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Opening up Rosetta

By Lev Osherovich, Senior Writer

Merck & Co. Inc.'s soon-to-be shuttered **Rosetta Inpharmatics Inc.** unit is to be reborn as **Sage**, a not-for-profit institute that aims to provide precompetitive open access to the pharma's integrative genomics data set. This development takes on added significance now that newly published experiments help to validate Rosetta's intensive computational approach to metabolic disease target identification.

The mouse study in *Nature Genetics* shows that eight proteins involved in various aspects of metabolism and immunity could potentially be targeted to treat obesity and dyslipidemia.¹ The paper makes the most compelling case yet for the Rosetta approach, which involves predicting key genetic players in disease by sifting through massive sets of gene expression, protein-protein interactions, SNPs and quantifiable physiological traits data.

Merck is now winding Rosetta down, and the team behind the study plans to spin the division out as Sage. The goal is to bring academic biologists and computer scientists, plus industry pharmacogenomics researchers, together in a "precompetitive space," said Eric Schadt, the study's coauthor and formerly executive scientific director of Rosetta and now VP and CSO of Sage.

The key idea behind Sage, said Schadt, is to make Merck's previously proprietary data accessible to all interested parties without any IP strings attached. Open access to genomic data could move the discovery side of the industry away from a competitive model and toward consortium-style collaborations with academia, Schadt told *SciBX*.

Schadt and Rosetta founder Stephen Friend plan to launch Sage in July as a not-for-profit organization to continue Rosetta's collaborations with academia and industry and to build open-access software for genomic data analysis. Friend will be president and CEO of Sage.

Merck is backing the project by donating computers, and it plans to release most of the genomic data gathered by Rosetta into the public domain via Sage.

Although it will be another 3–5 years before Internet users will have full access to Sage, the team is already working with academics in three U.S. universities to open up Merck's database to new collaborators.

Fat city

Although previous studies by the Rosetta team had pointed to genes likely to play roles in obesity and diabetes in mice and humans,^{2,3} broad experimental proof had been lacking until now.

"This paper pulls together the validation that the algorithm is really quite predictive of biological significance on a gene-by-gene basis," said



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EDITORIAL
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Writers: Jesse Beckstein; Aaron Bouchie; Michael Flanagan; Tim Fulmer, Ph.D.; Michael Haas; Stephen Hansen; Kai-Jye Lou; Lauren Martz; Brian Moy; Lev Osherovich, Ph.D.; Steve Usdin

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Production Editor: Amanda Crawford

Copy Editor: Nicole DeGennaro

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Design: Claudia Bentley; Miles Davies

 For inquiries, contact editorial@scibx.com
PUBLISHING
Publisher: Peter Collins, Ph.D.

Associate Publishers: Melanie Brazil, Ph.D.; Eric Pierce

Marketing: Sara Girard; Tim Tulloch

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OFFICES
BioCentury Publications, Inc.

San Francisco

PO Box 1246

San Carlos, CA 94070-1246

T: +1 650 595 5333

Chadds Ford

223 Wilmington-West Chester Pike

Chadds Ford, PA 19317

T: +1 610 558 1873

Chicago

20 N. Wacker Drive, Suite 1465

Chicago, IL 60606-2902

T: +1 312 755 0798

Oxford

287 Banbury Road

Oxford OX4 7JA

United Kingdom

T: +44 (0)18 6551 2184

Washington, DC

2008 Q Street, NW, Suite 100

Washington, DC 20009

T: +1 202 462 9582

Nature Publishing Group

New York

75 Varick Street, 9th Floor

New York, NY 10013-1917

T: +1 212 726 9200

London

The Macmillan Building

4 Crinan Street

London N1 9XW

United Kingdom

T: +44 (0)20 7833 4000

Tokyo

Chiyoda Building 6F

2-37 Ichigayatamachi

Shinjuku-ku, Tokyo 162-0843

Japan

T: +81 3 3267 8751

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Thomas Drake, professor of pathology, laboratory medicine and clinical chemistry at the **University of California, Los Angeles**, and the senior author of the *Nature Genetics* study. "This opens up the possibility of identifying many more significant genes than you could with classical genetic approaches."

Classical approaches involve identifying mutants based on their phenotypes rather than trying to predict phenotype from computational models.

In previous studies, Rosetta and UCLA teams jointly analyzed integrative genomic data to come up with a list of the genes most likely to influence obesity and metabolic disease.⁴ In the new study, the researchers made knockout or transgenic mice with altered expression of the nine statistically strongest candidate genes.

The team then fed high-fat diets to the mutant mice and measured their body weight, plasma lipid composition and fat-to-muscle ratio. Eight of the nine mutant strains displayed abnormal fat-related phenotypes.

For example, mice with extra copies of *zinc finger protein 90 homolog (ZFP90)* and *β-lactamase (LACTB)*, as well as mice missing *complement component 3a receptor 1 (C3AR1; C3AR)* and *lipoprotein lipase (LPL)*, had higher overall fat levels than wild-type controls.

ZFP90 and C3AR were not previously known to affect lipid metabolism, and the role of LACTB in normal lipid metabolism was poorly understood.

Conversely, the team found that mice overexpressing *growth arrest-specific 7 (GAS7)* or *glutathione peroxidase 3 plasma (GPX3)* and mice lacking *NADP-dependent malic enzyme (ME1)* or *transforming growth factor-β receptor II (TGFB2)* had lower fat-related profiles than wild-type controls.

Altogether, the findings suggest ZFP90, ME1, LACTB and TGFB2 could be antagonized to treat obesity, whereas C3AR, LPL, GAS7 and GPX3 could be agonized to achieve a similar effect.

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UCLA's Drake believes the next step will be to choose targets from this list for pharmacological discovery and development. Indeed, most of the proteins on the list are either enzymes or receptors and are considered druggable.

Merck did not disclose whether it was pursuing any of the targets in the study.

Drake also thinks the approach won't be limited to obesity and expects that the technique could be used to identify metabolic genes involved in cancer. "There are close relationships between all of these basic body response mechanisms and cancer metabolism," he said.

Schadt added that the method's eight of nine success rate at predicting which mutations lead to obesity phenotypes could convince companies to dive headlong into higher-risk projects.

Typically, drug development doesn't begin until a large body of preclinical data provides a rationale for targeting a protein. However, Schadt believes that it may be worthwhile to launch small molecule screens against proteins pegged as key players based on computer modeling alone.

"If our predictions are achieving this kind of accuracy, you might be willing to place bigger bets without doing the animal [knockout] experiments," he said.

Jeff Shrager, CTO of computational biology company **CollabRx Inc.** and associate professor of symbolic systems at **Stanford University**, said the *Nature Genetics* study highlights the statistical power of Rosetta's approach.

"They're doing a very good job of putting numbers to their results. They can tell you not just what molecules are relevant, but can put statistical values on their predictions," he said.

However, Shrager cautioned that the genes chosen for *in vivo* validation in the *Nature Genetics* study may have been skewed toward enzymes with plausible biological roles in lipid metabolism due to overfitting of the computer models. If both computation and human expertise influenced the decision about which genes to study, the method may not be as useful for more poorly understood areas of biology, he said.

Shrager noted that the study lacked negative controls of mouse knockouts or transgenics chosen at random or from among genes that the computer deemed unlikely to be relevant to obesity.

Drake maintained that it was impractical to perform an extensive metabolic analysis on negative controls aside from wild-type mice and said it was highly unlikely that the eight of nine correct predictions were due to chance.

He said no new IP had been filed on the discoveries in the *Nature Genetics* study. A Merck spokesperson said some of the methods used in the study are covered by previous patents, which the company plans to make available to Sage.

Genomics clearinghouse

Schadt and Friend now plan to make the methodology used in the *Nature Genetics* study available to all Sage members. The goal of the project, said Friend, is to allow any researcher to probe Merck's database for interesting genetic interactions in other disease areas.

"Seven years, \$100 million and a lot of data in metabolism have shown us that we can build rather simple models to allow prediction of

targets with real effects," said Friend.

Rosetta was acquired by Merck in 2001, and the pharma invested heavily in building the computers needed to perform Rosetta's integrative genomic analyses. Although Rosetta went on to identify genetic networks that underlie metabolic disease in animal models and humans, Merck announced plans to shutter Rosetta's research division as part of a 2008 restructuring. Rosetta Biosoftware, a separate Merck subsidiary that sells genomic analysis tools, will continue to operate.

Sage has already raised \$5 million via angel investors and hopes to receive more funding through NIH and disease foundation grants.

Schadt and Friend plan to relocate the core of Rosetta's staff to three academic centers: the **Fred Hutchinson Cancer Research Center**, **Yale University** and another yet-to-be-determined academic institution on the West coast. Once settled, Sage will spend 3–5 years developing software tools to rework Merck's data into a more user-friendly, standardized form and put it on the Internet.

In the interim, researchers keen to comb Merck's data will need to collaborate with Sage's academic staff at the three host universities, according to Schadt.

Friend and Schadt hope the *Nature Genetics* study will entice academic and industry researchers to use Sage's data to make computational models of disease mechanisms and eventually add their own genomic data to the core dataset from Merck.

"This data set is only 1% of the biology for which you could potentially want to make models," said Friend, who said additional data would increase the predictive power of the database and could yield better results than solo in-house efforts.

"Currently, information generated in proprietary zones is smaller and less sufficient for models of disease than something in a larger public space like Sage," he said. "Doing the disease modeling work in a precompetitive space will free up resources for the real business of developing therapeutics."

Once Sage's software interface is in place, academic and industry researchers will be able to query and contribute to a large collection of data to generate testable hypotheses that will lead to publications, IP and, potentially, products (see **Figure 1**, "New value chain in genomics").

The Sage system is "going to be free and in the public domain," akin to the sequence data from the Human Genome Project, said John Wilbanks, executive director of the not-for-profit advocacy group **Science Commons** and a Sage SAB member.

