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A super kind of cytokine

By Tracey Baas, Senior Editor

Stanford and Zurich researchers have engineered a variant of IL-2 that shows a better antitumor response in mice than wild-type IL-2.¹ The new IL-2 superkine variant, dubbed super-2, has been licensed by **Teva Pharmaceutical Industries Ltd.**, which is planning additional preclinical studies of the compound.

IL-2 is an immunostimulatory cytokine that binds and activates a wide range of immune cells. **Novartis AG** markets Proleukin aldesleukin IL-2 to treat metastatic melanoma and renal cancer.

In patients with metastatic melanoma or metastatic renal cell carcinoma, high-dose IL-2 delivery, either alone or in combination with tumor vaccines, has led to therapeutic responses in about 13%–20% of cases and to long-term survival in about 10% of cases.² However, components of IL-2's biology have limited its use.

One of the three parts of the cytokine's receptor complex—IL-2 receptor β -chain (IL2-RA; CD25)—is often expressed at very low levels or not at all on key immune cells such as cytotoxic T cells and NK cells. Those cells are rather insensitive to IL-2 (see **Figure 1, "IL-2 regulation of T cells"**). As a result, an IL-2-based immunotherapy has to be given at high doses in order to achieve significant stimulation of cytotoxic T cells, which play a central role in the host antitumor and antiviral response.

However, delivering high levels of systemic IL-2 can trigger vascular leak syndrome, leading to pulmonary edema, liver cell damage and renal failure.³ This process is thought to be CD25 dependent.²

To address those limitations, researchers from the **Stanford University School of Medicine, Stanford University, University Hospital Zurich** and the **University of Zurich** set out to eliminate the functional requirement of IL-2 for CD25. The group started by using *in vitro* evolution to produce IL-2 mutant libraries and screened for IL-2 variants—superkines—that bound the receptor complex and activated IL-2 signaling independently of CD25, thus generating a T cell response even when CD25 was absent.

In vitro, the top three variants bound IL-2 receptor β -chain (IL2-RB; CD122), another component of the receptor complex, much more strongly than wild-type IL-2. Structural studies showed the superkines' increased affinity for CD122 resulted from mutations in the core of the protein.

Next, the researchers set out to confirm that the increased affinity for CD122 was sufficient to activate IL-2 signaling in T cells independent of CD25.

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Indeed, one of the superkines triggered proliferation in both CD25-deficient T cells and NK cells as well as in CD25-expressing T cells and NK cells.

The team then compared the effects of the superkine with those of both wild-type IL-2 and an IL-2-anti-IL-2 mAb complex. In prior mouse studies, the mAb complex had a longer half-life² and generated more potent antitumor responses with less CD25-dependent pulmonary edema³⁻⁵ than wild-type IL-2.

In healthy mice, the superkine induced more than three times the number of cytotoxic T cells and led to less pulmonary edema than wild-type IL-2 ($p < 0.01$).

In mice with melanoma, lung cancer or colon cancer, the superkine significantly decreased tumor growth after 18 days and induced

less edema compared with wild-type IL-2 ($p < 0.05$). The superkine and mAb complex produced similar results, and a detailed comparison of the two molecules awaits further studies.

Results were published in *Nature*.

“The work gives a good indication of increased antitumor effects, but more work is needed to discern effects on primary T cell responses versus simply bystander memory T cell expansion.”

— William Murphy
University of California, Davis

More super

The next step for the superkine is longer-term studies in a variety of animal models.

“The work gives a good indication of increased antitumor effects, but more work is needed to discern effects on primary T cell responses versus simply bystander memory T cell expansion,” said William Murphy, professor of dermatology and internal medicine at the **University of California, Davis**. “In addition, long-term efficacy, possible toxicities and immunogenicity against the superkine will have to be evaluated. Their study follows the treatment for only 18 days to provide a rather isolated snapshot of immunomodulation.”

He said mouse studies of cancer immunotherapies need to run much longer to detect any signs of an impaired secondary antitumor response, long-term toxicities with repeated administration and potential tumor or immune rebound effects.

The *Nature* findings “can be validated by testing in nonhuman primates,” said Jeffrey Bluestone, executive vice chancellor and provost and professor of medicine, pathology, microbiology and immunology at the **University of California, San Francisco**. “The structure of mouse IL-2 is very different from human IL-2. However, nonhuman primate IL-2 is very similar to human IL-2. Therefore, providing evidence that their human IL-2 superkine has an effect in monkeys would lend support to their strategy.”

Regardless of animal type, Peter Rhode, VP of R&D at **Altor BioScience Corp.**, said it will be important to better characterize the half-life of the superkines. Proleukin has a short half-life and is dosed every eight hours for five days per cycle in an in-patient hospital setting. Whether the IL-2 superkine can alter this dosing regimen needs to be probed, he said.

