *SCN4A* recapitulated disease symptoms, including transient loss of muscle excitability and absence of myotonia. Next steps include using the model to screen for disease-modifying interventions. ***SciBX* 4(37); doi:10.1038/scibx.2011.1052** **Published online Sept. 22, 2011**	Patent and licensing status undisclosed	Wu, F. *et al. J. Clin. Invest.*; published online Sept. 1, 2011; doi:10.1172/JCI57398 **Contact:** Stephen C. Cannon, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas e-mail: steve.cannon@utsouthwestern.edu
Transgenic, metabotropic glutamate receptor subtype 5 (mGluR5; GRM5)-expressing mouse models of melanoma	Transgenic mice that express wild-type mGlur5 in melanocytes could be useful for identifying melanoma therapies. In the transgenic mice, melanoma tumors developed on hairless skin of the ear, tail and other areas, and in lymph nodes. The mice also developed invasive tumors in muscle and bone that were consistent with malignant or metastatic human melanoma. Future studies could include testing melanoma therapies in the models. ***SciBX* 4(37); doi:10.1038/scibx.2011.1053** **Published online Sept. 22, 2011**	Unpatented; available for licensing from the NIH **Contact:** Betty B. Tong, National Institutes of Health, Bethesda, Md. e-mail: tongb@mail.nih.gov	Choi, K.Y. *et al. Proc. Natl. Acad. Sci. USA*; published online Sept. 6, 2011; doi:10.1073/pnas.1107304108 **Contact:** Katherine W. Roche, National Institutes of Health, Bethesda, Md. e-mail: rochek@ninds.nih.gov
Drug platforms			
Genetically attenuated *Mycobacterium smegmatis* as a tuberculosis (TB) vaccine vector	Genetically attenuated strains of *M. smegmatis* could be used as vectors for TB vaccines. *M. smegmatis* strains lacking the *esx-3* locus were modified to carry the orthologous *esx-3* locus from the closely related *M. tuberculosis*. In mouse models of *M. smegmatis* infection, the modified strain had attenuated virulence compared with wild-type strains. In a mouse model of lethal *M. tuberculosis* infection, immunization with the *M. smegmatis* strains increased survival compared with immunization with the bacillus Calmette-Guérin (BCG) vaccine. Next steps include stabilizing expression of the inserted genes and identifying specific genes encoding TB antigens that could improve the resulting immune response. The *M. smegmatis*–based TB vaccine program at Aeras is in discovery stages (*see* ***Smegmatis* meets *tuberculosis*, page 6**). ***SciBX* 4(37); doi:10.1038/scibx.2011.1054** **Published online Sept. 22, 2011**	Patent pending; use of *M. smegmatis* vaccine vector for TB licensed to Aeras; use of *M. smegmatis* vaccine vector for other indications available for licensing	Sweeney, K.A. *et al. Nat. Med.*; published online Sept. 4, 2011; doi:10.1038/nm.2420 **Contact:** William R. Jacobs Jr., Albert Einstein College of Medicine of Yeshiva University, New York, N.Y. e-mail: jacobsw@hhmi.org
Markers			
Using CD34-negative and stem cell factor receptor tyrosine kinase (c-Kit; KIT; CD117)-positive cell levels to predict systemic mastocytosis severity	Studies in patient samples suggest $CD34^-$/c-Kit^+ cell levels could predict systemic mastocytosis prognosis. In serum samples from patients with mastocytosis, $CD34^-$/c-Kit^+ cell levels were higher than those in serum from healthy controls ($p<0.005$) and correlated with disease severity. Next steps could include validating the association in a larger patient cohort. ***SciBX* 4(37); doi:10.1038/scibx.2011.1055** **Published online Sept. 22, 2011**	Patent and licensing status unavailable	Georgin-Lavialle, S. *et al. Blood*; published online Aug. 30, 2011; doi:10.1182/blood-2011-02-335950 **Contact:** Olivier Hermine, University Paris Descartes, Paris, France e-mail: ohermine@gmail.com

Company and institution index

Target and compound index