Wilbanks expects most users to initially look at Merck's data without contributing their own observations to the common pool. However, users will get the most out of the analysis when they upload their own data sets and compare them against Merck's findings, he said.

The value proposition

Keith Yamamoto, professor of cellular and molecular pharmacology and executive vice dean for research at the **University of California, San Francisco**, thinks Sage is "the vanguard of a broader agenda to change academic-industry relations."

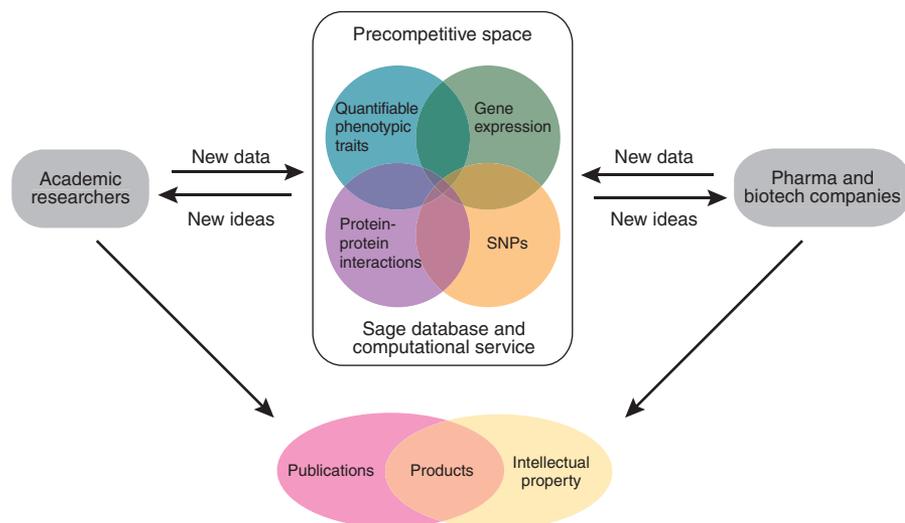
According to Yamamoto, the complexity of genomic data exceeds the capacity of any one company or academic group to comprehend it,

"Doing the disease modeling work in a precompetitive space will free up resources for the real business of developing therapeutics."

—Stephen Friend, Sage

Figure 1. New value chain in genomics.

According to the founders of **Sage**, an open-access genomics institute spun out of **Merck & Co. Inc.**, industry and academic researchers will be able to access Sage's database of 'precompetitive' gene expression data and other genomic information donated by Merck. But the ultimate richness of the data set will hinge on persuading other users to add to the database. Sage hopes the data will enable researchers to generate, test and publish papers on new hypotheses. The founders also expect new IP to be generated as scientists inside academia and corporations create new products inspired by the data.



making data sharing and collaboration essential for further progress.

“Consortia of academic and industry groups can take on complicated preclinical problems and biological processes that could yield benefits to both sides,” he said. “These could include truly predicting toxicology, making better animal models or—as Schadt is doing—developing predictive models.”

William Chin, SVP of discovery research and clinical investigation at **Eli Lilly and Co.**, said that pharmas will need to cooperate to understand the complex underpinnings of disease, but doing so will require changes in corporate culture to encourage data sharing.

“In fully integrated pharmaceutical companies, the focus is on control and ownership,” he said. “But we now realize that we don’t need to own everything.”

Chin said that because Sage is still in its embryonic stages, Lilly is not yet committing any resources to the project. He did say the company would be willing to play if the Sage team can demonstrate a usable product.

“Details on contributing data will still require working out, but philosophically we would want to go down this road,” said Chin.

Anthony Ford-Hutchinson, SVP and franchise head at Merck, said the company isn’t really giving up anything by opening its database to public users.

“When you discover targets, there really isn’t much defensible IP around it,” he said. “The proof will be when people start generating results from the data.”

“We’re hoping that Sage provides a platform to generate IP, not to have IP itself,” said Friend. “Merck is transferring a significant amount of data from which it has filed IP, but another group looking at the identical information could have different interpretations.”

“When you discover targets, there really isn’t much defensible IP around it. The proof will be when people start generating results from the data.”

—Anthony Ford-Hutchinson,
Merck & Co. Inc.

CollabRx’s Shrager was less sanguine, however, suggesting Merck may have already picked over the data for relevant IP opportunities. “If it’s so useful, why is Merck putting it out the door?” he said.

Friend disagreed. “You can bet that the majority of discoveries of value are still there” in the data set, he said.

CollabRx does plan to include access to Sage as part of its web-based collaborative biocomputing software, which is in beta testing.

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COMPANIES AND INSTITUTIONS MENTIONED

CollabRx Inc., Palo Alto, Calif.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Fred Hutchinson Cancer Research Center, Seattle, Wash.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
National Institutes of Health, Bethesda, Md.
Rosetta Inpharmatics Inc. (NASDAQ:RSTA), Kirkland, Wash.
Sage, Seattle, Wash.
Science Commons, San Francisco, Calif.
Stanford University, Stanford, Calif.
University of California, Los Angeles, Calif.
University of California, San Francisco, Calif.
Yale University, New Haven, Conn.

Next-gen polyamine attack

By Brian Moy, Staff Writer

The development of eflornithine monotherapy to treat cancer suffered a significant setback in 2004 when Ilex Oncology Inc., since acquired by **Genzyme Corp.**, reported that the polyamine biosynthesis inhibitor failed to prevent recurrence of bladder cancer in a Phase III trial. Although polyamine metabolism is frequently dysregulated in cancer cells, eflornithine monotherapy was stymied by two issues: toxicity at high doses and the ability of cells to import polyamines from external sources and circumvent the action of polyamine biosynthesis inhibitors.

Aminex Therapeutics Inc. has developed a series of lipophilic lysine-spermine conjugates that may address both problems. The conjugates, which act as polyamine transport inhibitors, were used in combination with eflornithine (DFMO) in a two-pronged attack to deprive cancer cells of the polyamines they need for continued cell growth and proliferation.

The company used a mouse model of squamous cell carcinoma that overexpressed ornithine decarboxylase (ODC)—the rate-limiting enzyme in polyamine biosynthesis that is eflornithine's target. As reported in the *Journal of Medicinal Chemistry*, the combination of DFMO and a lysine-spermine conjugate resulted in substantially fewer visible tumors six weeks after treatment compared with that seen using either agent alone.¹

In 8 of 17 mice receiving the combination for 4 weeks, no tumors were detected following 6 weeks off treatment. By contrast, tumors regrew in all mice receiving the polyamine transport inhibitor alone and in 11 of 12 mice receiving DFMO alone.

"The potential of the polyamine transport inhibitors and the resulting two-drug combination therapy to become a next-generation chemotherapeutic regimen is very promising, as demonstrated by the positive results in the murine model," said Mark Burns, lead author of the *JMC* paper and CEO of Aminex.

Aminex is developing polyamine-based therapies to treat epithelial-based cancers, including squamous cell carcinoma of the head and neck (SCCHN), melanoma and colon cancer. The company hopes to submit an IND by 1Q10 for a polyamine transport inhibitor plus DFMO to treat SCCHN.

Burns characterized the lysine-spermine conjugates while he was working at **MediQuest Therapeutics Inc.** Last year, he left the company and formed Aminex, which holds an exclusive license from MediQuest to patents covering the compounds.

Toxic limitations

The next steps for the combination therapy involve determining potential toxicity and finding an optimal dosing regimen. A key issue is that DFMO monotherapy has been associated with gastrointestinal and hematological side effects and loss of hearing at high doses.²

Recent studies have shown that lower doses of DFMO administered over long periods of time can still be effective in lowering polyamines

without producing toxic side effects.³ Thus, Burns said that detailed studies will be needed to determine the best ratio of the individual components of the combination therapy.

"The efficacy of polyamine transport inhibitors looks very promising in experimental models. However, the major question is whether or not there will be toxicity when the compounds are administered to humans," said Eugene Gerner, director of the Arizona Cancer Center's gastrointestinal cancer program and a professor of cell biology, anatomy, biochemistry and molecular biophysics at the **University of Arizona**.

He added: "It will be important to conduct Phase I safety and toxicity studies in patients with advanced cancers, and then, in the context of those studies, there needs to be some indication of benefit."

Laurence Marton, CSO at cancer company **Progen Pharmaceuticals Ltd.**, agreed. "The next step is to look more formally at toxicity and see how the animal as a whole is affected when treated with the transport inhibitors alone, with DFMO alone and then with combination therapy."

Other polyamine approaches

Aminex is not the only company developing cancer therapies that interfere with the polyamine pathway.

Progen is developing polyamine analogs that are transported into cells and are incorporated into intracellular polyamine binding sites. Once bound, the analogs have altered function compared with natural polyamines, modulating polyamine biosynthetic pathways and altering cell growth by inducing apoptosis and cell-cycle arrest.

The company's PG11047 polyamine analog is in Phase I testing to treat advanced cancer as monotherapy and in combination with marketed drugs.

Cancer Prevention Pharmaceuticals LLC, a company spun out of the University of Arizona and the **University of California, Irvine**, is developing compounds to prevent cancer in people with increased risk for disease. The company hopes to submit an NDA in 2010 for a combination of DFMO and sulindac to prevent colorectal cancer. Sulindac is a generic NSAID.

Gerner, who is Cancer Prevention's CSO, noted that the company's approach is aimed at inhibiting synthesis and promoting export of polyamines, whereas the approach reported in the *JMC* paper seeks to inhibit synthesis and block polyamine transport and uptake.

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COMPANIES AND INSTITUTIONS MENTIONED

Aminex Therapeutics Inc., Seattle, Wash.
Cancer Prevention Pharmaceuticals LLC, Tucson, Ariz.
Genzyme Corp. (NASDAQ:GENZ), Cambridge, Mass.
MediQuest Therapeutics Inc., Bothell, Wash.
Progen Pharmaceuticals Ltd. (ASX:PGL; NASDAQ:PGLA), Brisbane, Australia
University of Arizona, Tucson, Ariz.
University of California, Irvine, Calif.