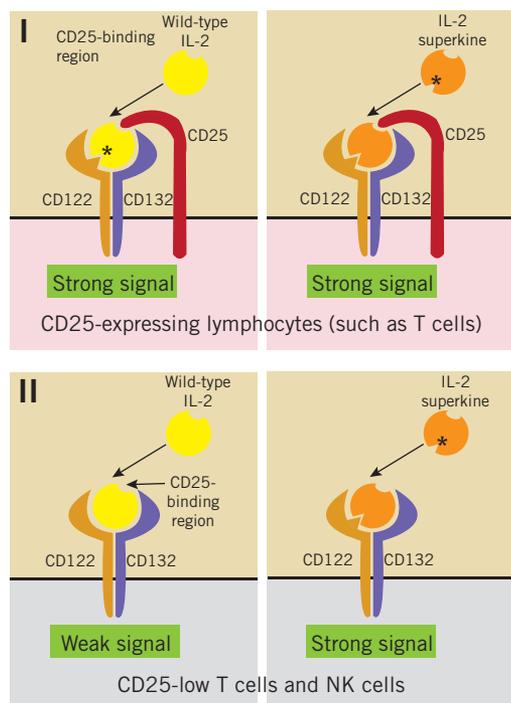


Figure 1. IL-2 regulation of T cells. IL-2 binds and signals through a complex consisting of IL-2, IL-2 receptor α -chain (IL2-RA; CD25), IL-2 receptor β -chain (IL2-RB; CD122) and IL-2 receptor γ -chain (IL2-RG; CD132).

(I) In CD25-expressing lymphocytes (such as T cells), CD25 binds to IL-2, leading to an optimized receptor-binding conformation (*) of wild-type IL-2, thus increasing the affinity of IL-2 for CD122 and CD132 and inducing efficient cell signaling and expansion. The IL-2 superkine already contains this optimized receptor-binding conformation. Because both cytokine forms interacting with the receptor complex have optimal receptor-binding conformation, the signaling in and expansion of CD25-competent cells are similar for both cytokine forms.

(II) In CD25-low T cells and NK cells, CD25 is not available to optimize the receptor-binding conformation of wild-type IL-2. Because the IL-2 superkine already contains the optimized receptor-binding conformation (*), even when CD25 is not present, the superkine binds with a higher affinity to the receptor complex and induces stronger cell signaling and expansion than wild-type IL-2. Cytotoxic T cells play a central role in antitumor and antiviral responses.

Bluestone said that even if the IL-2 superkine has a similar or

Cephalon Inc., which was acquired by Teva in 2011. Teva has the IL-2 superkine in preclinical development.

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REFERENCES

1. Levin, A.M. *et al. Nature*; published online March 25, 2012; doi:10.1038/nature10975
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2. Boyman, O. & Sprent, J. *Nat. Rev. Immunol.* **12**, 180–190 (2012)
3. Boyman, O. *et al. Science* **311**, 1924–1927 (2006)
4. Krieg, C. *et al. Proc. Natl. Acad. Sci. USA* **107**, 11906–11911 (2010)
5. Létourneau, S. *et al. Proc. Natl. Acad. Sci. USA* **107**, 2171–2176 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

Altor BioScience Corp., Miramar, Fla.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Stanford University, Stanford, Calif.
Stanford University School of Medicine, Stanford, Calif.
Teva Pharmaceutical Industries Ltd. (NASDAQ:TEVA), Petah Tikva, Israel
University of California, Davis, Calif.
University of California, San Francisco, Calif.
University Hospital Zurich, Zurich, Switzerland
University of Zurich, Zurich, Switzerland

shorter half-life than wild-type IL-2, it may not matter if the superkine is used in conjunction with a tumor vaccine. “Delivering the superkine as a short pulse with tumor vaccine inoculation may be sufficient to provide a strong antigen-specific immune response that could help initiate responses to tumors and not require continual treatment,” he said.

This would depend on “whether IL-2 is used *in vitro* or *in vivo* to stimulate antigen-specific T cells,” said Onur Boyman, professor of the Swiss National Science Foundation at the University of Zurich, senior consultant physician with the Allergy Unit of University Hospital Zurich and co-corresponding author on the *Nature* paper. “Moreover, it also depends whether IL-2 signaling is required for the survival or function of antigen-specific T cells *in vivo*.” Those outcomes would have to be shown.

Altor’s ALT-801, a fusion protein of IL-2 and a soluble T cell receptor (TCR) that specifically recognizes tumor cells that overexpress p53 antigen, is in Phase Ib/II testing to treat metastatic melanoma and metastatic urothelial cancer.

Stanford has filed for a patent covering super-2. The IP is licensed to

Building tools against autism

By Lev Osherovich, Senior Writer

As information about the genetic underpinnings of autism spectrum disorder has proliferated, so too have questions about how subtle changes in a seemingly diverse set of genes can lead to similar clinical pathology. This month, an academic-industry consortium headed by **King's College London** and **Roche** launched with €29.6 million (\$38.9 million) to develop research tools and diagnostics for the disorder and to help select clinical endpoints for future trials.

Up to 40% of autism spectrum disorder (ASD) cases are now thought to stem from either single mutations or a combination of multiple genetic variants. For example, a trio of recent exome sequencing studies identified spontaneous mutations that substantially increase the risk for ASD.¹⁻³

However, the underlying causes of the majority of ASD cases that lack a clear genetic component remain mysterious. As a result, only a handful of companies are pursuing ASD therapeutics.

The new consortium, dubbed the European Autism Interventions—A Multicentre Study for Developing New Medications (EU-AIMS), hopes to change that by uncovering common pathophysiological features across a range of ASD cases, identifying biomarkers for stratifying patients and developing preclinical and clinical assays to assess drug efficacy.

The consortium's work has been subdivided into six projects concerning cellular assays, animal models, MRI methods, PET radioligands, biomarker identification and clinical research network building.

