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Turning lupus against cancer

By Lauren Martz, Staff Writer

Yale School of Medicine researchers have shown that a lupus autoantibody inhibited DNA repair mechanisms in cancer cells and sensitized mice to radiation and chemotherapy.[1] The group is planning Phase I trials of the autoantibody in patients with cancer.

Although DNA damage repair responses are necessary to combat the toxic effects of environmental and chemical stressors, the responses can reduce or block the efficacy of chemotherapy and radiation therapies.

To increase the efficacy of chemotherapy and radiation, researchers have begun to identify compounds that inhibit the DNA damage repair response in cancer cells and could be delivered as adjuncts to chemotherapy. One approach in the clinic is inhibition of poly(ADP-ribose) polymerase (PARP), which is an upstream component of a single-strand DNA break repair pathway. Inhibition of PARP sensitizes cancers to DNA-damaging therapies but only reduces activity of the single-strand DNA break repair pathway. At least eight companies have PARP inhibitors in clinical testing to treat various cancers.

Now, Peter Glazer and colleagues at Yale have shown that a lupus autoantibody blocks the DNA damage repair response in cancer cells.

Glazer is chairman of the Department of Therapeutic Radiology and professor of genetics at Yale School of Medicine.

In 1999, researchers at the **University Hospital of Lausanne** tested a DNA-targeting lupus autoantibody, 3E10, that was identified in a mouse model of systemic lupus erythematosus (SLE) as a vaccine in patients with SLE.[2] The team found that the antibody was safe, but they dropped development because of competing priorities and because it crossed the cell membrane and entered into the nucleus, which could cause negative effects on cellular gene expression.

Francois Spertini, associate professor and internist in the Department of Immunology and Allergy at the University Hospital of Lausanne and lead author on the 1999 study, told *SciBX* that his team did not pursue 3E10 further due to competing priorities, although the vaccine was immunogenic. Despite potential risks of nuclear penetration, his team did not see any related safety issues in the patients with SLE.

Subsequent studies found that the antibody entered cells via interactions between its single-chain variable fragment (scFv) and the equilibrative nucleoside transporter 2 (ENT2) surface receptor.[3]

Building on those previous studies, Glazer and colleagues set out to use 3E10 as a delivery vehicle that enhances the radioprotective effect of heat shock protein 70 (Hsp70) in breast cancer cells. However, the team found that 3E10 alone was sufficient to improve the effects of radiation.

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In addition, both breast cancer and glioma cells had greater sensitivity to the DNA-damaging chemotherapeutic doxorubicin when treated with 3E10.

In mice with human glioma xenografts, 3E10 plus doxorubicin or radiation increased tumor suppressive effects compared with doxorubicin or radiation alone.

In vitro, the antibody selectively bound DNA and decreased the efficiency of repair pathways for both single- and double-stranded DNA.

The group next tested whether 3E10 would have increased efficacy against tumors with intrinsic deficiencies in DNA damage responses, such as breast, ovarian and prostate cancers with mutations in *breast cancer 2 early onset* (*BRCA2*).

"[The 3E10 autoantibody] inhibits two important DNA repair pathways that many cancers depend on to resist chemotherapy and radiation. Existing therapies, such as PARP inhibitors, inhibit just one of these pathways, so the antibody has the potential to be more effective than PARP inhibitors in some settings."

—Peter Glazer, Yale School of Medicine

Indeed, 3E10 alone triggered cell death in *BRCA2*-deficient human ovarian cancer cells but not in *BRCA2*-proficient cells. 3E10 plus doxorubicin or radiation further improved the anticancer effect in *BRCA2*-deficient ovarian or prostate cancer cells.

The findings were published in *Science Translational Medicine*.

The 3E10 autoantibody "inhibits two important DNA repair pathways that many cancers depend on to resist chemotherapy and radiation. Existing therapies, such as PARP inhibitors, inhibit just one of these pathways, so the antibody has the potential to be more effective than PARP inhibitors in some settings," said corresponding author Glazer.

The paper also included researchers from the **VA Greater Los Angeles Healthcare System**, the **Beckman Research Institute at City of Hope**, the **University of California, Los Angeles** and **The University of Vermont**.

Clinical safety

Glazer told *SciBX* that his group's next steps "are to determine the impact of 3E10 on cancer cells with a range of deficiencies in DNA repair to determine the tumors that will be most sensitive to the antibody."

He plans to start Phase I testing of the antibody in two to three years in glioblastoma multiforme (GBM) and certain breast, ovarian and pancreatic tumors. "Our initial laboratory work has shown that the antibody is especially good at radiosensitizing malignant gliomas. Since the standard of care for high-grade gliomas is radiation therapy followed by surgical resection, we think that clinical testing in this setting would make sense."

Spertini said it is not yet clear from the mouse trials how often the antibody will need to be given. "The antibodies do not have a long half-life *in vivo*. We often treat autoimmune patients with monoclonal antibodies, and we need to repeat administration every month in most

cases for a sustained effect."

"One issue with treating humans with this antibody is that it is a murine antibody, and it is possible that humans could develop neutralizing antibodies. In the human trial in 1999, it appears that 3E10 did induce significant neutralizing antibodies, suggesting that one might need to modify the antibody for prolonged human use," said Andrew Allen, EVP of clinical and preclinical development and CMO of **Clovis Oncology Inc.**

Clovis' rucaparib, an oral PARP inhibitor, is in Phase I testing to treat breast and ovarian cancers. The company also has a partnership with **Foundation Medicine Inc.** for a companion diagnostic that sequences the tumors to identify patients with *BRCA* mutations or related mutations that would best benefit from the treatment.

Glazer countered that "it is not necessary to humanize the antibody if it will be used in cancer therapy regimens in one or a few short doses."

He added that the limited doses also prevent the risk of causing lupus. "For cancer therapy, the antibody would just be given a few times and would be administered transiently. To cause lupus, it would need to be consistently present in high amounts," he said.

Allen said another potential issue is that mice received a dose of the antibody that equates "to about 50 mg/kg in humans," which would likely be too expensive to manufacture.

He added, "The other problem with such high doses is that they can create toxicities by nonspecific binding."

Glazer told *SciBX* that his team is working to improve the potency of the antibody to reduce the doses required for efficacy. He also said commercial antibody production should lead to higher activity and purity than the antibodies used in the mouse studies.

Additionally, he said that "our preliminary work in *BRCA2*-deficient ovarian cancer cells suggests that low doses of the antibody may be very effective in such cells."

Glazer said the Yale School of Medicine has filed a patent application covering the work. The IP is available for licensing.