Susceptibility loci for COPD

By Lauren Martz, Staff Writer

A genomewide association study from **GlaxoSmithKline plc** and **Duke University** has identified two new susceptibility loci for COPD that might not only help assess disease risk, but also lead to new therapeutic targets.¹ A much larger, long-term study is already underway to address whether the loci are indeed associated with disease and not simply with smoking dependence.

Chronic obstructive pulmonary disease (COPD) is primarily caused by smoking and involves restricted airflow to the lungs. Emphysema and chronic obstructive bronchitis are two common forms of the disease. However, not all smokers develop the disease, and studies suggest a genetic component is involved in smokers' risk of developing COPD.²

To date, deficiency of serpin peptidase inhibitor clade A member 1 (SERPINA1; ATT; A₁AT) due to the presence of a mutated version of its gene, known as the Z allele, is the only proven genetic risk factor for COPD.³ According to Sreekumar Pillai, a geneticist at GSK, the variant is only present in 1–2% of patients.

In their paper in *PLoS Genetics*, Pillai and colleagues now report the identification of variants on chromosomes 4 and 15 that might affect a larger swath of patients.

In an initial genomewide association study involving 823 COPD patients and 810 smoking controls, the 100 SNPs most highly associated with COPD were chosen for additional analysis. That set included variants on chromosome 15 that have been associated with lung cancer and peripheral arterial disease (PAD) in previous studies⁴ and a variant on chromosome 4 that has recently shown a genomewide significant association to lung function ($p < 5 \times 10^{-8}$).⁵

In three additional cohorts comprising over 3,000 patients and controls, the researchers replicated the association of two polymorphisms at the locus on chromosome 15 for variants of cholinergic receptor, nicotine, $\alpha 3$ (CHRNA3) and CHRNA5, the CHRNA3/CHRNA5 locus.

The variants, rs8034191 and rs1051730, were significantly associated with COPD ($p = 1.48 \times 10^{-10}$ and $p = 5.74 \times 10^{-10}$, respectively). The team estimated that the C allele of the rs8034191 SNP could be present in about 12.2% of COPD patients.

The *hedgehog interacting protein* (HHIP) locus on chromosome 4 showed a nonsignificant association with COPD in the studies. But the researchers hope the association will be revealed to be significant in the ongoing ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study, which could validate HHIP as a previously unknown susceptibility factor.

Tim Higenbottam, director of corporate clinical development at **Chiesi Farmaceutici S.p.A.**, told *SciBX* that if the loci are further validated, they could be used to diagnose COPD risk and to identify the mechanisms responsible for its pathogenesis.

Chiesi's Atimos, a pressured metered dose inhaler formulation of formoterol fumarate, is marketed for long-term treatment of asthma and COPD.

Further validation

In ECLIPSE, about 28,000 well-characterized patients and controls are being followed for up to 3 years to understand the molecular pathology of the loci and their association with COPD.

Noor Kalsheker, professor of clinical chemistry at the Institute of Genetics of **The University of Nottingham**, said the larger trial is necessary because "most genomewide association studies require a minimum of 2,000 subjects."

According to Kalsheker, the problem with genomewide scans is that "very rare variants and SNPs in certain regions of the genome are not picked up very well. Rare variants in a gene that might confer very high risk probably won't be picked up despite the high density of the screens."

Pillai told *SciBX* that his team is thinking of doing a deep sequencing and genotyping study to identify more genetic variants in the regions of interest, including high-risk SNPs that might be missed with a genomewide approach.

Takahiro Yoshikawa, senior lecturer of sports medicine at the **Osaka City University Graduate School of Medicine** and a medical doctor specializing in respiratory medicine, especially

asthma and COPD, said it will be important to determine whether the findings vary among different ethnicities.

"It is likely that racial/ethnic background might affect the findings in a genetics study," he said. "In addition, the phenotype of COPD also seems to vary among countries. For example, patients with the bronchitis type are predominant in the U.K., whereas those with the emphysema type are predominant in Japan."

Both Yoshikawa and Kalsheker also wanted to see additional confirmation that the loci in the *PLoS Genetics* article are specifically linked to COPD and not to related conditions or phenotypes.

"There is still no clear indication as to whether the SNPs that have been identified are a marker for addiction or of COPD specifically," said Kalsheker.

Yoshikawa noted that some patients in the genomewide study had a history of bronchial asthma, including smoking asthma. "Before we use these specific loci for screening purposes, it is necessary to examine whether the susceptibility gene for COPD in the study is not overlapped with that for asthma and is strictly associated with the COPD phenotype alone," he said.

Previous studies have linked the loci identified in the *PLoS Genetics* paper to the risk of lung cancer.⁴ Kalsheker said those studies raised the same question as to whether the relationship was actually to lung cancer and not just to nicotine addiction.

Pillai and his team did address the issue of smoking dependence in their paper.

"Several analytical methodologies were used to assess whether these loci were linked to smoking dependence. We used statistical analyses techniques to factor out the effect of smoking, and the association was still genomewide significant," he said.

(Continues on p. 7)

"There is still no clear indication as to whether the SNPs that have been identified are a marker for addiction or of COPD specifically."

—Noor Kalsheker,
The University of Nottingham

Wounded T cells

By Kai-Jye Lou, Staff Writer

Researchers at **The Scripps Research Institute** think they may have uncovered a key reason why chronic wounds are so persistent: functionally impaired epidermal T cells.¹ But before these findings can be translated into a therapeutic, the mechanism underlying the impairment needs to be uncovered.

The Scripps group had previously found hints that certain epidermal T cell populations might be involved in wound healing. In 2002, Wendy Havran showed that mouse epidermal T cells regulate wound repair.² In 2005, her group reported that these cells also regulate skin homeostasis through production of insulin-like growth factor 1 (IGF1).³ Increased levels of IGF1 at a wound site are a hallmark of early-stage repair. However, the involvement of human epidermal T cell populations in the healing process was not known.

In a new paper in *The Journal of Experimental Medicine*, Havran's group translated the rodent results into a human wound repair model. The team not only demonstrated the role of human epidermal T cell populations in wound healing, but also showed that the cells are

“This is the first demonstration of the role of epidermal T cell populations in a human wound healing model.”

—Wendy Havran,
The Scripps Research Institute

functionally impaired in chronic wounds.

In human skin cultures, stimulation of the two known epidermal T cell populations— $\alpha\beta$ and $\gamma\delta$ —increased IGF1 levels and accelerated wound closure compared with what was seen in unstimulated controls. Blocking IGF1 signaling with an antibody reversed the increase in wound closure speed.

Most important was the difference in $\alpha\beta$ and $\gamma\delta$ epidermal T cells isolated from patients with acute wounds compared with those from patients with chronic wounds. The former showed an increase in IGF1 production during the tissue repair process and were responsive to stimulation. The latter showed no increase in IGF1 and were less responsive to stimulation.

“This is the first demonstration of the role of epidermal T cell populations in a human wound healing model,” said Havran, who is a professor in the Department of Immunology and Microbial Science at Scripps. “People have always wanted to know if the results from mouse wound healing models will translate to humans because the mouse only has a $\gamma\delta$ epidermal T cell population, whereas humans and primates have both $\alpha\beta$ and $\gamma\delta$ epidermal T cells. The really exciting result for us was finding out that epidermal T cell populations in chronic wounds were nonfunctional.”

(Continues on p. 8)

(Continued from “Susceptibility loci for COPD,” p. 6)

Pillai added: “Though the *CHRNA* locus has been shown to be associated with smoking dependence, here we’ve shown that there is something more than smoking dependence going on, and this probably will relate to inflammation.”

Tests and targets

If the three-year ECLIPSE study does confirm the *PLoS Genetics* findings, the path toward a COPD risk screen could be straightforward. In addition, the genes of interest might lead to the identification of new pathways and molecules that could be targeted to treat the disease.

“As far as a diagnostic, we don’t need to do a lot of work because the association is very convincing,” said Pillai. “If we need to use this information for screening the smokers for propensity to develop COPD, the results can be directly used to develop *in vitro* diagnostics.”

“Once validated, these loci could provide a very powerful risk profile,” said Kalsheker. “There is definitely a huge demand for COPD risk assessment methods, in part because the disease is often detected too late. Anything to help detect affected individuals earlier could have a great impact on public health.”

Regarding therapeutics, Pillai said the next step is to better understand the biological role of the identified genes in COPD.

“For utilizing this knowledge in therapeutic interventions, we need to do functional studies including *in vitro* experiments to find the biological role of the genes in lung disease, followed by drug discovery

efforts,” he said. “We have already found that the *CHRNA3/CHRNA5* gene is related to emphysema (destruction of the lung tissue), which is one of the mechanisms in COPD.”

Pillai said the preliminary results show that *HHIP* variants contribute to airway disease.

According to Pillai, the findings in the *PLoS Genetics* article have not been patented. Their licensing status is undisclosed.

Martz, L. *SciBX* 2(14); doi:10.1038/scibx.2009.563
Published online April 9, 2009

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Contact: David B. Goldstein, Duke University, Durham, N.C.
e-mail: d.goldstein@duke.edu
- Contact:** Sreekumar G. Pillai, GlaxoSmithKline Research and Development, Research Triangle Park, N.C.
e-mail: sreekumar.g.pillai@gsk.com
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COMPANIES AND INSTITUTIONS MENTIONED

Chiesi Farmaceutici S.p.A., Parma, Italy
Duke University, Durham, N.C.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Osaka City University Graduate School of Medicine, Osaka, Japan
The University of Nottingham, Nottingham, U.K.