“The goal of the consortium is to speed up the development of infrastructure that would facilitate the development of new treatments.”

—Declan Murphy,
King's College London

The consortium is being funded by the **Innovative Medicines Initiative** (IMI), Roche and other industry participants, and the patient advocacy group **Autism Speaks** (see Table 1, “Participants in the European Autism Interventions—A Multicentre Study for Developing New Medications (EU-AIMS) consortium”).

Autism Speaks is contributing about €500,000 (\$656,000) as a grant to academic researchers in the consortium; industry partners will contribute about €10 million (\$13 million) in services, reagents and facilities; IMI will provide about €19 million (\$25 million) in grant support over 5 years.

Framing the challenge

According to Declan Murphy, professor of psychiatry and brain maturation at King's College London and leader of the consortium's U.K. team, the challenges in understanding ASD include the apparent heterogeneity of the genetic causes of the disease, a lack of good preclinical models and the complex behavioral manifestation of the disease in the clinic.

“This is a mental health disorder, and there are a lot of pharmas getting out of the area. We don't understand the biology well enough,” said Murphy. “The goal of the consortium is to speed up the development of infrastructure that would facilitate the development of new treatments.”

The key questions, he said, are “can we stratify individuals with autism? Can we develop assays and biomarkers that are predictive of outcomes? Can we demonstrate efficacy in mice and humans?”

Luca Santarelli, global head of Roche Neuroscience and point person for the pharma's involvement with EU-AIMS, said the consortium is operating on the hypothesis that there is set of shared disease mechanisms that apply to the bulk of ASD patients.

Roche's RO5028442, a small molecule with an undisclosed target, is in Phase I testing in autistic patients. Roche also has another autism

Table 1. Participants in the European Autism Interventions—A Multicentre Study for Developing New Medications (EU-AIMS) consortium.

Academic centers and research organizations	Companies
Autism Speaks, New York, N.Y.	Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Biozentrum of the University of Basel, Basel, Switzerland	Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Birkbeck, University of London, London, U.K.	Servier, Neuilly-sur-Seine, France
Campus Bio-Medico University, Rome, Italy	Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Central Institute of Mental Health, Mannheim, Germany	Pfizer Inc. (NYSE:PFE), New York, N.Y.
European Molecular Biology Laboratory, Heidelberg, Germany	Galenica Ltd. (SIX:GALN), Berne, Switzerland
French Alternative Energies and Atomic Energy Commission, Saclay, France	deCode genetics ehf, Reykjavik, Iceland
Institute of Education, London, U.K.	NeuroSearch A/S (CSE:NEUR), Ballerup, Denmark
Karolinska Institute, Stockholm, Sweden	
Max Planck Institute of Experimental Medicine, Goettingen, Germany	
Pasteur Institute, Paris, France	
Radboud University Nijmegen, Nijmegen, the Netherlands	
University Medical Center Utrecht, Utrecht, the Netherlands	
University of Cambridge, Cambridge, U.K.	
University of Ulm, Ulm, Germany	

compound, the arginine vasopressin receptor 1A (AVPR1A) antagonist RG7314, in Phase I testing in healthy volunteers.

“Genetics offers a very wide variety of potential reasons why brain physiology might be altered leading to ASD,” said Santarelli. “On one hand, you have many mutations that can lead to ASD. On the other hand, you have a lot of complex phenotypes. What we need is a more reductionist, simple model that explains how different types of genetic lesions may lead to common alterations in the brain.”

Thus, he said, one of the consortium’s goals is to understand the common features of brain pathophysiology across the autism spectrum.

“It’s more than likely that we will converge on a handful of common pathways that lie downstream of a variety of genetic risk factors,” agreed Robert Ring, VP of translational research at Autism Speaks.

Game plan

Santarelli and Ring said the theory they favor is that ASD is a disorder of brain connectivity in which alterations in a range of genes lead to changes in synaptic structure and function. According to this theory, some patients with ASD may have overly excitable synapses, whereas other patients may suffer from the opposite problem.

“We clearly have an interest in the balance of inhibition and excitation in certain brain regions. There is a very fine-tuned balance between these activities both in development and adulthood,” said Santarelli. “With this hypothesis in mind, it’s clear that we need appropriate cell and animal models to dissect the biology. In this consortium, cell models and animal models are the two pillars. We will start with modeling these mutations in cell systems and iPS [induced pluripotent stem] cells from patients, then we will move into animal models.”

In parallel with model building, the consortium will search for imaging data or other biomarkers to shed light on the functional consequences of brain connection problems in ASD.

Academic centers participating in the consortium will develop functional MRI methods and PET radioligands for *in vivo* imaging. The

“What we need is a more reductionist, simple model that explains how different types of genetic lesions may lead to common alterations in the brain.”

—Luca Santarelli, Roche

consortium also hopes to uncover proteomic biomarkers of the disease that can be used to guide treatment decisions and assess efficacy of future interventions.

The hope, said Santarelli, is to classify patients with ASD into less than 10 functional categories that will help guide what kind of therapy would be most appropriate.

Knowing how autistic brains are different from normal brains also will help guide selection of endpoints in future trials. Thus, Autism Speaks will work with clinics within the consortium to build a patient registry and a clinical trial network.