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Animal instincts

By Tim Fulmer, Senior Writer

Experimental design and reporting requirements taken for granted in clinical trials are often lacking in preclinical research, making it difficult to predict the translational potential of an early stage finding. Now, a workshop convened by the **NIH**'s **National Institute of Neurological Disorders and Stroke** has generated a set of standards for designing and reporting on animal studies.[1] The challenge will be to implement the standards throughout the research community and determine which preclinical studies should adhere to them.

In June, NINDS convened a two-day workshop entitled Optimizing the Predictive Value of Preclinical Research, which was attended by researchers, journal editors and grant reviewers with the express goal of developing preclinical reporting standards similar to those used in the clinical research community.

Participants included researchers from **Roche** and **Bayer AG**, grant reviewers from NINDS, editors from *The Journal of the American Medical Association*, *Nature*, *Nature Neuroscience*, *Science*, *Cell*, *Neuron* and *Neurology*, and researchers from a variety of universities, institutes and foundations, including the NIH's **National Center for Advancing Translational Sciences** (NCATS).

The resulting standards were published last month in *Nature* and addressed four areas the participants agreed were under-reported in grant applications and the peer-reviewed literature: randomization, blinding, sample-size estimation and data handling.

Many of the standards are obvious but surprisingly not part of common practice. For example, a review of 100 articles published in *Cancer Research* in 2010 found that only 28% of papers reported the use of randomization in animal studies, and just 2% of papers reported that the investigators were blinded during treatment.[2]

According to the new standards, researchers should randomly assign animals to experimental groups and should report the actual method of randomization. Moreover, researchers need to be blinded to what group a given animal is assigned, and the blinding should remain intact over the duration of the experiment.

Each animal study should have sample sizes that ensure sufficient statistical power to detect meaningful differences between groups, and the method of estimation should be reported.

Rules for stopping data collection, criteria for including and excluding data and all endpoints should be defined prospectively and reported. Investigators also should report how often a particular experiment was performed and how well it repeated over a range of conditions.

Finally, participants discussed strategies for implementing the new standards.

The workshop said funding agencies and journals need to provide peer reviewers with a "minimum set of standards that should routinely be considered in evaluating the appropriateness of a study."

Also, authors should be asked to provide information addressing the reporting guidelines on a standardized check-box form that accompanies manuscript submission. Such standardized forms are used by clinical research journals.

Other recommendations included encouraging investigators and journals to publish negative findings, creating a database for negative results and encouraging independent replication of studies.

Standard application

The push to implement the new standards "should come from the key levers that control research behavior—publishers and funders," said Elizabeth Iorns, CEO of **Science Exchange**, a research service provider that links individual researchers with CROs. "A check-box solution at points of publication and grant submission would be the most obvious place to start."

"Peer reviewers would have the primary role to ensure that methodological specifications are provided," added Daniele Fanelli, a research fellow at **The University of Edinburgh** who has written about publication bias in the life and social sciences.[3–5] "Researchers would simply have to comply and, since adherence to the standards would become a mark of quality, most journals and institutions would eventually adopt the standards voluntarily."

> **"The key issue here is that translational research and basic biological research may make use of animal models in different ways. The experimental design required to show that a compound has a therapeutic effect in an animal model is likely different from an experimental design that uses an animal model to explore a basic biological process."**
>
> ***—Kalyani Narasimhan, Nature Neuroscience***

Earlier this year, Science Exchange and online publisher **PLOS** launched the Reproducibility Initiative to help researchers carry out and publish the replication of preclinical translational experiments.[6]

Neither Iorns nor Fanelli participated in the NINDS workshop.

At first, journals should adopt the standards and post online guidance on how experiments should be done, said workshop participant Katrina Kelner, editor of *Science Translational Medicine*. Then, with increased awareness of the need for better reporting in the preclinical research community, it might be possible for journals to require that elements such as blinding and randomization be included in publications, she said.

Not always applicable

Although introducing a set of experimental design and reporting standards to help better assess the translational value of animal studies would bring obvious benefits, careful thought will have to be given to what sort of preclinical experiments such standards should be applied to in the first place.

For example, very early stage observational experiments looking for any possible difference between groups of animals would be exempt from the standards. This hypothesis-generating work "is frequently conducted using a small sample size, does not have a primary outcome and is often unblinded" and is thus distinct from hypothesis-testing experiments, the authors wrote.

Even with the reporting standards agreed upon and in place, editors and reviewers will have to be cautious not to apply them indiscriminately to judge all preclinical research, said workshop participant Kalyani

Narasimhan, chief editor of *Nature Neuroscience*.

"Many preclinical animal studies focus on basic biological phenomena and may not be designed to have their findings directly translated into drug discovery efforts," said Narasimhan. "In some cases, for example, lack of blinding or randomization may not necessarily negate the findings and may not, by itself, be a reason for not publishing the paper."

She added, "The key issue here is that translational research and basic biological research may make use of animal models in different ways. The experimental design required to show that a compound has a therapeutic effect in an animal model is likely different from an experimental design that uses an animal model to explore a basic biological process."

Shai Silberberg acknowledged that "it is unrealistic to expect hypothesis-generating studies with no prespecified endpoints to meet all the proposed experimental standards, and certainly it is okay to publish those studies. Nonetheless, even in those cases, we expect the researchers to make clear to the reader that they used an exploratory experimental design, with perhaps a small number of animals and a lack of blinding and randomization."

Silberberg is a program director at NINDS and was corresponding author on the *Nature* paper describing the workshop's recommendations.

Purely practical matters may also make it difficult for standard academic labs to design experiments that meet the reporting standards, said Iorns. Many preclinical studies "are conducted by a single postdoc or grad student who designs and conducts the experiment and analyzes the data by themselves. They cannot necessarily be expected to do blinding, as it is only them conducting the research."

The reporting standards and individual presentations from the June workshop are posted on the NINDS homepage.

Looking beyond reporting

Poor reporting standards are only one part of the difficulties associated with translating published research.

"While promoting better reporting and better experimental design are obviously things we should strive to improve in scientific publications, those are not the only issues at the preclinical level responsible for poor translation into the clinic," said Narasimhan. "Animal models of CNS conditions and other diseases are often inherently poor and often poorly predictive of human disease pathology."

Indeed, two recent commentaries highlighted the myriad limitations of preclinical research programs.

In a commentary published this month in *Nature*, Jessica Bolker said the reliance of research biologists on a small handful of model organisms, such as the fly, mouse and worm, has significantly narrowed the types of hypotheses that can be accurately tested.[7]

If researchers use standard models that leave out "key causal elements such as environmental influences, we cannot hope to construct a complete picture of the mechanisms that underlie crucial variations, for example in development and disease," wrote Bolker, who is associate professor of zoology at the **University of New Hampshire**.