“These findings should have much impact on our understanding of chronic wound persistence, which in the light of Havran’s new finding can be perceived as a T cell defect,” said Willi Born, a professor in the Department of Immunology at **National Jewish Health** and the **University of Colorado Denver**. “The data also imply that these T cells are in fact a critical source of IGF1 and not just one among several sources.”

Thus, Born told *SciBX*, the *JEM* paper “provides convincing evidence for a role of human skin-resident T cells in wound healing.”

Therapeutic directions

Unlike acute wounds, the three main types of chronic wounds—diabetic, pressure and venous ulcers—will not heal without constant intervention. Standard care remains a combination of daily dressing changes and devices to remove weight and pressure from the wound site.⁴

The lone biologic on the market is Regranex becaplermin, a gel formulation of recombinant platelet-derived growth factor- β (PDGFB; PDGF- β) sold by **Johnson & Johnson** to treat diabetic foot ulcers. Last June, however, J&J updated the product’s label to include a black box warning of an increased risk of cancer in patients treated with three or more tubes of Regranex.

Another approach is wound debridement, in which dead, damaged or infected tissue is surgically removed to promote the healing potential of the remaining healthy tissue.

Medical devices such as skin substitutes have also been approved for chronic wounds.

“There is a lot of interest in identifying new ways to treat patients with chronic wounds,” said Havran. The results in the *JEM* article “support the idea of developing strategies to reactivate epidermal T cells or transplanting these cells from healthy regions of the body into the chronic wound. I would see treatment strategies based off these findings complementing current wound treatment strategies.”

Born said it was “very encouraging that the human skin-resident T cells behave similarly to mouse skin-resident T cells.” However, he added that the findings of the Scripps team “are largely derived from studies *in vitro*. It is difficult to predict from such studies what might be found *in vivo*.”

If the findings do translate to the clinic, Born thinks the result could be more specific wound treatments that avoid the side effects of less-targeted approaches. “T cells can be targeted specifically because they express cell-surface molecules that are not found on other cells in the skin,” he said.

For example, Born noted that skin-resident T cells are sensitive to mitogens and cytokines that have no effect on keratinocytes.

Rebecca O’Brien, also a professor in the Department of Immunology at National Jewish Health and the University of Colorado Denver, noted that T cell-targeting approaches still would need to avoid stimulating $\alpha\beta$ and $\gamma\delta$ T cell populations elsewhere in the body because of the potential for undesirable immune responses. She suggested that localized T cell stimulation with a topical formulation such as a cream may be feasible.

“T cells can be targeted specifically because they express cell-surface molecules that are not found on other cells in the skin.”

—Willi Born,
University of Colorado Denver

Mechanisms before therapies

Before the results in *JEM* can be translated into therapeutics, researchers contacted by *SciBX* wanted to see additional studies that elucidate the function of epidermal T cells and the mechanism by which they become impaired in chronic wounds.

“In mouse models, we were able to show that the $\gamma\delta$ epidermal T cells are major contributors to the wound healing process, but at this point we still don’t know how important

the $\alpha\beta$ and $\gamma\delta$ epidermal T cell populations are in humans,” Havran told *SciBX*. “We still don’t know if just targeting these epidermal T cell populations is enough to promote healing of chronic wounds in humans.”

She added: “We certainly expect that epidermal T cells are not the only functionally impaired cell types in the chronic wound environment.”

Both Born and O’Brien also wanted to see additional studies that elucidate and compare the function of human $\alpha\beta$ epidermal T cells with the function of $\gamma\delta$ cells.

Havran said the key next steps for her group will be to identify a phenotype that distinguishes functional cells from impaired cells and to discern the mechanism behind the impairment. “We want to know if there are cell-surface markers that distinguish responsive T cells from unresponsive T cells,” she said.

Indeed, Havran thinks the development of epidermal T cell-based therapies for chronic wounds hinges on understanding why they become functionally impaired.

“If it happens to be the case that these cells are exhausted and just won’t respond anymore, then transplanting cells from another part of the body may be a viable approach. We may be able to isolate functional T cells from healthy parts of the body, activate them *ex vivo*, and then transplant them to the site of the chronic wound,” she said. “If they are functionally impaired for some other reason, however, then we may be able to develop strategies or compounds that reactivate these T cell populations in the chronic wound.”

Scripps has not disclosed the patent and licensing status of the *JEM* findings.

Lou, K.-J. *SciBX* 2(14); doi:10.1038/scibx.2009.564
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COMPANIES AND INSTITUTIONS MENTIONED

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
National Jewish Health, Denver, Colo.
University of Colorado Denver, Denver, Colo.
The Scripps Research Institute, La Jolla, Calif.