IMI requires that the money be spent in the EU, so it brought in Autism Speaks to insure that the consortium does not repeat the work of other autism research consortia in the U.S., such as the Biomarkers Consortium, managed by the **Foundation for the National Institutes of Health**, and the Autism Epidemiology Network of the **Centers for Disease Control and Prevention**. Autism Speaks will help coordinate between EU-AIMS and American researchers to avoid duplication of effort.

Murphy said that the consortium’s work will be openly accessible.

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REFERENCES

1. Sanders, S.J. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature10945
2. O’Roak, B.J. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature10989
3. Neale, B.M. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature11011

COMPANIES AND INSTITUTIONS MENTIONED

Autism Speaks, New York, N.Y.
Centers for Disease Control and Prevention, Atlanta, Ga.
Foundation for the National Institutes of Health, Bethesda, Md.
Innovative Medicines Initiative, Brussels, Belgium
King’s College London, London, U.K.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

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Blocking p75 NTR in diabetes

By Lauren Martz, Staff Writer

University of California, San Francisco researchers have shown that genetic deletion of the p75 neurotrophin receptor improves insulin sensitivity in diabetic mice.¹ Although targeting this receptor may offer a new way to treat insulin resistance, the challenge will be figuring out how to inhibit it in skeletal muscle and adipose tissue without impairing its function in neurons.

Insulin resistance in muscle and fat cells reduces glucose uptake, leading to chronically high blood glucose and type 2 diabetes. In most forms of insulin resistance, trafficking of solute carrier family 2 facilitated glucose transporter member 4 (SLC2A4; GLUT4) to the plasma membrane is impaired.² Unfortunately, it has remained unclear how to target GLUT4 to improve glucose uptake and insulin sensitivity.

Prior work by groups at the University of Liverpool and E. Medea Scientific Institute had shown that the p75 neurotrophin receptor (p75 NTR), a protein originally identified in the nervous system, is expressed in white adipose tissue and skeletal muscle tissue, in which it interacts with small GTPases that regulate GLUT4 trafficking.^{3,4} In the nervous system, p75 NTR is involved in many neuronal functions including the development of sensory neurons.⁵

Based on those findings, Katerina Akassoglou and colleagues at UCSF hypothesized that targeting p75 NTR might indirectly influence GLUT4 trafficking in muscle and fat tissues and thus improve glucose uptake and insulin sensitivity.

Akassoglou is associate investigator of neurology at UCSF's Gladstone Institute of Neurological Disease. The team also included researchers from the University of California, San Diego, the University of Michigan and Baylor College of Medicine.

The group first showed that knockout of *p75 ntr* in mice fed a normal diet did not alter food consumption or body weight but lowered glycemic excursions during a glucose tolerance test and increased hypoglycemia by 30%. Those results suggested insulin sensitivity in the knockouts was greater than that in wild-type controls. Also in the knockout mice, insulin-stimulated glucose disposal was higher than that in wild-type controls.

Insulin-stimulated glucose uptake was greater in adipocytes derived from the *p75 ntr*^{-/-} mice than in cells from wild-type mice. The same effect was seen from small hairpin RNA-mediated *p75 ntr* knockdown and in myocytes. Those findings suggested that blocking p75 NTR signaling in skeletal muscle and white adipose tissue could help increase insulin sensitivity and glucose tolerance.

Also in adipocytes, coimmunoprecipitation studies showed p75 NTR forms a complex with the RAB5 family members RAB5A member RAS oncogene family (RAB5A) and RAB31 member RAS oncogene family (RAB31). In *p75 ntr*^{-/-} adipocytes, expression of a dominant negative

Rab5a mutant prevented the increase in glucose uptake caused by *p75 ntr* knockout, suggesting p75 NTR interacts with RAB5 GTPases to block GLUT4 trafficking and glucose uptake.

The findings were published in the *Proceedings of the National Academy of Sciences*.

Akassoglou told *SciBX* that next steps include identifying inhibitors that specifically block the interaction of RAB5 family GTPases with p75 NTR.

"Potentially, the work in this paper could lead to the development of agents that can correct a key defect in human type 2 diabetes, which is reduced glucose uptake in white adipose tissue and skeletal muscle," said Cord Dohrmann, CSO of **Evotec AG**. "Based on the phenotype of p75 NTR mice, this may be possible without causing weight gain, which is a major liability of the currently marketed TZD class of insulin-sensitizing drugs."

Current strategies to improve insulin sensitivity include agonizing peroxisome proliferation-activated receptor- α (PPARG; PPAR α) with compounds including the thiazolidinedione (TZD) class of agonists.

However, PPARG agonists "lack specificity and cause elevation in lipid levels. These drugs are also associated with fluid retention, weight gain and increases in the number and size of adipocytes. There are also a variety of other side effects including increased risk for congestive heart failure," said Richard Gregg, CSO of **Vitae Pharmaceuticals Inc**.

Vitae has a hydroxysteroid 11 β dehydrogenase 1 (HSD11B1; HSD1) inhibitor in Phase I testing to treat type 2 diabetes. The compound is partnered with **Boehringer Ingelheim GmbH**.

Evotec and **Harvard University** "have conducted screens to identify novel

mechanisms and targets that enhance β cell mass and function. These screens have identified several high-potential target candidates, a number of which have reached initial proof of concept in animal models," Dohrmann told *SciBX*.

Evotec's β cell regeneration factor, EVT 770, is in preclinical testing to treat diabetes. The compound is partnered with **AstraZeneca plc**.