Thus, choosing a research model "should be more than a matter of convenience or convention," wrote Bolker. "Scientists need to ask more questions—about the goals of a specific experiment, how suitable a given model is to reaching those goals and what environmental or other factors might be relevant to how well the model works."

Bolker concluded her commentary by calling on NCATS to "support the development of new systems for investigating problems that are not tractable in currently favored models."

In a commentary published in *Nature Reviews Drug Discovery*, three **AstraZeneca plc** researchers—Ian Peers, Peter Ceuppens and Chris Harbron—argued that "the systematic incorporation of expert statistical input into the design, analysis and interpretation of preclinical and translational research will help improve its quality, robustness and reproducibility."[8]

Noting that a high level of statistical rigor is required in the clinical phases of drug development, the authors asked, "Why is it then considered appropriate to conduct preclinical research without insisting on the same level of statistical rigor and quality?"

Among the reasons for the lack of rigor, the authors cited limited regulatory oversight, the limited number of qualified preclinical statistical experts and a general lack of awareness among researchers of the value added by good statistical practice to preclinical work.

To help remedy the problem, the authors suggested the involvement of statisticians in preclinical research "be organized in a systematic way with clear roles and accountabilities, not on a 'we'll call you when needed' basis, which is a common situation" in preclinical research.

Moreover, detailed statistical reviews should be incorporated in industrial governance processes and academic review processes "to set an expectation across the scientific community of the need to ensure that conclusions from data are justified," according to the authors.

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COMPANIES AND INSTITUTIONS MENTIONED

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Science Exchange, Palo Alto, Calif.
The University of Edinburgh, Edinburgh, U.K.
University of New Hampshire, Durham, N.H.

MuSIC by design

By Tracey Baas, Senior Editor

A **Harvard Medical School** and **Tsinghua University** team has developed a technology, dubbed MuSIC, that identifies synergistic drug pairs.[1] The group showed proof of concept by finding new combinations of therapeutics for HIV, but weeding out false negatives could prove challenging.

Finding synergistic drug combinations typically involves either a hypothesis-driven approach or an unbiased pairwise combinatorial screen that uses two compounds per well. The former approach can miss unanticipated interactions between targets not thought to be mechanistically linked, whereas the latter can be too unwieldy for most academic labs.

The HMS-Tsinghua team opted for a different approach called multiplex screening for interacting compounds (MuSIC), which was able to evaluate 10 compounds per well.

"Compared to the direct combination screen that is used widely in industry, MuSIC affords higher efficiency from screening a large number of combinations by multiplexing."

—Stephen Elledge, Harvard Medical School

The team used MuSIC to examine about 500,000 drug pairs from 1,000 FDA-approved or clinically tested drugs and showed that the technology covered all 2-drug combinations using <3% of the number of wells needed in a standard unbiased screen.

A key strategy that makes MuSIC so efficient is an algorithm that guarantees each drug pair occurs in at least one well, minimizes the number of redundant pairs and provides an arrayed compound library made up of 13,106 wells—or pools—distributed in multiple 384-well plates (*see* **Figure 1, "MuSIC strategy"**).

Thus, the researchers could evaluate 13,106 drug pools rather than 500,000 drug pairs.

The team then used a two-part cellular assay to evaluate the pools with HIV-infected cells during early and late stages of the virus' lifecycle. Part one of the assay monitored viral infection from entry to protein translation. Part two reinforced part one and also monitored viral infection during assembly, budding and infectivity.

Based on low infection rates and low cytotoxicity, 288 pools were selected and 12,904 unique drug pairs were identified. The researchers then constructed a secondary arrayed compound library and used it to home in on the top 116 drug pairs. The pairs were further validated using concentration titrations of the two drugs in each well (*see* **Figure 1, "MuSIC strategy"**).

Many of the hits belonged to a small set of drug classes including nonsteroidal anti-inflammatory drugs (NSAIDs), anticholinergics and glucocorticoids. Indeed, four glucocorticoids appeared most frequently within the top drug pairs.

To validate these results, the team did a pairwise screen of a generic glucocorticoid, prednisolone, with the same drugs used in the MuSIC screen and showed that 7 of the top 15 hits of the pairwise screen had also been identified using MuSIC, providing an estimated discovery rate of about 47%.

The researchers next looked more closely at the molecular pair with the highest efficacy: prednisolone and the antiprotozoal drug nitazoxanide.

In cell-based assays, nitazoxanide affected the viral lifecycle after entry but before, or at, reverse transcription. Prednisolone affected the virus lifecycle after reverse transcription. The researchers hypothesized that the synergy between the drugs resulted from their targeting different steps in the HIV lifecycle.

Interestingly, the cell-based assay that focused on the early HIV lifecycle revealed enrichment for many drugs with known anti-HIV activity and anti-inflammatory functions, whereas the cell-based assay that focused on the late HIV lifecycle revealed only one drug with known anti-HIV activity and others that were new targets for HIV therapies.

Although chronic inflammation is known to contribute to infection-associated pathology,[2] the new results suggest that anti-inflammatory therapies can actually inhibit virus propagation.

Results were reported in *Nature Biotechnology*.

Mixing the MuSIC

"Compared to the direct combination screen that is used widely in industry, MuSIC affords higher efficiency from screening a large number of combinations by multiplexing," said team leader Stephen Elledge, professor of genetics and medicine at Harvard Medical School.

"This work is a great example of combining clever computational and experimental approaches to screen for undiscovered and effective combinations on a vast scale," added Brent Stockwell, associate

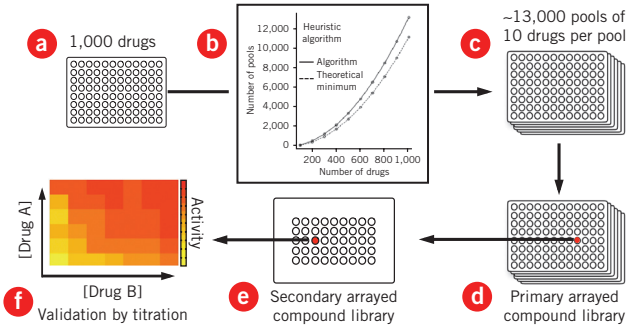

Figure 1. MuSIC strategy. Multiplex screening for interacting compounds (MuSIC) technology is able to identify synergistic drug pairs. The technology involves distributing 1,000 approved or clinically tested drugs [**a**] into an arrayed compound library. An algorithm [**b**] ensures each of the possible 500,000 interactions between two given molecules is represented in 13,106 pools [**c**]. The pools in the primary arrayed compound library are evaluated for activity against HIV-infected cells [**d**]. Hits (red wells) from the primary screen are evaluated, and identified synergistic pairs are used to construct a secondary arrayed compound library, which also is evaluated for antiviral activity [**e**]. Hits (red wells) from the secondary library are validated using concentration titrations of the two drugs [**f**]. The analyses of antiviral efficacy for steps [**d**] and [**e**] involved a two-part cell-based assay that measured effects of molecules on early and later stages of the virus' lifecycle.

professor of biological sciences and chemistry at **Columbia University**. "The disadvantage is that with the complexity of the pool, there could be a high rate of false positives and false negatives."