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Lupus	Kallikrein 1 (KLK1); KLK3	A study in human samples and in mice suggests that increasing kallikrein expression may help prevent spontaneous lupus nephritis. In a genotype analysis of three patient cohorts, SNPs in <i>KLK1</i> and the <i>KLK3</i> promoter region were associated with lupus and lupus nephritis. Kidneys from mice sensitive to antibody-induced nephritis had significantly lower expression of 10 kallikrein-family genes than kidneys from mice that were insensitive to antibody-induced nephritis ($p < 0.001$). Next steps include evaluating the effects of long-term kallikrein modulation on spontaneous lupus nephritis <i>in vivo</i> .	Patent and licensing status unavailable	Liu, K. <i>et al. J. Clin. Invest.</i> ; published online March 23, 2009; doi:10.1172/JCI36728 Contact: Chandra Mohan, University of Texas Southwestern Medical Center, Dallas, Texas e-mail: chandra.mohan@utsouthwestern.edu Contact: Edward Wakeland, same affiliation as above e-mail: ward.wakeland@utsouthwestern.edu Contact: Marta Alarcón-Riquelme, Uppsala University, Uppsala, Sweden e-mail: marta.alarcon@genpat.uu.se
Multiple sclerosis (MS)	T cell receptor (TCR)	Studies in mice suggest that a recombinant TCR ligand could treat MS. In mice with experimental autoimmune encephalitis (EAE) induced by two different peptides, the disease was reversed by a single recombinant ligand as long as its target T cells were present. Also in the EAE mice, three different TCR ligands lowered IL-17 production, increased IL-10 and IL-13 in splenocytes and decreased spinal cord inflammatory lesions. Next steps include determining the minimum concentration of target T cells needed to trigger the therapeutic effects in EAE. GlaxoSmithKline plc's AnergiX, which targets the TCR, is in Phase I testing to treat MS.	Patent and licensing status unavailable	Sinha, S. <i>et al. J. Neurosci.</i> ; published online March 25, 2009; doi:10.1523/JNEUROSCI.5812-08.2009 Contact: Halina Offner, Portland Veterans Affairs Medical Center, Portland, Ore. e-mail: offnerva@ohsu.edu
Systemic lupus erythematosus (SLE)	Interleukin-1 receptor-associated kinase 1 (IRAK1); SNP rs2239673; SNP rs763737; SNP rs3027907; SNP rs5945174; SNP rs7061789	Studies in cell culture and in mice identified SNPs in <i>IRAK1</i> on chromosome X that could help predict susceptibility to SLE. Analysis of human DNA samples from patients with SLE in four different ethnic groups revealed that the rs2239673, rs763737, rs3027907, rs5945174 and rs7061789 SNPs were associated with both adult- and childhood-onset SLE. In mice with SLE disease loci, <i>Irak1</i> deficiency attenuated several lupus-associated phenotypes, including lymphocyte activation and renal disease, compared with what was seen in controls. Next steps include validating the results in other animal models of SLE.	Patent and licensing status unavailable	Jacob, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 23, 2009; doi:10.1073/pnas.09011811106 Contact: Chandra Mohan, University of Texas Southwestern Medical Center, Dallas, Texas e-mail: chandra.mohan@utsouthwestern.edu Contact: Chaim O. Jacob, University of Southern California, Los Angeles, Calif. e-mail: jacob@usc.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Bone metastases	Tubulin	<p><i>In vitro</i> studies suggest that a conjugate consisting of hydroxypropyl methacrylamide, paclitaxel and alendronate could treat bone metastases. <i>In vitro</i>, the conjugate bound to a bone tissue mimic via the alendronate component of the conjugate. Also <i>in vitro</i>, the conjugate inhibited proliferation of human prostate cells and blocked formation of angiogenic structures. Next steps could include testing the conjugate in animal models to investigate tissue specificity and tumor accumulation.</p> <p>At least 15 companies have paclitaxel compounds in development stages ranging from preclinical to marketed to treat cancer.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.568 Published online April 9, 2009</p>	Patent and licensing status unavailable	<p>Miller, K. <i>et al. Angew. Chem. Int. Ed. Engl.</i>; published online March 17, 2009; doi: 10.1002/anie.200805133</p> <p>Contact: Ronit Satchi-Fainaro, Tel Aviv University, Tel Aviv, Israel e-mail: ronitsf@post.tau.ac.il</p>
Brain cancer	Mammalian target of rapamycin (mTOR; FRAP; RAFT1); protein kinase B (PKB; Akt); tribbles homolog 3 (TRIB3, TRB3)	<p>A study in patient samples and in mice suggests that tetrahydrocannabinol (THC) could help treat glioma. In a human glioma xenograft mouse model, THC increased autophagic cell death compared with that seen using vehicle. In tumor samples isolated from two patients, levels of autophagy following THC treatment were higher than those existing prior to treatment. Cell-culture studies showed that THC promoted autophagy via TRB3-dependent inhibition of Akt/mTOR complex 1 signaling. Next steps include evaluating THC and other cannabinoid-based agents in a clinical trial.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.569 Published online April 9, 2009</p>	Patented for treatment of brain tumors; licensing status undisclosed	<p>Salazar, M. <i>et al. J. Clin. Invest.</i>; published online April 1, 2009; doi:10.1172/JCI37948</p> <p>Contact: Guillermo Velasco, Complutense University of Madrid, Madrid, Spain e-mail: gvd@bbm1.ucm.es</p>
Breast cancer	<i>Basic helix-loop-helix family, member e41 (BHLHE41; SHARP-1); cyclin G2 (CCNG2)</i>	<p><i>In vitro</i> studies and clinical specimen analysis suggest that expression of <i>SHARP-1</i> and <i>CCNG2</i> could be prognostic biomarkers of breast cancer. In gene expression datasets from primary breast cancer patients, those with low expression of <i>SHARP-1</i> and <i>CCNG2</i> had a significantly higher probability of cancer recurrence than patients with high expression of the gene signature. Next steps include investigating the mechanisms by which <i>SHARP-1</i> and <i>CCNG2</i> act as metastasis suppressors <i>in vivo</i>.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.570 Published online April 9, 2009</p>	Patent application filed for prognosis of breast cancer patients by monitoring expression of <i>SHARP-1</i> and <i>CCNG2</i> ; unlicensed	<p>Adorno, M. <i>et al. Cell</i>; published online April 2, 2009; doi:10.1016/j.cell.2009.01.039</p> <p>Contact: Stefano Piccolo, University of Padua, Padua, Italy e-mail: piccolo@civ.bio.unipd.it</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	CD8; interferon- α (IFN- α); toll-like receptor 9 (TLR9)	<p>A study in mice suggests that inducing type I interferons could help reverse tumor-specific T cell tolerance in cancer. In a mouse model of tumor-specific T cell tolerance, the TLR9 ligand CpG and a dendritic cell (DC) vaccine induced an IFN-α-mediated tumor-specific CD8⁺ T cell response and prolonged tumor-free survival compared with what was seen using either compound separately or a control vaccine. Antibodies against IFN-α significantly lowered the tumor-specific T cell response compared with what was seen using control antibodies ($p < 0.001$). Next steps include evaluating DC vaccines in combination with recombinant type I IFN or type I IFN-inducing agents in animal lymphoma models.</p> <p>Roche's Roferon-A IFN α-2a is marketed for multiple cancers and hepatitis.</p> <p>Peg-IFN peginterferon α-2b, a pegylated recombinant IFN-α-2b from Schering-Plough Corp. and Enzon Pharmaceuticals Inc., is under review to treat melanoma.</p> <p>At least five other companies have IFN-based compounds in Phase III or earlier to treat cancer.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.571 Published online April 9, 2009</p>	Patent pending for treatment of lymphoma and leukemia in bone marrow transplant setting; licensing status undisclosed	<p>Horkheimer, I. <i>et al. Blood</i>; published online March 11, 2009; doi:10.1182/blood-2008-05-155150</p> <p>Contact: Yiping Yang, Duke University Medical Center, Durham, N.C. e-mail: yang0029@mc.duke.edu</p>
Cancer	Granulocyte macrophage colony-stimulating factor (CSF2; GM-CSF); VEGF; prokineticin 2 (PROK2; Bv8)	<p>Studies in mice suggest that targeting GM-CSF or Bv8 could help treat tumors resistant to anti-VEGF therapies. Avastin-resistant murine tumors exhibited high levels of GM-CSF and Bv8 compared with Avastin-sensitive tumors. In tumor-bearing mice, an anti-GM-CSF or anti-Bv8 antibody lowered growth of resistant tumors 30–35% compared with that seen in Avastin-sensitive tumors. Either antibody plus Avastin lowered growth of resistant tumors 60–80% compared with that seen in Avastin-sensitive tumors. Future studies could include testing the combination therapies in other animal models of cancer.</p> <p>Roche's Genentech Inc. unit markets Avastin bevacizumab, an antibody against VEGF, to treat breast cancer, metastatic colorectal cancer, renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC).</p> <p>BioVex Inc.'s OncoVEX GM-CSF, a modified herpes simplex virus (HSV-1) encoding GM-CSF, is in Phase III testing to treat melanoma.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.572 Published online April 9, 2009</p>	Patent and licensing status undisclosed	<p>Shojaei, F. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 30, 2009; doi:10.1073/pnas.0902280106</p> <p>Contact: Napoleone Ferrara, Genentech Inc., South San Francisco, Calif. e-mail: nf@gene.com</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Suppressor of cancer cell invasion (C9orf126; SCAI)	<p>Studies in cell culture suggest that upregulating SCAI could be useful for treating cancer. In several human cancer cell lines, small interfering RNA-mediated depletion of SCAI led to greater tumor cell invasion than that seen in untreated cells, whereas overexpression of SCAI suppressed the invasive potential of the cancer cells. RNA analysis showed that SCAI was downregulated in six of seven tumor types analyzed. Next steps include investigating further the mechanisms underlying SCAI downregulation in cancers and exploring its potential as a cancer diagnostic.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.573 Published online April 9, 2009</p>	Unpatented; unlicensed	<p>Brandt, D. <i>et al. Nat. Cell Biol.</i>; published online April 6, 2009; doi:10.1038/ncb1862</p> <p>Contact: Robert Grosse, University of Heidelberg, Heidelberg, Germany e-mail: robert.grosse@pharma.uni-heidelberg.de</p>
Melanoma	Actin-related protein 2/3 complex, subunit 2 (ARPC2); fibronectin 1 (FN1); osteopontin (OPN; SPP1); regulator of G-protein signaling 1 (RGS1); wingless-type MMTV integration site family member 2 (WNT2)	<p>A study in human biopsies revealed five molecular markers to help diagnose melanoma. In 693 melanocytic neoplasms, immunohistochemical screening for overexpression of ARPC2, FN1, SPP1, RGS1 and WNT2 distinguished melanoma samples from benign melanocytic lesions with 95% specificity and 91% sensitivity. Next steps include implementing the diagnostic approach in the clinic.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.574 Published online April 9, 2009</p>	Patents covering findings filed through the University of California; Melanoma Diagnostics Inc. has an exclusive license to the IP	<p>Kashani-Sabet, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 30, 2009; doi:10.1038/pnas.0901185106</p> <p>Contact: Mohammed Kashani-Sabet, University of California, San Francisco Comprehensive Cancer Center, San Francisco, Calif. e-mail: kashanim@derm.ucsf.edu</p>
Squamous cell carcinoma of the head and neck (SCCHN)	Polyamine transport	<p>An SAR study characterized a series of lipophilic lysine-spermine conjugates as polyamine transport inhibitors that could help treat SCCHN in combination with eflornithine (DFMO), a polyamine biosynthesis inhibitor. Cancer cells can overcome the action of polyamine biosynthesis inhibitors by importing polyamines from external sources. In a mouse model of squamous cell carcinoma, one of the conjugates plus DFMO resulted in substantially fewer visible tumors six weeks after treatment compared with what was seen using either agent alone. Next steps include toxicology and pharmacokinetic studies.</p> <p>SkinMedica Inc. markets Vaniqa eflornithine to decrease the growth of unwanted facial hair in women (<i>see Next-gen polyamine attack, page 5</i>).</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.575 Published online April 9, 2009</p>	Polyamine transport inhibitors patented by MediQuest Therapeutics Inc.; exclusively licensed to Aminex Therapeutics Inc.	<p>Burns, M. <i>et al. J. Med. Chem.</i>; published online March 12, 2009; doi:10.1021/jm801580w</p> <p>Contact: Mark R. Burns, Aminex Therapeutics Inc., Seattle, Wash. e-mail: markburns@aminextherapeutics.com</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Various cancers	HER2 (ERBB2); VEGF	An <i>in vitro</i> and mouse study suggests that a mAb that simultaneously binds HER2 and VEGF could help treat cancer. An <i>in vitro</i> binding screen identified mutational variants of Herceptin, an anti-HER2 mAb, that could bind VEGF and HER2. In cultured human cells, one of the mAb variants inhibited cell growth at lower concentrations than Herceptin. In a mouse xenograft tumor model, the dual-specificity mAb lowered mean tumor volume compared with that seen in controls treated with comparable amounts of Herceptin or Avastin, an anti-VEGF mAb. Herceptin trastuzumab is marketed by Roche's Genentech Inc. unit to treat breast cancer. Avastin bevacizumab is marketed by Genentech to treat metastatic colorectal cancer, non-small cell lung cancer (NSCLC) and metastatic breast cancer. SciBX 2(14); doi:10.1038/scibx.2009.576 Published online April 9, 2009	Patents filed by Genentech for production and use of dual specificity antibodies; licensing status undisclosed	Bostrom, J. <i>et al. Science</i> ; published online March 20, 2009; doi:10.1126/science.1165480 Contact: Germaine Fuh, Genentech Inc., South San Francisco, Calif. e-mail: gml@gene.com
Endocrine disease				
Precocious puberty; endometriosis	Kisspeptin 10 (KISS10)	<i>In vitro</i> and <i>in vivo</i> studies suggest that antagonizing kisspeptins could help treat gonadotropin-releasing hormone (GnRH)-dependent reproductive disorders. In mouse brain slices, a Kiss10 peptide antagonist blocked the firing of GnRH neurons. In pubescent rhesus monkeys, the peptide antagonist lowered GnRH secretion from neurons. The antagonist also inhibited kisspeptin-induced release of luteinizing hormone (LH) in rats and mice, and it inhibited the rise in LH following castration in sheep, rats and mice. Next steps include clinical studies and creating new peptides with better pharmacokinetics. SciBX 2(14); doi:10.1038/scibx.2009.577 Published online April 9, 2009	Findings patented by MRC Technology; available for licensing	Rosweir, A. <i>et al. J. Neurosci.</i> ; published online March 25, 2009; doi:10.1523/JNEUROSCI.5740-08.2009 Contact: Robert P. Millar, The Queens Medical Research Institute, Edinburgh, U.K. e-mail: r.millar@hrsu.mrc.ac.uk
Type 2 diabetes	Sphingosine 1-phosphate receptor 2 (S1PR2)	A study in cell culture, <i>in silico</i> and in mice suggests that S1PR2 could be antagonized to treat type 2 diabetes. In cultured mouse adipocytes, a small interfering RNA knockdown screen identified 126 genes that modulated free fatty acid secretion, a proxy for insulin sensitivity. Computational analysis of genetic and protein interaction networks and tissue-expression data identified <i>S1PR2</i> as the gene with the highest degree of connectedness to known insulin regulators. <i>S1pr2</i> knockout mice fed a high-fat diet had significantly higher serum insulin levels than wild-type controls ($p=0.03$). Next steps could include characterizing other type 2 diabetes biomarkers in <i>S1PR2</i> knockouts and developing selective antagonists of S1PR2. SciBX 2(14); doi:10.1038/scibx.2009.578 Published online April 9, 2009	Patents on methods filed by Merck & Co. Inc.; company plans to make methods and data available to Sage, a not-for-profit company spun out of Merck's Rosetta Inpharmatics Inc. subsidiary	Tu, Z. <i>et al. Genome Res.</i> ; published online March 8, 2009; doi:10.1101/gr.087890.108 Contact: Eric Schadt, Merck & Co. Inc., Seattle, Wash. e-mail: eric.schadt@gmail.com