Selective targeting and side effects

The big challenge moving forward will be to figure out how to target p75 NTR in muscle and adipose tissue without blocking the protein's function in neural tissue.

"p75 is a difficult target because it has a lot of biological implications. In addition to the small GTP-binding proteins involved in glucose transporter activity, it also interacts with other small binding molecules and has a lot of functions in neuronal activity," said Gregg. "Whether a new therapeutic would be able to have specificity for the beneficial effects on insulin sensitivity without the CNS toxicity is a concern."

Barbara Hempstead, professor of medicine at **Weill Cornell Medical College**, agreed. "p75-null animals have altered glucose homeostasis but also have other consequences including defects in sensory perception, shortened lifespan and hippocampal defects. Therefore, it might be helpful to confirm the results in a targeted manner," she said.

Dohrmann added, "In light of the fact that p75 knockout mice have

"Potentially, the work in this paper could lead to the development of agents that can correct a key defect in human type 2 diabetes, which is reduced glucose uptake in white adipose tissue and skeletal muscle."

—Cord Dohrmann, *Evotec AG*

a range of neuronal defects, any interference with the receptor probably needs to be highly specific.”

“Selective targeting of the interaction of p75 NTR with RAB5A in peripheral tissues might lead to therapies with less side effects,” said Akassoglou. However, she said, “appropriate methodologies applicable for targeting p75 NTR will have to be developed and tested.”

Another issue related to blocking p75 NTR, according to Gregg, is that “p75 NTR appears to be part of an intracellular protein-protein interaction. You need intracellular activity from a

therapeutic like a small molecule, yet it is difficult to target protein-protein interactions with small molecules. Protein biologics are better suited for these kinds of interactions, but they are hard to get into cells.”

He added that an important next step would be to gain a better understanding of the structure-function interaction at the crystallography level. “If the team is able to identify a site for small molecule binding with therapeutic activity, it still could be feasible to target the interaction, although still very hard,” he said.

In addition to targeting p75 NTR interactions that are specific for insulin signaling, specificity and reduced side effects could be achieved by selectively targeting the appropriate tissues.

“Another next step would be to look at the effects of interfering

with RAB5A and RAB31 interactions in various cell types. Specific targeting to adipocytes and myocytes in the periphery could give you the efficacy in diabetes without the dysfunction in neurons. Again, though, this would be difficult to execute,” said Gregg.

Akassoglou told *SciBX* that UCSF has filed a patent application covering the findings and that the IP is available for licensing.

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REFERENCES

1. Baeza-Raja, B. *et al. Proc. Natl. Acad. Sci. USA*; published online March 28, 2012; doi:10.1073/pnas.1103638109
Contact: Katerina Akassoglou, University of California, San Francisco, Calif.
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2. Lodhi, I.J. *et al. Cell Metab.* **5**, 59–72 (2007)
3. Peeraully, M.R. *et al. Am. J. Physiol. Endocrinol. Metab.* **287**, E331–E339 (2004)
4. Deponti, D. *et al. Mol. Biol. Cell* **20**, 3620–3627 (2009)
5. Chao, M.V. *Nat. Rev. Neurosci.* **4**, 299–309 (2003)

COMPANIES AND INSTITUTIONS MENTIONED

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Boehringer Ingelheim GmbH, Ingelheim, Germany
E. Medea Scientific Institute, Bosisio Parini, Italy
Evotec AG (Xetra:EVT), Hamburg, Germany
Gladstone Institute of Neurological Disease, San Francisco, Calif.
Harvard University, Cambridge, Mass.
University of California, San Diego, La Jolla, Calif.
University of California, San Francisco, Calif.
University of Liverpool, Liverpool, U.K.
University of Michigan, Ann Arbor, Mich.
Vitae Pharmaceuticals Inc., Fort Washington, Pa.
Weill Cornell Medical College, New York, N.Y.

“p75 is a difficult target because it has a lot of biological implications. Whether a new therapeutic would be able to have specificity for the beneficial effects on insulin sensitivity without the CNS toxicity is a concern.”

—Richard Gregg,
Vitae Pharmaceuticals Inc.

RNA profiling pathogens

By Tim Fulmer, Senior Writer

Massachusetts researchers have developed an RNA-based method for the rapid detection of pathogens in clinical samples.¹ The team is now designing an integrated diagnostic platform that contains a comprehensive set of bacterial, viral and fungal probes to help pinpoint specific pathogens and their degree of drug resistance more efficiently than conventional diagnostics.

Most hospitals rely on culture-based methods to diagnose infectious diseases and determine drug resistance. Culturing infectious agents typically takes two to four days, and determining a pathogen's drug resistance profile can take up to a month. The long delay necessitates the use of broad-spectrum antibiotics to treat the early stages of infection and also can increase a patient's risk of death because the optimal treatment regimen remains unidentified.

The primary strategy to replace culture-based methods has been to use pathogens' genome sequences as sources of unique biomarkers that can be readily detected in patient fluids using standard PCR and DNA sequencing.

Although such approaches can help detect the presence of a particular pathogen, they do not provide insight into drug resistance because in many cases the DNA mutations that cause a particular form of resistance are unknown.

Now, a team of researchers from the **Broad Institute of MIT and Harvard** and from **Harvard Medical School** has zeroed in on RNA as a potentially better diagnostic tool than DNA for infectious diseases. The group was led by Deborah Hung, an infectious disease physician at **Brigham and Women's Hospital** and **Massachusetts General Hospital** and a researcher at Broad.