"While the method will miss unusual combinations that aren't strong hits, I like the MuSIC method because it allows for very efficient screening through many combinations, and I would be excited to see this methodology applied across a large panel of microbial assays," noted Joseph Lehar, associate director of bioinformatics at the **Novartis Institutes for BioMedical Research** and adjunct assistant professor at **Boston University**.

"Any pooled screening method will miss possible combinations—these techniques cannot find all interactions. I think more studies are necessary to understand the true false-positive and false-negative rates."
—Alexis Borisy, Third Rock Ventures

"Any pooled screening method will miss possible combinations—these techniques cannot find all interactions," said Alexis Borisy, a partner at **Third Rock Ventures**. "I think more studies are necessary to understand the true false-positive and false-negative rates. The team shows one validation set and says they find 47% of all possible combinations, but this of course will vary between the experiment types selected for each disease indication."

Prior to joining Third Rock, Borisy was president and CEO of CombinatoRx Inc. (now **Zalicus Inc.**), which developed combinations of approved drugs using combination high throughput screening (cHTS) technology.

Chen Yu Zong, professor of pharmacy and lead of the Bioinformatics and Drug Design Group at the **National University of Singapore**, had another caveat. In the study, the researchers excluded highly active antiretroviral therapy (HAART) drugs and other antivirals to avoid the screen being dominated by these drugs. By doing so, said Zong, the researchers are precluding the discovery of potentially new or more potent drug combinations.

Birgit Schoeberl, VP of discovery at **Merrimack Pharmaceuticals Inc.**, said it would be interesting to compare the drug combinations identified by the screen with the standard-of-care HAART regimen or to add prednisolone and nitazoxanide to HAART in animal models of HIV infection.

Going forward, Schoeberl could see MuSIC applied to identify new drug combinations in other infectious diseases, such as hepatitis C or malaria, or in oncology.

"Cancer drug screens could be done using a malignant cell line and a benign cell line to look for drug combinations that specifically kill the malignant cells, and the readout could be any cell viability assay," said Xu Tan, postdoctoral researcher in the Elledge lab and lead author of the paper describing the findings. "Any disease with a cell culture model could be screened using the MuSIC method."

Ongoing work includes testing combinations identified in the study to inhibit HIV and pathogenic viruses and using MuSIC to evaluate combinations that could be used to treat other infectious diseases, cancer or asthma.

The Harvard Medical School team's work is not patented or licensed.

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COMPANIES AND INSTITUTIONS MENTIONED

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IBD's bacteria cafeteria

By Kai-Jye Lou, Staff Writer

The challenges of delivering the protease inhibitor elafin to the gut have stymied efforts to use this anti-inflammatory protein as a therapeutic for intestinal inflammation. Now, researchers in France have engineered food-grade lactic acid bacteria that secrete elafin.[1] Oral delivery of the engineered bacteria reduced inflammation and restored intestinal homeostasis in mouse models of inflammatory bowel disease.

ViThera Pharmaceuticals Inc. holds a license to the technology and thinks it will be ready to move the engineered bacteria into a Phase I trial by late 2014 in patients with mild to moderate ulcerative colitis (UC).

Elafin is a protease inhibitor that targets elastase and proteinase-3. In the gut of healthy individuals, elafin is primarily produced by intestinal epithelial cells. Downregulated elafin expression and elevated proteolytic activity in the gut are linked to Crohn's disease and UC, the two major forms of IBD.[2–4]

In 2011, a French research group led by Nathalie Vergnolle published data from genetic studies in mice suggesting elafin can protect against intestinal inflammation.[5]

"Elafin is a multifunctional protein with multiple protective properties that make it a good choice for use in IBD," said Vergnolle, deputy director of The Physiopathology Center of Toulouse-Purpan at the **Institut National de la Santé et de la Recherche Médicale** (INSERM). "The protein can restore the balance of intestinal proteolytic activity, inhibit the recruitment of inflammatory cells and their release of proinflammatory factors, has antimicrobial properties and also could help re-equilibrate the gut microflora."

The problem is that digestive processes in the gut destroy elafin, and the layer of mucus lining the gut acts as a physical barrier that prevents the protein from efficiently reaching its site of action at the gut epithelium. Delivering high concentrations of the protein to the gut would be impractical in IBD and also could interfere with digestion.

The group thus looked to the intestinal microflora to supplement the gut mucosa with a steady supply of elafin. To do so, the team settled on two strains of lactic acid bacteria—*Lactococcus lactis* and *Lactobacillus casei*—as vectors for elafin delivery. These bacteria are adapted to survive in the gut microenvironment and have a generally recognized as safe (GRAS) status with the FDA.

"Lactic acid bacteria are known to colonize the gut when ingested and are found in the normal intestinal microflora," Vergnolle told *SciBX*. "Thus we sought to transform the bacteria to have them produce and secrete elafin."

In a mouse model of chemically induced colitis, oral delivery of elafin-secreting *L. lactis* or *L. casei* restored proteolytic homeostasis and reduced gut inflammation, whereas wild-type strains did not. In human colon epithelial cell culture, elafin-secreting *L. lactis* protected the cells from inflammation-induced loss of barrier function, whereas wild-type *L. lactis* did not. *L. casei* was not evaluated in the latter study.

Results were published in *Science Translational Medicine*. Philippe Langella, a research director at the **French National Institute for Agricultural Research** (INRA) and cofounder of ViThera, was a coauthor of the study.

"Our data show that we can very significantly reduce inflammation in the gut by treating mice orally with our engineered lactic acid bacteria," said Vergnolle, the corresponding author.

Benefits of bacteria

ViThera founder and president Johannes Fruehauf said that the data demonstrate the utility of the company's EnLact platform, which uses engineered lactic acid bacteria to deliver therapeutic proteins to the gut.

"In our mind, engineered lactic acid bacteria are the only way to get effective delivery of therapeutic proteins to the intestinal epithelium," he told *SciBX*. "We don't think capsule-based delivery of elafin itself, or any other therapeutic protein, would be very effective because the protein will be released into the intestinal lumen and will still need to get through a mucous barrier before it reaches the intestinal epithelium. The intestine is rich in proteases and because of this, very little of the protein would be able to reach the intestinal epithelium before it is destroyed."