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Bacterial infection; fungal infection	Not applicable	<i>In vitro</i> studies suggest that analogs of gramicidin S could treat a range of systemic bacterial and fungal infections. The antibiotic gramicidin S, a cyclic 10-residue peptide with activity against many Gram-positive and Gram-negative bacteria, cannot be used systemically because of toxic hemolytic side effects. A series of synthetic gramicidin analogs with ring sizes of 10–16 residues showed significant <i>in vitro</i> activity against 15 species of bacteria and 2 species of fungi. Two lead analogs had potencies similar to gramicidin but were 5–10 times less toxic to human blood cells than gramicidin. Ongoing work includes lead optimization and the rational design of additional cyclic peptide antibiotics, including those that could target antibiotic-resistant microbes.	Unpatented; unlicensed	Jelokhani-Niaraki, M. <i>et al. J. Med. Chem.</i> ; published online March 12, 2009; doi:10.1021/jm801648n Contact: Masoud Jelokhani-Niaraki, Wilfrid Laurier University, Waterloo, Ontario, Canada e-mail: mjelokhani@wlu.ca
		SciBX 2(14); doi:10.1038/scibx.2009.579 Published online April 9, 2009		
Epstein-Barr virus (EBV)	Inducible T cell kinase (ITK); IL-2	Studies in patient samples and in cell culture identified an ITK mutation that could help diagnose fatal EBV-associated lymphoproliferation. Samples from two consanguineous sisters who died from EBV-associated lymphoproliferation contained <i>ITK</i> genes carrying a missense mutation, were ITK-deficient and lacked natural killer T cells. In human embryonic kidney cells expressing the mutated <i>ITK</i> , levels of the protein were almost undetectable compared with those seen in wild-type cells. Next steps include confirming the marker by screening additional patient samples for the mutated protein. Valomaciclovir, a varicella zoster DNA polymerase inhibitor from Medivir AB and Epiphany Biosciences Inc., is in Phase II testing to treat EBV infection. AstraZeneca plc and GlaxoSmithKline plc have an EBV vaccine using EBV surface antigen in Phase II testing. BioSante Pharmaceuticals Inc. has an EBV vaccine using a calcium phosphate (CAP) nanoparticle adjuvant in preclinical testing.	Work unpatented; licensing status not applicable	Huck, K. <i>et al. J. Clin. Invest.</i> ; published online April 1, 2009; doi:10.1172/JCI37901 Contact: Arndt Borkhardt, Heinrich Heine University, Dusseldorf, Germany e-mail: arndt.borkhardt@med.uni-duesseldorf.de
		SciBX 2(14); doi:10.1038/scibx.2009.580 Published online April 9, 2009		
HBV	Major histocompatibility complex class II DP α 1 (HLA-DPA1); HLA-DPB1	A genomewide association study identified SNPs in <i>HLA-DP</i> that could help predict susceptibility to chronic HBV. Genetic analysis of Japanese patients with chronic HBV identified 11 SNPs within or around <i>HLA-DPA1</i> and <i>HLA-DPB1</i> that were significantly associated with disease ($p=3.62\times 10^{-8}$). Two of the SNPs were confirmed in additional Japanese and Thai cohorts with chronic HBV. Next steps could include confirming the markers in other ethnic populations.	Unpatented; <i>HLA-DP</i> findings in public domain	Kamatani, Y. <i>et al. Nat. Genet.</i> ; published online April 6, 2009; doi:10.1038/ng.348 Contact: Yusuke Nakamura, University of Tokyo, Japan e-mail: yusuke@ims.u-tokyo.ac.jp
		SciBX 2(14); doi:10.1038/scibx.2009.581 Published online April 9, 2009		

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
HIV/AIDS	Tat protein; interferon- γ (IFN- γ); signal transducer and activator of transcription 1 (STAT1); suppressor of cytokine signaling 2 (SOCS2)	Studies in human cells suggest that targeting SOCS2 could help treat HIV infection. In healthy human blood monocytes, HIV's Tat protein induced production of SOCS2, which led to increased inhibition of IFN- γ production compared with that seen in controls. In Tat protein-treated human embryonic kidney cells, IFN- γ levels were inversely correlated with SOCS2 levels. Next steps could include identifying small molecule inhibitors of SOCS2 and testing them in HIV-1-infected cells. SciBX 2(14); doi:10.1038/scibx.2009.582 Published online April 9, 2009	Patent and licensing status undisclosed	Cheng, S. <i>et al. Blood</i> ; published online March 23, 2009; doi:10.1182/blood-2008-10-183525 Contact: Allan S.Y. Lau, The University of Hong Kong, Hong Kong, China e-mail: asylau@hku.hk
Tuberculosis	Decaprenylphosphoryl- β -D-ribose 2'-epimerase (dpE1)	<i>In vitro</i> and mouse studies suggest that 1,3-benzothiazin-4-one (BTZ) compounds could treat drug-resistant strains of tuberculosis. <i>In vitro</i> , the minimum inhibitory concentrations against 2 tuberculosis strains were 2.3 nM and 9.2 nM, respectively. Similar activities were seen against resistant strains. The BTZs blocked dpE1, disrupting synthesis of cell wall arabinans. <i>Ex vivo</i> , the lead BTZ protected macrophages from <i>Mycobacterium tuberculosis</i> . In mice infected by a low-dose TB aerosol, the lead compound lowered bacterial burden in the lungs and spleen without adverse effects. Next steps could include testing the lead BTZ in combination therapies to treat resistant TB. At least 15 companies have TB vaccines and antibiotics in development stages ranging from preclinical to marketed. SciBX 2(14); doi:10.1038/scibx.2009.583 Published online April 9, 2009	Patent and licensing status unavailable	Makarov, V. <i>et al. Science</i> ; published online March 19, 2009; doi:10.1126/science.1171583 Contact: Stewart T. Cole, Global Health Institute Lausanne, Lausanne, Switzerland e-mail: stewart.cole@epfl.ch
Inflammation				
Allergy; asthma	Toll-like receptor 4 (TLR4)	A study in mice suggests that antagonizing TLR4 on airway epithelial cells may help prevent allergy-induced asthma. In wild-type mice sensitized to a house dust mite allergen, intrapulmonary delivery of a TLR4 antagonist lowered airway inflammation and inflammatory cytokine levels after allergen challenge compared with what was seen using vehicle control. Next steps include confirming the results in additional animal models of asthma. Eritoran, a TLR4 antagonist from Eisai Co. Ltd., is in Phase III testing to treat sepsis. TAK-242, a TLR4 signal transduction inhibitor from Takeda Pharmaceutical Co. Ltd., is in Phase III for sepsis. SciBX 2(14); doi:10.1038/scibx.2009.584 Published online April 9, 2009	Findings unpatented; licensing status undisclosed	Hammad, H. <i>et al. Nat. Med.</i> ; published online March 29, 2009; doi:10.1038/nm.1946 Contact: Bart N. Lambrecht, Ghent University, Ghent, Belgium e-mail: bart.lambrecht@ugent.be