Just like a DNA signature, an RNA profile contains sufficient information to accurately identify the presence of a pathogen. In contrast to DNA analysis, RNA profiling can help determine whether a pathogen is drug resistant because antibiotic exposure triggers stress-induced changes in the RNA profile of a drug-sensitive pathogen, whereas little or no change is seen in the profiles of resistant pathogens.²

To test this idea, the team first designed a set of fluorescent oligonucleotide probes that targeted mRNA sequences unique to *Mycobacterium tuberculosis* and to three different Gram-negative pathogens: *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

Using these probes, the researchers detected and distinguished each of the four pathogens in pure culture and in complex mixtures containing eight additional pathogens. Next, they designed probes that identified nonbacterial pathogens, including viruses (influenza, HSV-2 and HIV-1), a fungus (*Candida albicans*) and a parasite (*Plasmodium falciparum*), suggesting that the mRNA detection platform was

applicable across a broad range of infectious agents.

The team then tested whether the approach could also be used to determine drug susceptibility of pathogens.

Following a 10-minute exposure of wild-type and ciprofloxacin-resistant *E. coli* strains to the antibiotic, the researchers saw changes in mRNA levels of a subset of genes. The result was an mRNA ciprofloxacin-susceptibility signature in the wild-type strains. Two other antibiotics, gentamicin and ampicillin, also elicited unique mRNA drug-susceptibility signatures in *E. coli*.

The researchers then looked for such signatures in other organisms. They found a ciprofloxacin-susceptibility signature in *P. aeruginosa* and *M. tuberculosis*. The latter also had isoniazid- and streptomycin-susceptibility signatures.

Finally, the researchers looked at whether they could detect mRNA signatures in clinical samples.

In 34 urine specimens collected from patients who had tested positive for a urinary tract infection, the method identified all 17 *E. coli*-positive samples. In a second set of 13 *E. coli*-positive urine samples, the method differentiated ciprofloxacin-sensitive and ciprofloxacin-resistant *E. coli* strains. The bacterial loads detected in these clinical samples were 10⁵-10⁹ cells/mL.

The findings were published in the *Proceedings of the National Academy of Sciences*.

"Our method can potentially identify infectious pathogens within three to four hours, compared, for example, to the two to three days typically required for diagnosing a MRSA infection or the three weeks needed to diagnose tuberculosis," said Hung.

According to Jeremy Bridge-Cook, SVP of the assay group at **Luminex Corp.**, one advantage of the method is that "direct detection of mRNA provides information that could indicate the presence of active infection by live, metabolizing organisms," which stands in contrast to approaches that analyze genomic nucleic acids.

Luminex markets molecular diagnostics for infectious disease that use the company's PCR-based xTAG technology, including the xTAG Respiratory Viral Panel (xTAG RVP) and the xTAG Gastrointestinal Pathogen Panel (xTAG GPP).

Mark Perkins, CSO of the **Foundation for Innovative New Diagnostics** (FIND), added that by focusing on the mRNA signature, "you could test for resistance when the knowledge of resistance-associated mutations is incomplete or when the resistance mechanisms are known but difficult to detect with conventional platforms."

FIND is developing DNA-based molecular diagnostics for a range of infectious diseases including malaria,³ salmonella⁴ and tuberculosis.⁵

Getting realistic

The Broad-Harvard team plans to continue working "to define the most robust mRNA signatures for a wide variety of drug-sensitive and drug-resistant pathogens. That work is essential to ensure we arrive at a set of signatures that clearly distinguishes the various organisms," Hung said.

"Our method can potentially identify infectious pathogens within three to four hours, compared, for example, to the two to three days typically required for diagnosing a MRSA infection or the three weeks needed to diagnose tuberculosis."

**—Deborah Hung,
Broad Institute of MIT and Harvard**

She added: “On the engineering side, we are designing a benchtop device to house the diagnostic that can potentially be used in any doctor’s office as well as in the developing world. The long-term

goal is to have a device that can quickly analyze a urine or saliva sample and indicate the general type of infection—bacterial, viral or fungal—as well as the specific infectious species within those types.”

Tom Lowery, VP of diagnostics R&D at **T2 Biosystems Inc.**, said that to

prove the clinical relevance of the approach, it will be important to show the method enables the detection of pathogens present at cell counts much lower than those tested in the paper.

T2 is developing an NMR-based molecular diagnostic platform to detect different *Candida* species in whole blood from candidemia patients.

According to Garth Ehrlich, professor of microbiology and immunology and executive director of the Center for Genomic Sciences at the **Drexel University College of Medicine**, “The problem of most previous molecular diagnostics was that their coverage was too narrow. So, if the diagnostic showed a negative result, it wasn’t because someone wasn’t infected but because your assay didn’t cover that infection.”

In addition, Ehrlich said the researchers will have to show that their RNA-based method “can differentiate log-fold differences in concentrations of different bacterial species that might occur in polymicrobial infections.”

Ultimately, to deal with samples that include multiple infectious agents, it will be necessary “to create very large mRNA probe sets that do not interfere with each other and collectively cover all potential

pathogens within a domain—for bacteria and fungi that is hundreds of species each,” said Ehrlich. “On top of that, it will be necessary to identify the antibiotic-sensitivity signals for each of those pathogens.”