> **"If our approach works, it could be used in conjunction with current treatments to help push the disease into remission, prolong the time the disease stays in remission and reduce the need for immunosuppressive drugs in patients."**
>
> ***—Johannes Fruehauf, ViThera Pharmaceuticals Inc.***

Fruehauf noted that the engineered bacteria described in the paper attach to the intestinal epithelium, which is the site where elafin needs to be delivered. He also said secreted elafin acts locally and is unlikely to have systemic effects.

Fruehauf added that systemically delivered antiprotease therapies are known to be associated with significant side effects such as joint toxicity.

He thinks the engineered bacteria could be used in many types of IBD. "I think our approach can be applied across the entire range of IBD patients, from those who have very severe disease to those who have very mild disease, and possibly even in those whose disease is in remission," he said. "Current data in IBD patients show that there is still unbalanced proteolytic activity in the noninflamed regions of the gut, so we may be able to use our engineered bacteria to restore that balance."

The company uses fermentation to produce large quantities of the engineered bacteria. The purification step "is a simple and cost-effective process involving filtration," according to Fruehauf.

Restore and reduce

Fruehauf and Vergnolle both think elafin-secreting bacteria could be used together with marketed IBD drugs such as glucocorticoids, methotrexate and anti–tumor necrosis factors (TNFs) as an adjunctive therapy to restore intestinal functionality.

Existing drugs that reduce inflammation by suppressing the immune system also increase the risk of serious infections and cancer. Moreover, glucocorticoids can disrupt lipid and glucose metabolism.

"For now, we think our approach using these engineered bacteria could supplement existing therapies to treat IBD but won't necessarily

replace them," said Fruehauf. "If our approach works, it could be used in conjunction with current treatments to help push the disease into remission, prolong the time the disease stays in remission and reduce the need for immunosuppressive drugs in patients."

ViThera is developing an attenuated, nondisseminating strain of elafin-secreting *L. casei* for use in humans. The product likely will involve freeze-dried bacteria in a capsule with a polysaccharide coating that facilitates targeted release in the large intestine. He said the company opted for engineered *L. casei* over *L. lactis* because the former is better at attaching to the intestinal epithelium.

INSERM, INRA, the **Pasteur Institute** and **Paris Diderot University** have cofiled for a patent covering recombinant probiotic bacteria to treat and prevent IBD and irritable bowel syndrome (IBS). The IP is licensed to ViThera.

Lou, K.-J. *SciBX* 5(44); doi:10.1038/scibx.2012.1154
Published online Nov. 8, 2012

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e-mail: nathalie.vergnolle@inserm.fr
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COMPANIES AND INSTITUTIONS MENTIONED

Institut National de la Santé et de la Recherche Médicale, Toulouse, France
French National Institute for Agricultural Research, Paris, France
Paris Diderot University, Paris, France
Pasteur Institute, Paris, France
ViThera Pharmaceuticals Inc., Cambridge, Mass.

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				
Cancer	β-Catenin (CTNNB1)	*In vitro* and cell culture studies identified a CTNNB1 antagonist that could help treat wingless-type MMTV integration site (WNT) and CTNNB1–driven cancers. A stapled peptide, identified by a combination of structure-based design and directed evolution, bound CTNNB1 at a coactivator recruitment site with nanomolar affinity. In colorectal cancer cell lines driven by WNT and CTNNB1 signaling, the stapled peptide decreased cell proliferation compared with an inactive control peptide. Next steps could include testing the efficacy of the stapled peptide *in vivo*. ***SciBX* 5(44); doi:10.1038/scibx.2012.1155** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Grossmann, T.N. *et al. Proc. Natl. Acad. Sci. USA*; published online Oct. 15, 2012; doi:10.1073/pnas.1208396109 **Contact:** Gregory L. Verdine, Harvard University, Cambridge, Mass. e-mail: gregory_verdine@harvard.edu