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Asthma; allergy; inflammation	IL-1; IL-5; IL-13; tumor necrosis factor- α (TNF- α)	A study in cell culture identified marine microbe-derived inhibitors of proinflammatory cytokine release that could help treat asthma and other inflammatory disorders. In allergen-induced murine lymphocytes, two of the lactone-based inhibitors blocked IL-5 and IL-13 release with nanomolar IC ₅₀ values comparable to those for the generic corticosteroid dexamethasone. In a separate cytokine production assay, the two compounds inhibited IL-1 and TNF- α at values slightly lower than those of dexamethasone. Next steps could include evaluating preclinical toxicology and ADME properties of these compounds. SciBX 2(14); doi:10.1038/scibx.2009.585 Published online April 9, 2009	Work unpatented; licensing status not applicable	Strangman, W.K. <i>et al. J. Med. Chem.</i> ; published online March 26, 2009; doi:10.1021/jm801111j Contact: William Fenical, University of California, San Diego, La Jolla, Calif. e-mail: wfenical@ucsd.edu
Inflammatory disease	Glucocorticoid receptor (NR3C1; GCCR); peroxisome proliferator-activated receptor- α (PPARA; PPAR α)	<i>In vitro</i> and mouse studies suggest that a combination of a GCCR agonist and a PPAR α agonist could help treat chronic inflammatory diseases. In several cell lines, the GCCR α variant agonist dexamethasone combined with different PPAR α agonists had additive effects in preventing NF- κ B-driven gene expression and suppressing inflammatory cytokine production. In a mouse model of hyperinsulinemia, dexamethasone plus the PPAR α agonist fenofibrate prevented glucose intolerance and hyperinsulinemia, which are side effects of glucocorticoid treatment for inflammation. Next steps include testing additional PPAR α agonist combination therapies in other relevant disease models. At least eight companies have PPAR α agonists in clinical and preclinical testing to treat diabetes and dyslipidemia. SciBX 2(14); doi:10.1038/scibx.2009.586 Published online April 9, 2009	Patent application filed covering therapeutic applications of findings; Ghent University is seeking an industrial partner to develop a combination product	Bougarne, N. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 30, 2009; doi:10.1073/pnas.0806742106 Contact: Karolien De Bosscher, Ghent University, Gent, Belgium e-mail: karolien.debosscher@ugent.be
Inflammatory disease	Purinergic receptor P2X ligand-gated ion channel 7 (P2RX7; P2X7 receptor); sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1; acid sphingomyelinase)	Studies in cell culture suggest that antagonizing P2RX7 or acid sphingomyelinase could help treat neuroinflammatory diseases. In astrocytes, P2RX7 activation led to downstream activation of acid sphingomyelinase and release of the inflammatory cytokine IL-1 β . P2RX7-induced IL-1 β release was blocked in mouse glial cells lacking acid sphingomyelinase. Next steps could include screening for P2RX7 receptor antagonists or acid sphingomyelinase inhibitors. AZD9056, a P2RX7 receptor antagonist from AstraZeneca plc, is in Phase II testing to treat rheumatoid arthritis (RA). SciBX 2(14); doi:10.1038/scibx.2009.587 Published online April 9, 2009	Patent and licensing status unavailable	Bianco, F. <i>et al. EMBO J.</i> ; published online March 19, 2009; doi:10.1038/emboj.2009.45 Contact: Claudia Verderio, CNR Institute of Neuroscience, Milan, Italy e-mail: c.verderio@in.cnr.it

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Metabolic disease				
Obesity	Component 3a receptor 1 (C3AR1); transforming growth factor- β receptor II (TGFB2); growth arrest-specific gene 7 (GAS7); glutathione peroxidase 3, plasma (GPX3); zinc finger protein 90 homolog (ZFP90); malic enzyme 1, cytosolic (ME1); β -lactamase (LACTB); lipoprotein lipase (LPL)	<p>A study in mice suggests that eight proteins identified through integrative genomic analysis could be targeted to treat obesity. Mice lacking or overexpressing any one of these eight genes—<i>C3ar1</i>, <i>Tgfb2</i>, <i>Gas7</i>, <i>Gpx3</i>, <i>Zfp90</i>, <i>Me1</i>, <i>Lactb</i> or <i>Lpl</i>—had higher or lower adiposity and/or body weight than wild-type controls. The effects of loss- and gain-of-function mutations in these eight genes were influenced by the gender of the animal. Mutations in two genes, <i>C3ar1</i> and <i>Tgfb2</i>, had opposite effects on fat metabolism in male mice compared with those seen in female mice. Next steps include combining mutations to understand obesity-related metabolic pathways and selecting candidate proteins as drug targets.</p> <p>Merck & Co. Inc. is testing compounds against undisclosed targets related to this work in obesity.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.588 Published online April 9, 2009</p>	Patents on methods filed by Merck; company plans to make methods and data available to Sage, a not-for-profit company spun out of Merck's Rosetta Inpharmatics Inc. subsidiary	<p>Yang, X. <i>et al. Nat. Genet.</i>; published online March 8, 2009; doi:10.1038/ng.325</p> <p>Contact: Thomas A. Drake, University of California, Los Angeles, Calif. e-mail: tdrake@mednet.ucla.edu</p>
Musculoskeletal disease				
Wounds	Insulin-like growth factor 1 (IGF1); IGF1 receptor (IGF1R)	<p>A study in human samples and in tissue cultures suggests that stimulating epidermal T cell production of IGF1 could be useful for accelerating wound healing. <i>In vitro</i>, stimulation of epidermal T cells resulted in increased levels of IGF1, which significantly accelerated wound closure compared with that seen in untreated controls ($p=0.012$). An anti-IGF1R antibody blocked the effects of T cell stimulation on wound closure. In contrast to cells isolated from acute wounds, human epidermal T cells isolated from chronic wounds did not produce IGF1 during the wound repair process, suggesting that IGF1 is a key contributor to chronic wound healing. Next steps include identifying IGF1 agonists and elucidating the mechanism behind impaired IGF1 functionality in chronic wounds (<i>see Wounded T cells, page 7</i>).</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.589 Published online April 9, 2009</p>	Patent and licensing status undisclosed	<p>Toulon, A. <i>et al. J. Exp. Med.</i>; published online March 23, 2009; doi:10.1084/jem.20081787</p> <p>Contact: Wendy L. Havran, The Scripps Research Institute, La Jolla, Calif. e-mail: havran@scripps.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	Anterior pharynx defective 1 homolog B (APH1B)	<p>A study in cell culture and in mice suggests that targeting APH1B could help treat AD. APH1B is a subunit of γ-secretase, an enzyme that cleaves amyloid-β (Aβ) precursor protein (APP) into the AD-associated β-amyloid (Aβ) protein. <i>In vitro</i>, murine cells with deletions of <i>Aph1B</i> and a mouse-specific duplicate gene, <i>Aph1C</i>, had lower levels of toxic Aβ peptides than cells with functional <i>Aph1B</i> and <i>Aph1C</i>. In a mouse model of AD, <i>Aph1B</i> and <i>Aph1C</i> knockout led to lower levels of toxic Aβ peptides and higher cognitive performance than what was seen in AD mice with intact <i>Aph1B</i> and <i>Aph1C</i>. The knockouts also had normal levels of Notch, a γ-secretase substrate required for normal immunity and development. Next steps include screening for small molecule antagonists of APH1B.</p> <p>Eli Lilly and Co.'s LY450139, a nonselective γ-secretase inhibitor, is in Phase III trials for AD. Eisai Co. Ltd. and Wyeth have γ-secretase modulators in Phase I trials for AD. Elan Corp. plc and Cellzome Inc. have preclinical γ-secretase programs.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.590 Published online April 9, 2009</p>	<p><i>Aph1b</i> knockout mice patented by the Catholic University Leuven; available for licensing</p> <p>Contact: Karine Clauwaert, Flanders Interuniversity Institute for Biotechnology, Leuven, Belgium e-mail: Karine.Clauwaert@vib.be</p>	<p>Serneels, L. <i>et al. Science</i>; published online March 19, 2009; doi:10.1126/science.1171176</p> <p>Contact: Bart De Strooper, Catholic University Leuven, Leuven, Belgium e-mail: Bart.destrooper@med.kuleuven.be</p>
Convulsions; epilepsy; seizures	Histone deacetylase (HDAC)	<p>Studies in rodents have identified a cyclic analog of valproic acid that may be useful as an anticonvulsant with decreased side effects. In a rat anticonvulsant model, the cyclic valproic acid analog had an ED₅₀ of 6 mg/kg and was 120-fold more potent than valproic acid. Similar effects were seen in a mouse psychomotor seizure model and a rat epilepsy model. Next steps could include evaluating the safety and efficacy of the analog in additional animal models.</p> <p>DP-VPA, a phospholipid derivative of valproic acid formulated with Regulated Activation of Prodrugs (D-RAP) technology from D-Pharm Ltd., is in Phase II testing to treat epilepsy.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.591 Published online April 9, 2009</p>	<p>Patent and licensing status unavailable</p>	<p>Pessah, N. <i>et al. J. Med. Chem.</i>; published online March 18, 2009; doi:10.1021/jm900017f</p> <p>Contact: Boris Yagen, The Hebrew University of Jerusalem, Jerusalem, Israel e-mail: yagen@cc.huji.ac.il</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Neuropathic pain	Adenosine A ₁ receptor (ADORA ₁)	<p>An SAR study characterized a series of N⁶-cyclopentyl-adenosine and N⁶-(endo-norborn-2-yl) adenosine derivatives as ADORA₁ agonists that could help treat neuropathic pain. Several compounds had higher affinity and selectivity for ADORA₁ over other adenosine receptor subtypes when compared with their parent compounds.</p> <p>In a murine model of pain, one compound decreased nociceptive behavior compared with that seen in controls. Next steps include evaluating the compounds in other animal models of neuropathic pain.</p> <p>T-62, an adenosine A₁ allosteric enhancer from King Pharmaceuticals Inc., is in Phase II testing to treat neuropathic pain.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.592 Published online April 9, 2009</p>	Unpatented; unlicensed	<p>Franchetti, P. <i>et al. J. Med. Chem.</i>; published online March 24, 2009; doi:10.1021/jm801456g</p> <p>Contact: Mario Grifantini, University of Camerino, Camerino, Italy e-mail: mario.grifantini@unicam.it</p>
Neuropathy	Sodium channels	<p>Human serum and rat studies suggest that targeting inactivated sodium channels could help treat certain forms of neuropathy in critically ill patients. In three patients who recovered from sepsis, sensory and motor nerve response decreased during worsening of critical illness but increased during recovery, suggesting that neuropathy may be rapidly reversible. In a rat model of sepsis, neuropathy was rapidly reversible and nerve action potential was restored with hyperpolarizing pulses, suggesting that sodium channel inactivation contributed to the rapidly reversible form of neuropathy. Next steps include studying how sodium channels are inactivated to determine how to target them. At least 14 companies have compounds to treat neuropathy in clinical and preclinical development.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.593 Published online April 9, 2009</p>	Findings unpatented; currently unavailable for licensing	<p>Novak, K. <i>et al. J. Clin. Invest.</i>; published online April 1, 2009; doi:10.1172/JCI36570</p> <p>Contact: Mark M. Rich, Wright State University, Dayton, Ohio e-mail: mark.rich@wright.edu</p>
Stroke	Adenosine A ₃ receptor (ADORA ₃)	<p>A study in cell and tissue cultures identified a triazolopyrazinone-based ADORA₃ antagonist that may help treat stroke. In rat hippocampal tissue slices, 10nM of the triazolopyrazinone derivative prevented or delayed the neuronal depolarization that can lead to the irreversible loss of neurotransmission. Also in the rat hippocampal slices, the derivative induced significant recovery of neurotransmission compared with that seen using no treatment ($p < 0.001$). Next steps could include evaluating the ADORA₃ antagonist in animal stroke models.</p> <p>DT0738, a small molecule antagonist of ADORA₃ from Domain Therapeutics S.A., is in preclinical testing for glaucoma.</p> <p>SciBX 2(14); doi:10.1038/scibx.2009.594 Published online April 9, 2009</p>	Patent and licensing status unavailable	<p>Colotta, V. <i>et al. J. Med. Chem.</i>; published online March 20, 2009; doi:10.1021/jm8014876</p> <p>Contact: Vittoria Colotta, University of Firenze, Firenze, Italy e-mail: vittoria.colotta@unifi.it</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Stroke	Protein kinase B (PKB; Akt); thioesterase superfamily member 4 (THEM4; CTMP)	A study in rats suggests that inhibiting CTMP may help prevent stroke-induced neuronal death. In a rat model of stroke, microRNA-mediated inhibition of CTMP decreased ischemia-induced neuron degeneration compared with that seen using control nontargeting miRNA. CTMP inhibition increased neuronal survival via Akt signaling in the rats. Next steps include identifying and evaluating CTMP inhibitors in animal stroke models.	Work unpatented; licensing status not applicable	Miyawaki, T. <i>et al. Nat. Neurosci.</i> ; published online April 6, 2009; doi:10.1038/nn.2299 Contact: R. Suzanne Zukin, Albert Einstein College of Medicine of Yeshiva University, Bronx, N.Y. e-mail: zukin@aecom.yu.edu
Ophthalmic disease				
Choroidal neovascularization (CNV)	VEGFB	<i>In vitro</i> and <i>in vivo</i> studies suggest that antagonizing VEGFB could help treat neovascular diseases. Antagonizing VEGFA is already established as a strategy to block blood vessel growth in age-related macular degeneration (AMD) and cancer. In a mouse model of CNV, intravitreal injection of small hairpin RNA targeting VEGFB or antibodies against VEGFB increased expression of proapoptotic genes, decreased expression of prosurvival genes and inhibited CNV. In a mouse model of ischemia-induced retinal neovascularization, the shRNAs and antibodies inhibited retinal neovascularization. Next steps include identifying anti-VEGFB compounds for antiangiogenic effects in different disease models.	Patent application filed; technology available for licensing through the NIH Office of Technology Transfer	Zhang, F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 30, 2009; doi:10.1073/pnas.0813061106 Contact: Xuri Li, National Institutes of Health, Farmington, Conn. e-mail: lixur@nei.nih.gov
Pulmonary disease				
Cystic fibrosis (CF); muscular dystrophy; mucopolysaccharidosis I (MPS-I; Hurler's syndrome); Usher syndrome	Nonsense mutations causing premature translation termination	<i>In vitro</i> studies suggest that a new aminoglycoside derivative could help treat genetic diseases caused by nonsense mutations. In an <i>in vitro</i> assay using DNA fragments containing nonsense mutations found in Usher syndrome, CF, Duchenne muscular dystrophy and Hurler's syndrome, the derivative was more effective at reading through mutant stop codons than a predecessor compound, gentamicin, or paromomycin. In three kidney cell lines, in cochlear explants and in mice, the derivative showed lower toxicity than the other two compounds. Ongoing studies are testing the lead compound in a mouse model of CF. Next steps could also include studying the effects on animal models of the other diseases.	Findings patented; available for licensing from Technion-Israel Institute of Technology for the treatment of diseases in which nonsense mutation is an underlying cause	Nudelman, I. <i>et al. J. Med. Chem.</i> ; published online March 23, 2009; doi:10.1021/jm801640k Contact: Timor Baasov, Technion-Israel Institute of Technology, Haifa, Israel e-mail: chtimor@tx.technion.ac.il