Ehrlich and colleagues used a mass spectrometry-based approach to show that the adenoids of children undergoing adenoidectomy serve as reservoirs of polymicrobial biofilms.⁶

Hung agreed that a key next step is to identify RNA signatures that are sufficiently robust to identify low levels of a particular pathogen in the presence of other pathogens in clinical samples. She declined to provide additional details.

The *PNAS* findings are covered by patents that are available for licensing from the Broad Institute.

Fulmer, T. *SciBX* 5(16); doi:10.1038/scibx.2012.408
Published online April 19, 2012

REFERENCES

1. Barczak, A.K. *et al. Proc. Natl. Acad. Sci. USA*; published online April 2, 2012; doi:10.1073/pnas.1119540109
Contact: Deborah T. Hung, Broad Institute of MIT and Harvard, Cambridge, Mass.
e-mail: hung@molbio.mgh.harvard.edu
2. Sangurdekar, D.P. *et al. Genome Biol.* **7**, R32 (2006)
3. Polley, S.D. *et al. J. Clin. Microbiol.* **48**, 2866–2871 (2010)
4. Francois, P. *et al. FEMS Immunol. Med. Microbiol.* **62**, 41–48 (2011)
5. Boehme, C.C. *et al. N. Eng. J. Med.* **363**, 1005–1015 (2010)
6. Nistico, L. *et al. J. Clin. Microbiol.* **49**, 1411–1420 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

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T2 Biosystems Inc., Lexington, Mass.

“Direct detection of mRNA provides information that could indicate the presence of active infection by live, metabolizing organisms.”

—**Jeremy Bridge-Cook**,
Luminex Corp.

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Acute lymphoblastic leukemia (ALL); chronic myelogenous leukemia (CML)	Not applicable	Cell culture and mouse studies suggest a quinolinylhydrazone analog could help treat ALL and CML. Compound screening in zebrafish and testing in primary human and mouse ALL cell lines and primary mouse CML cells identified a quinolinylhydrazone analog, lenaldekar, as a submicromolar inhibitor of leukemic cell growth. In xenograft mouse models of ALL, lenaldekar decreased tumor growth and increased survival compared with vehicle. Ongoing work includes elucidating the molecular target of lenaldekar and testing its activity against leukemia-initiating cells. SciBX 5(16); doi:10.1038/scibx.2012.409 Published online April 19, 2012	Patented; available for licensing or partnering	Ridges, S. <i>et al. Blood</i> ; published online April 9, 2012; doi:10.1182/blood-2011-12-398818 Contact: Nikolaus S. Trede, The University of Utah, Salt Lake City, Utah e-mail: nikolaus.trede@hci.utah.edu
Breast cancer	NF- κ B	<i>In vitro</i> and mouse studies suggest dithiolethiones could help treat estrogen receptor (ER)-negative breast cancers. Dithiolethiones are known to inhibit NF- κ B activity by an unknown mechanism. In human ER-negative breast cancer cells, dithiolethiones inhibited NF- κ B-mediated transcription of tumor progression- and metastasis-promoting genes by directly blocking NF- κ B-DNA binding. In a xenograft mouse model of ER-negative human breast cancer, intraperitoneal injection of a dithiolethione decreased tumor growth compared with injection of vehicle control. Next steps include increasing the <i>in vivo</i> stability of the compounds. At least five companies have NF- κ B inhibitors in clinical and preclinical testing for various indications. SciBX 5(16); doi:10.1038/scibx.2012.410 Published online April 19, 2012	Patented; available for licensing	Switzer, C.H. <i>et al. Cancer Res.</i> ; published online March 21, 2012; doi:10.1158/0008-5472.CAN-11-3115 Contact: David A. Wink, National Institutes of Health, Bethesda, Md. e-mail: david.wink@nih.gov
Cancer	APEX nuclease multifunctional DNA repair enzyme 1 (APEX1)	<i>In vitro</i> studies identified APEX1 inhibitors that could help prevent resistance to chemotherapeutics. <i>In vitro</i> , a compound identified in a high throughput screen and related analogs inhibited APEX1 at low micromolar concentrations. In HeLa cells, the inhibitors improved the cytotoxic activity of the generic DNA-alkylating chemotherapeutics methyl methanesulfonate and temozolomide. Next steps include testing the effects of the compounds in combination with additional chemotherapeutics in different cancer indications. SciBX 5(16); doi:10.1038/scibx.2012.411 Published online April 19, 2012	Patent applications filed; available for licensing	Rai, G. <i>et al. J. Med. Chem.</i> ; published online March 28, 2012; doi:10.1021/jm201537d Contact: David J. Maloney, National Institutes of Health, Bethesda, Md. e-mail: maloneyd@mail.nih.gov Contact: David M. Wilson III, same affiliation as above e-mail: wilsonda@mail.nih.gov