Cancer	Not applicable	Mouse studies suggest oncolytic viruses could help prevent cancer metastasis following surgery. In multiple mouse models of cancer, surgery-induced stress suppressed the activity of NK cells, which led to pulmonary metastases. In the same mouse models, perioperative delivery of the oncolytic virus JX-594 or the oncolytic parapoxvirus dubbed orf activated NK cells and decreased pulmonary metastases compared with no treatment. Next steps include evaluating other ways of stimulating the innate immune system in cancer. JX-594, a recombinant vaccinia virus from Jennerex Inc., is in Phase II testing to treat various cancers. ***SciBX* 5(44); doi:10.1038/scibx.2012.1156** **Published online Nov. 8, 2012**	JX-594 patented by Jennerex; patent filed by Ottawa Hospital Research Institute covering the orf oncolytic parapoxvirus; available for licensing **Contact:** Anouk Fortin, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada phone: 613-737-8899 x78930 e-mail: afortin@ohri.ca	Tai, L.-H. *et al. Cancer Res.*; published online Oct. 22, 2012; doi:10.1158/0008-5472.CAN-12-1993 **Contact:** Rebecca A. Auer, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada e-mail: rauer@ohri.ca
Prostate cancer	MicroRNA-23b (miR-23b)	Patient sample and mouse studies suggest increasing miR-23b signaling could help treat prostate cancer. In patient samples, miR-23b expression was lower in prostate cancer tissue than in benign prostatic hyperplasia and normal tissue. In a mouse xenograft model of prostate cancer, intratumoral delivery of miR-23b decreased tumor growth compared with delivery of control miRNA. Next steps could include evaluating vehicles for targeted delivery of miR-23b in prostate cancer models. ***SciBX* 5(44); doi:10.1038/scibx.2012.1157** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Majid, S. *et al. Cancer Res.*; published online Oct. 16, 2012; doi:10.1158/0008-5472.CAN-12-2181 **Contact:** Rajvir Dahiya, San Francisco VA Medical Center and University of California, San Francisco, Calif. e-mail: rdahiya@urology.ucsf.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Serotonin; tryptophan hydroxylase 1 (TPH1; TPH)	Mouse studies suggest inhibiting synthesis of gut-derived serotonin through TPH1 could help treat type 2 diabetes. In mice, *Tph1* deficiency, which leads to reduced synthesis of gut-derived serotonin, increased insulin and glucose tolerance compared with normal *Tph1* expression. In mice fed a high-fat diet, pharmacological inhibition of Tph1 normalized insulin tolerance and increased glucose tolerance compared with no inhibition. Next steps could include identifying other targets for inhibiting gut-derived serotonin synthesis. ***SciBX* 5(44); doi:10.1038/scibx.2012.1158** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Sumara, G. *et al. Cell Metab.*; published online Oct. 18, 2012; doi:10.1016/j.cmet.2012.09.014 **Contact:** Gerard Karsenty, Columbia University Medical Center, New York, N.Y. e-mail: gk2172@columbia.edu
Metabolic syndrome; obesity	Lacto-N-fucopentaose III (LNFPIII)	*In vitro* and mouse studies suggest LNFPIII could help treat metabolic diseases. In macrophages, LNFPIII led to greater expression of anti-inflammatory IL-10 than vehicle. In mice with high-fat diet–induced obesity and metabolic syndrome, LNFPIII prevented hepatic steatosis and increased glucose tolerance and insulin sensitivity compared with vehicle. Next steps include improving the delivery method for the glycan and determining long-term effects. ***SciBX* 5(44); doi:10.1038/scibx.2012.1159** **Published online Nov. 8, 2012**	Patent Cooperation Treaty patent application filed; currently under option with an undisclosed company; unavailable for licensing	Bhargava, P. *et al. Nat. Med.*; published online Oct. 28, 2012; doi:10.1038/nm.2962 **Contact:** Chih-Hao Lee, Harvard School of Public Health, Boston, Mass. e-mail: clee@hsph.harvard.edu **Contact:** Donald A. Harn, The University of Georgia, Athens, Ga. e-mail: dharn@uga.edu
Hematology				
Neutropenia	E selectin (SELE; CD62E)	Mouse studies suggest blocking SELE could help prevent neutropenia during chemotherapy or radiation therapy. In mice receiving chemotherapy or radiotherapy, *Sele* knockout increased hematopoietic stem cell (HSC) survival and leukocyte numbers compared with *Sele* expression. In wild-type mice receiving chemotherapy, pretreatment with the pan-selectin antagonist GMI-1070 promoted HSC quiescence and self-renewal and neutrophil recovery, and it led to increased survival compared with saline pretreatment. Ongoing work includes designing SELE-specific antagonists and optimizing for bioavailability. GMI-1070, a pan-selectin inhibitor from GlycoMimetics Inc. and partner Pfizer Inc., is in Phase II testing to treat sickle cell disease. ***SciBX* 5(44); doi:10.1038/scibx.2012.1160** **Published online Nov. 8, 2012**	Multiple issued and pending patents covering GMI-1070 and related pan-selectin antagonists; licensed to Pfizer	Winkler, I.G. *et al. Nat. Med.*; published online Oct. 21, 2012; doi:10.1038/nm.2969 **Contact:** Jean-Pierre Lévesque, Mater Medical Research Institute, South Brisbane, Queensland, Australia e-mail: jplevesque@mmri.mater.org.au **Contact:** Ingrid G. Winkler, same affiliation as above e-mail: iwinkler@mmri.mater.org.au