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			
High throughput screening using activity-based protein profiling (ABPP)	A high throughput screening method could identify leads against proteins with unknown biological function. The ABPP method uses a fluorescent probe that competes with substrates for binding to target enzymes. The probe shows a strong fluorescent signal when it binds an enzyme target. Hits from a compound library resulted in low fluorescence signal when the probe was displaced from the binding pocket. Screens of a 19,000-compound library identified inhibitors of two proteins of unknown biochemical function that have been implicated in cancer. Ongoing studies are using ABPP to screen other poorly characterized proteins implicated in human disease. Future studies will apply ABPP to the optimization of inhibitors identified by the method.	Patent and licensing status undisclosed	Bachovchin, D. <i>et al. Nat. Biotechnol.</i> ; published online March 29, 2009; doi:10.1038/nbt.1531 Contact: Benjamin F. Cravatt, The Scripps Research Institute, La Jolla, Calif. e-mail: cravatt@scripps.edu
Drug delivery			
Cell-specific sulfonated gallium(III) corrole-based cytotoxic agents	Cell-specific sulfonated gallium(III) corroles could be useful for treating a variety of diseases, including cancer, atherosclerosis, diabetes and numerous neurodegenerative conditions. In mice with HER2 (ERBB2)-positive tumors, a combination of sulfonated gallium corroles and a HER2-specific carrier protein slowed tumor growth and shrank existing tumors compared with what was seen using either compound delivered separately. The combination also had better efficacy than doxorubicin. Next steps include evaluating the safety and efficacy of the corrole-carrier protein complex in additional animal cancer models.	Corroles patented with additional patents pending; available for licensing from Technion-Israel Institute of Technology	Agadjanian, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 30, 2009; doi:10.1073/pnas.0901531106 Contact: Harry B. Gray, California Institute of Technology, Pasadena, Calif. e-mail: hgray@caltech.edu
Inflammation-dependent, cationic liposome-mediated blood-brain barrier (BBB) targeting	Studies in rats suggest that cationic liposomes could be used to deliver drugs to inflammatory sites on the BBB to treat neuroinflammatory diseases like multiple sclerosis (MS). In rats with experimental autoimmune encephalomyelitis (EAE), cationic liposomes injected into the tail veins accumulated in spinal cord endoneural vessels at levels that correlated with severity of neuroinflammation and disease progression. Liposome accumulation was detected at the early stages of disease progression. Next steps include determining the correlation between the targeting ability of the cationic liposomes and BBB permeability.	Patent status undisclosed; licensing status not applicable	Haas, H. <i>et al. Mol. Pharm.</i> ; published online March 12, 2009; doi:10.1021/mp8001478 Contact: Heinrich Haas, MediGene AG, Martinsried, Germany e-mail: h.haas@medigene.com

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Antibiotics produced by transformed plastids	<i>In vitro</i> studies suggest that plant plastids could be engineered to produce antibiotic proteins such as lysins. In tobacco plants, two different lysins—Pal and Cpl-1—were produced using plastid expression cassettes that included a bacterial transcription termination sequence upstream of the gene of interest, thereby allowing high lysin levels in tobacco. Protein extracts from the tobacco plants killed <i>Streptococcus pneumoniae</i> bacteria <i>in vitro</i> compared with what was seen using protein extracts from nontransformed tobacco. Next steps include optimizing the purification of the antibiotics from plants and testing the extracts in animals. SciBX 2(14); doi:10.1038/scibx.2009.601 Published online April 9, 2009	Unpatented; unlicensed	Oey, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 30, 2009; doi:10.1073/pnas.0813146106 Contact: Ralph Bock, Max-Planck Institute for Molecular Plant Physiology, Potsdam-Golm, Germany e-mail: rbock@mpimp-golm.mpg.de
Relaxin-based stem cell gene therapy to treat breast cancer	Relaxin-based stem cell gene therapy could be useful for treating breast cancer. Relaxin can degrade tumor stroma that prevent therapeutics and tumor-infiltrating immune cells from reaching cancer cells. Hematopoietic stem cells (HSCs) were transduced with relaxin-expressing lentivirus vectors and transplanted into mice with breast cancer. Doxycycline-induced production of relaxin lowered tumor growth compared with that seen in controls. Next steps include restricting relaxin expression to tumor-associated macrophages and using self-inactivating lentiviral vectors to decrease the risk of insertional mutagenesis. SciBX 2(14); doi:10.1038/scibx.2009.602 Published online April 9, 2009	Work unpatented; licensing status not applicable	Li, Z. <i>et al. Blood</i> ; published online March 27, 2009; doi:10.1182/blood-2008-10-187237 Contact: Andre Lieber, University of Washington, Seattle, Wash. e-mail: lieber00@u.washington.edu
Instrumentation			
High-resolution microfluidics-based NMR probe	A microfluidics-based NMR probe could track chemical reaction kinetics and measure the composition of nanomolar volumes of serum drawn from patients. High-resolution NMR spectra obtained with the device allowed for real-time, <i>in situ</i> monitoring of the kinetics of chemical reactions lasting from a few seconds to 30 minutes. The device also obtained high-resolution NMR spectra on micromolar concentrations of metabolites present in a 5 μ L sample of human cerebrospinal fluid. Ongoing work with the device includes studies of murine cerebrospinal fluid and examining the possibility of adding biological sample preparation into the probe design. SciBX 2(14); doi:10.1038/scibx.2009.603 Published online April 9, 2009	Patent and licensing status undisclosed	Bart, J. <i>et al. J. Am. Chem. Soc.</i> ; published online March 25, 2009; doi:10.1021/ja900389x Contact: Arno P.M. Kentgens, Radboud University, Nijmegen, the Netherlands email: a.kentgens@nmr.ru.nl

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P		Roferon-A IFN α -2a	11	Sulindac	5	Tribbles homolog 3	10
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