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
HCV	Protein kinase B (PKB; PKBA; AKT; AKT1); phosphoinositide 3-kinase (PI3K)	*In vitro* studies suggest inhibiting the PI3K and AKT pathway could help prevent HCV infection. In human hepatocytes, infection with a highly virulent strain of HCV led to AKT phosphorylation as early as 15 minutes after infection and peaked at 30 minutes. In the cells, AKT or PI3K inhibitors or small interfering RNA targeting AKT decreased HCV core protein levels compared with vehicle or control siRNA. Next steps could include testing the effects of AKT inhibition in animal models. At least 17 companies have PI3K inhibitors and at least 13 companies have AKT inhibitors in preclinical and clinical development to treat various cancers. ***SciBX* 5(44); doi:10.1038/scibx.2012.1161** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Liu, Z. *et al. J. Biol. Chem.*; published online Oct. 24, 2012; doi:10.1074/jbc.M112.414789 **Contact:** Jing-hsiung James Ou, University of Southern California Keck School of Medicine, Los Angeles, Calif. e-mail: jamesou@hsc.usc.edu
Malaria	Unknown	*In vitro* studies identified two fluoroalkylated γ-lactams derived from 4-aminoquinoline that could help treat malaria. In a chloroquine-sensitive and a multidrug-resistant strain of *Plasmodium falciparum*, the two most potent compounds inhibited the parasite with nanomolar IC_{50} values. Mouse model studies to demonstrate *in vivo* oral efficacy of the lead γ-lactams are ongoing. ***SciBX* 5(44); doi:10.1038/scibx.2012.1162** **Published online Nov. 8, 2012**	Patent application filed; available for licensing from University of Lyon Science Transfer **Contact:** Christine Duarte, University of Lyon, Lyon, France e-mail: christine.duarte@universite-lyon.fr	Cornut, D. *et al. J. Med. Chem.*; published online Oct. 29, 2012; doi:10.1021/jm301076q **Contact:** Maurice Medebielle, University of Lyon, Lyon, France e-mail: maurice.medebielle@univ-lyon1.fr **Contact:** Jean-Philippe Bouillon, University and National Institute of Applied Sciences of Rouen, Mont Saint Aignan, France e-mail: jeanphilippe.bouillon@univ-rouen.fr
Inflammation				
Inflammation	Bromodomain containing 4 (BRD4); IL-6	*In vitro* and rodent studies identified BRD4 inhibitors that could help treat inflammation. Fragment-based screening, chemical synthesis and *in vitro* testing of sulfonamide analogs of quinazolinone identified a lead compound as a nanomolar inhibitor of BRD4. In a human monocyte-based inflammation assay, the lead compound blocked lipopolysaccharide (LPS)-induced IL-6 production with a low micromolar EC_{50} value. In normal mice and rats, the lead compound showed oral bioavailability and good pharmacokinetics. Future studies could include testing the compound in animal models of inflammation. Resverlogix Corp.'s RVX-208, an inhibitor of the bromodomain and extra terminal domain (BET) family of bromodomain-containing proteins including BRD4, is in Phase II testing to treat diabetes and atherosclerosis and Phase I testing to treat Alzheimer's disease (AD). Mitsubishi Tanabe Pharma Corp. and Oncoethix S.A. have OTX015, a synthetic small molecule inhibitor of BET BRD2, BRD3 and BRD4, in Phase I testing to treat cancer. ***SciBX* 5(44); doi:10.1038/scibx.2012.1163** **Published online Nov. 8, 2012**	Patent and licensing status undisclosed	Fish, P. *et al. J. Med. Chem.*; published online Oct. 25, 2012; doi:10.1021/jm3010515 **Contact:** Dafydd R. Owen, Pfizer Worldwide R&D, Cambridge, Mass. e-mail: dafydd.owen@pfizer.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	Solute carrier family 25 member 38 (SLC25A38); β-amyloid 42	Human and rodent studies suggest inhibiting SLC25A38 could prevent neurodegeneration in AD. In the brains of patients with AD, SLC25A38 levels were higher than those in healthy controls. In primary rat and mouse neurons and in a human neuroblastoma cell line, β-amyloid 42 increased SLC25A38 levels and caspase-induced apoptosis compared with no treatment. In the rodent primary neurons and the cell line, small interfering RNA against *SLC25A38* decreased β-amyloid 42–induced apoptosis compared with control siRNA. Ongoing work includes evaluating the effects of knocking out *Slc25a38* in animal AD models. ***SciBX* 5(44); doi:10.1038/scibx.2012.1164** **Published online Nov. 8, 2012**	Unpatented; available for licensing or partnering	Zhang, H. *et al. J. Neurosci.*; published online Oct. 31, 2012; doi:10.1523/JNEUROSCI.3668-12.2012 **Contact:** Huaxi Xu, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: xuh@sanfordburnham.org **Contact:** Ye-Guang Chen, Tsinghua University, Beijing, China e-mail: ygchen@tsinghua.edu.cn
Ataxia	Potassium channel KCa2.2 (KCNN2); KCNN3; ataxin 2 (ATXN2; SCA2)	Mouse studies suggest positive allosteric modulators (PAMs) of KCNN2 could help treat spinocerebellar ataxia type 2. In *SCA2*-expressing transgenic mouse models of the condition, Purkinje neurons showed aberrant firing patterns. In cerebellar slices from those mice, NS13001, a PAM of KCNN2 and KCNN3, normalized Purkinje neuron firing patterns. In the mouse model, a PAM optimized for potency against KCNN2 increased motor performance compared with pretreatment baselines. NeuroSearch A/S plans to test NS13001 in other models of cerebellar and/or episodic ataxia. ***SciBX* 5(44); doi:10.1038/scibx.2012.1165** **Published online Nov. 8, 2012**	Patented by NeuroSearch; available for licensing	Kasumu, A.W. *et al. Chem. Biol.*; published online Oct. 26, 2012; doi:10.1016/j.chembiol.2012.07.013 **Contact:** Ilya Bezprozvanny, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: ilya.bezprozvanny@utsouthwestern.edu **Contact:** Palle Christophersen, NeuroSearch A/S, Ballerup, Denmark e-mail: pc@neurosearch.com
Cognitive dysfunction	IL-1 receptor	Rat studies suggest antagonizing IL-1 receptor in the brain could help prevent postoperative cognitive dysfunction in older individuals. In aged rats subjected to a laparotomy, brain infusion of an IL-1 receptor antagonist at the time of surgery prevented postoperative cognitive deficits and neuroinflammation, whereas intraperitoneal injection of the same antagonist did not. Next steps could include developing a strategy capable of delivering an IL-1 receptor antagonist into the CNS. Kineret anakinra, an IL-1 receptor antagonist from Amgen Inc. and Swedish Orphan Biovitrum AB, is marketed to treat rheumatoid arthritis. Arcalyst rilonacept, a recombinant protein with the heterodimeric IL-1 receptor linked to the Fc portion of human IgG from Regeneron Pharmaceuticals Inc., is marketed to treat NLR family pyrin domain containing 3 (NLRP3; NALP3; CIAS1)-associated periodic syndrome (CAPS). At least four other companies have IL-1 receptor inhibitors in Phase II testing or earlier to treat various indications. ***SciBX* 5(44); doi:10.1038/scibx.2012.1166** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Barrientos, R.M. *et al. J. Neurosci.*; published online Oct. 17, 2012; doi:10.1523/JNEUROSCI.2173-12.2012 **Contact:** Ruth M. Barrientos, University of Colorado at Boulder, Boulder, Colo. e-mail: ruth.barrientos@colorado.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pain; spinal cord injury (SCI)	Purinergic receptor P2X ligand-gated ion channel 4 (P2RX4)	An SAR study identified P2RX4 antagonists that could be useful for treating neuropathic pain and SCI. Genetic inactivation of *P2RX4* previously has been shown to reduce inflammatory and neuropathic pain associated with SCI. In a cell culture assay, the lead compound in a series of N-substituted phenoxazines inhibited human P2RX4 with an IC_{50} value of 0.189 μM and showed 35-fold higher selectively for P2RX4 than for related receptors. Next steps include optimizing potency, selectivity and oral availability of the compounds and evaluating them in mouse models of neuropathic pain. ***SciBX* 5(44); doi:10.1038/scibx.2012.1167** **Published online Nov. 8, 2012**	Unpatented; licensing status not applicable	Hernandez-Olmos, V. *et al. J. Med. Chem.*; published online Oct. 17, 2012; doi:10.1021/jm300845v **Contact:** Christa E. Müller, University of Bonn, Bonn, Germany e-mail: christa.mueller@uni-bonn.de

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			
Androgen receptor (AR) activation levels on circulating tumor cells (CTCs) to predict response to second-line therapy in castration-resistant prostate cancer (CRPC)	*In vitro* studies suggest AR activation on CTCs could help prostate cancer prognosis. In untreated patients with human prostate cancer, AR activation was greater on CTCs than on samples from healthy controls. CTCs from patients that responded to first-line androgen deprivation therapy showed activated AR phenotypes, whereas CTCs from patients with CRPC showed both activated and inactivated AR phenotypes. In patients with CRPC, having more than 10% CTCs with the mixed AR phenotype prior to second-line therapy or a highly activated AR phenotype after therapy was associated with reduced overall survival. Next steps could include confirming the findings in additional patients. ***SciBX* 5(44); doi:10.1038/scibx.2012.1168** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Miyamoto, D.T. *et al. Cancer Discov.*; published online Oct. 23, 2012; doi:10.1158/2159-8290.CD-12-0222 **Contact:** Daniel A. Haber, Massachusetts General Hospital, Charlestown, Mass. e-mail: haber@helix.mgh.harvard.edu **Contact:** Shyamala Maheswaran, same affiliation as above e-mail: maheswaran@helix.mgh.harvard.edu
Fluorescent sensor for γ-aminobutyric acid (GABA) and GABA receptor ligands	A fluorescent sensor could be useful for measuring concentrations of GABA and GABA receptor ligands on the cell surface. The sensor system uses a fluorescent fusion protein of a GABA-binding protein and a synthetic ligand that competes with GABA binding to its receptor. The sensor system measured micromolar to millimolar GABA concentrations on the surface of a cultured mammalian cell line. Next steps include determining whether the sensor system can measure GABA concentrations in neural synapses. ***SciBX* 5(44); doi:10.1038/scibx.2012.1169** **Published online Nov. 8, 2012**	Patent application filed covering technology used in the sensor system; licensed to New England Biolabs Inc.	Masharina, A. *et al. J. Am. Chem. Soc.*; published online Oct. 24, 2012; doi:10.1021/ja306320s **Contact:** Kai Johnsson, Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland e-mail: kai.johnsson@epfl.ch
Chemistry			
Synthesis of xanthofulvin and vinaxanthone	A method to synthesize the natural compounds xanthofulvin and vinaxanthone could help their development in spinal cord injury (SCI). Xanthofulvin was synthesized from tetronic acid via a 13-step process, which represents the first synthesis of the compound. Vinaxanthone was synthesized from tetronic acid via a 9-step process, whereas the previous method required 14 steps. In nematode worms, synthetic xanthofulvin and vinaxanthone increased neuronal outgrowth compared with vehicle. Next steps include identifying and testing synthetic derivatives of these compounds. ***SciBX* 5(44); doi:10.1038/scibx.2012.1170** **Published online Nov. 8, 2012**	Unpatented; licensing status not applicable	Axelrod, A. *et al. Angew. Chem. Int. Ed.*; published online Oct. 23, 2012; doi:10.1002/anie.201205837 **Contact:** Dionicio Siegel, The University of Texas at Austin, Austin, Texas e-mail: dsiegel@cm.utexas.edu
Disease models			
NADPH oxidase 2 (*Nox2*)-deficient, lupus-prone mice	*Nox2*-deficient, lupus-prone mice could be useful models for severe systemic lupus erythematosus (SLE). The mice were generated by crossing *Nox2*-deficient animals with mice that had a lupus-prone genetic background. The resulting mice had severe lupus symptoms including increased spleen weights, more severe renal pathology and high autoantibody levels compared with lupus-prone mice that expressed *Nox2*. Next steps could include using the mice to evaluate treatments for SLE. ***SciBX* 5(44); doi:10.1038/scibx.2012.1171** **Published online Nov. 8, 2012**	Patent and licensing status unavailable	Campbell, A.M. *et al. Sci. Transl. Med.*; published online Oct. 24, 2012; doi:10.1126/scitranslmed.3004801 **Contact:** Mark J. Shlomchik, Yale School of Medicine, New Haven, Conn. e-mail: mark.shlomchik@yale.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Transgenic rats expressing full-length *huntingtin* (*HTT*) as a model for Huntington's disease (HD)	Transgenic rats that express full-length *HTT* could help identify new HD therapies. Rats were generated that expressed a human bacterial artificial chromosome encoding full-length *HTT*, including 97 CAG/CAA repeats and all regulatory elements. The animals developed an early onset, progressive HD-like phenotype that recapitulated motor and behavioral impairments as well as brain histopathology. Next steps include a detailed cognitive characterization of the rat model and additional *in vivo* imaging studies. *SciBX* 5(44); doi:10.1038/scibx.2012.1172 Published online Nov. 8, 2012	Model unpatented; available for licensing	Yu-Taeger, L. *et al. J. Neurosci.*; published online Oct. 31, 2012; doi:10.1523/JNEUROSCI.1148-12.2012 **Contact:** Huu Phuc Nguyen, University of Tuebingen, Tuebingen, Germany e-mail: hoa.nguyen@med.uni-tuebingen.de
Xenograft mouse model for pediatric acute megakaryoblastic leukemia (AMKL)	A mouse xenograft model for pediatric AMKL could help identify new treatments for the cancer. Blast cells from the blood or bone marrow of patients with pediatric AMKL were injected into immunocompromised mice, with six of eight samples leading to successful engraftment. The models recapitulated aspects of the human disease, including low blast counts in the blood. In the model, the aurora kinase A (AURKA; aurora-A) inhibitor alisertib decreased leukemic blast levels and the incidence of paralysis and increased survival compared with placebo. Next steps include using this model to assess the efficacy of additional therapeutic candidates. Takeda Pharmaceutical Co. Ltd.'s alisertib (MLN8237) is in Phase III testing to treat peripheral T cell lymphoma (PTCL). The compound also is in Phase II testing or earlier to treat other cancers. *SciBX* 5(44); doi:10.1038/scibx.2012.1173 Published online Nov. 8, 2012	Patent and licensing status undisclosed	Thiollier, C. *et al. J. Exp. Med.*; published online Oct. 8, 2012; doi:10.1084/jem.20121343 **Contact:** Thomas Mercher, Institut National de la Santé et de la Recherche Médicale (INSERM), Vellejuif, France e-mail: thomas.mercher@inserm.fr
Drug platforms			
Elafin-secreting lactic acid bacteria for treating inflammatory bowel disease (IBD)	Elafin-secreting lactic acid bacteria could be useful for treating IBD. Two food-grade strains of lactic acid bacteria were engineered to express the protease inhibitor elafin, which is downregulated in the colons of patients with IBD. In a mouse model of chemically induced colitis, oral delivery of the engineered bacterial strain restored intestinal homeostasis and decreased gut inflammation compared with wild-type bacteria. Next steps include evaluating the safety of the engineered bacteria. ViThera Pharmaceuticals Inc. is developing the engineered bacteria for use in IBD (*see* **IBD's bacteria cafeteria, page 8**). *SciBX* 5(44); doi:10.1038/scibx.2012.1174 Published online Nov. 8, 2012	Patented; licensed to ViThera Pharmaceuticals	Motta, J.-P. *et al. Sci. Transl. Med.*; published online Oct. 31, 2012; doi:10.1126/scitranslmed.3004212 **Contact:** Nathalie Vergnolle, Institut National de la Santé et de la Recherche Médicale (INSERM), Toulouse, France e-mail: nathalie.vergnolle@inserm.fr
Markers			
Taste receptor type 2 member 38 (TAS2R38) genotyping for Gram-negative bacterial infection susceptibility	*In vitro* studies suggest TAS2R38 genotyping could help determine treatment regimens for Gram-negative bacterial infections. In human sinonasal cells, different genotypes of the TAS2R38 ion channel showed different levels of channel activation in response to molecules derived from Gram-negative bacteria. In human cells transfected with human TAS2R38 variants, Gram-negative bacterial killing was greater in cells with highly active channels than in those with less active channels. In patients with Gram-negative bacterial infections that did not respond to treatment and required surgery, none expressed the highly active TAS2R38 variant. Next steps include validating the association between TAS2R38 genotype and infection severity. *SciBX* 5(44); doi:10.1038/scibx.2012.1175 Published online Nov. 8, 2012	Patent application filed; available for licensing	Lee, R.J. *et al. J. Clin. Invest.*; published online Oct. 8, 2012; doi:10.1172/JCI64240 **Contact:** Noam A. Cohen, University of Pennsylvania, Philadelphia, Pa. e-mail: cohenn@uphs.upenn.edu

Company and institution index

Target and compound index