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	IL-2; IL-2 receptor α -chain (IL2-RA; CD25); IL-2 receptor β -chain (IL2-RB; CD122)	<i>Ex vivo</i> and mouse studies suggest an engineered IL-2 superkine, called super-2, could be used as an immunotherapy to help treat cancer. <i>In vitro</i> evolution was used to generate a mutant IL-2 that binds more strongly than the parent molecule to CD122. In human T cells, the superkine induced T cell proliferation regardless of T cell CD25 expression, whereas wild-type IL-2 induced proliferation of only CD25-expressing T cells. In four mouse tumor models, the superkine increased cytotoxic T cell expansion and decreased tumor growth and pulmonary edema compared with wild-type IL-2. Next steps include preclinical development (see A super kind of cytokine, page 1).	Patent application filed; licensed to Teva Pharmaceutical Industries Ltd.	Levin, A.M. <i>et al. Nature</i> ; published online March 25, 2012; doi:10.1038/nature10975 Contact: K. Christopher Garcia, Stanford University School of Medicine, Stanford, Calif. e-mail: kcgarcia@stanford.edu Contact: Onur Boyman, University of Zurich, Zurich, Switzerland e-mail: onur.boyman@uzh.ch
		SciBX 5(16); doi:10.1038/scibx.2012.412 Published online April 19, 2012		
Prostate cancer	6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4)	Cell culture and mouse studies suggest inhibiting PFKFB4 could help treat prostate cancer. In a panel of prostate cancer cell lines, small interfering RNA targeting PFKFB4 decreased cell viability compared with control siRNA. In a xenograft mouse model of prostate cancer, small hairpin RNA targeting PFKFB4 lowered tumor growth compared with control shRNA. Next steps include identifying markers of sensitivity to PFKFB4 inhibition.	Unpatented; licensing status not applicable	Ros, S. <i>et al. Cancer Discov.</i> ; published online March 22, 2012; doi:10.1158/2159-8290.CD-11-0234 Contact: Almut Schulze, London Research Institute, Cancer Research UK, London, U.K. e-mail: almut.schulze@cancer.org.uk
		SciBX 5(16); doi:10.1038/scibx.2012.413 Published online April 19, 2012		
Cardiovascular disease				
Cardiovascular disease	Purinergic receptor P2Y G protein-coupled 12 (P2RY12; P2Y12)	A study in rats suggests vicagrel may help prevent blood clotting in Plavix-resistant patients. People carrying specific polymorphisms in cytochrome P450 2C19 (CYP2C19) do not metabolize Plavix clopidogrel effectively. In rats, vicagrel, an ester prodrug of a clopidogrel intermediate that does not require CYP2C19 activation, decreased ADP-induced platelet aggregation more potently than Plavix and with potency similar to that of Effient prasugrel. Next steps include additional preclinical testing of vicagrel in preparation for filing an IND in China. Sanofi and Bristol-Myers Squibb Co. market the P2Y12 antagonist Plavix clopidogrel for a variety of cardiovascular indications. Daiichi Sankyo Co. Ltd. and Eli Lilly and Co. market the P2Y12 antagonist Effient for acute coronary syndrome.	Patent applications filed; available for licensing	Shan, J. <i>et al. J. Med. Chem.</i> ; published online March 19, 2012; doi:10.1021/jm300038c Contact: Hongbin Sun, China Pharmaceutical University, Nanjing, China e-mail: hbsun2000@yahoo.com
		SciBX 5(16); doi:10.1038/scibx.2012.414 Published online April 19, 2012		
Cardiovascular disease	Atrial natriuretic peptide (ANP); corin serine peptidase (CORIN)	Patient sample and mouse studies suggest upregulating CORIN or activating ANP could help treat preeclampsia, a condition characterized by hypertension and proteinuria during pregnancy. CORIN is a cardiac protease that activates ANP and helps regulate blood pressure. In uterine samples from humans and mice that were healthy and pregnant, CORIN expression was greater than that in nonpregnant, healthy controls. In pregnant mice lacking Corin or Anp, blood pressure and proteinuria were higher than those in wild-type controls. Next steps include experiments to understand why CORIN is upregulated during pregnancy.	Unpatented; licensing status not applicable	Cui, Y. <i>et al. Nature</i> ; published online March 21, 2012; doi:10.1038/nature10897 Contact: Qingyu Wu, Cleveland Clinic, Cleveland, Ohio e-mail: wuq@ccf.org
		SciBX 5(16); doi:10.1038/scibx.2012.415 Published online April 19, 2012		

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Obesity	Nuclear receptor subfamily 1 group D member 1 (NR1D1; Rev-ERBA α); NR1D2 (Rev-ERBA β)	<p>Mouse studies suggest dual NR1D1 and NR1D2 agonists could help treat obesity. In the first two studies, genomic analyses of normal mouse livers showed that Nr1d1 and Nr1d2 bind many of the same target genes, including those regulating lipid metabolism and circadian rhythms. In these studies, <i>Nr1d1</i> and <i>Nr1d2</i> double-knockout mice had higher plasma levels of glucose and triglycerides and/or greater hepatosteatosis than single-knockout and wild-type mice. In the third study, mouse models of obesity showed that dual NR1D1 and NR1D2 agonists decreased fat mass and plasma levels of glucose, triglycerides and cholesterol compared with vehicle. Ongoing work at Scripps Florida includes testing the dual NR1D1 and NR1D2 agonists in mouse models of atherosclerosis and testing the agonists' effects on the sleeping patterns of normal mice.</p> <p>SciBX 5(16); doi:10.1038/scibx.2012.416 Published online April 19, 2012</p>	<p>Patent and licensing status for findings in first two studies unavailable</p> <p>Findings in third study patented by The Scripps Research Institute; licensing status undisclosed</p>	<p>Bugge, A. <i>et al. Genes Dev.</i>; published online April 1, 2012; doi:10.1101/gad.186858.112 Contact: Mitchell A. Lazar, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: lazar@mail.med.upenn.edu</p> <p>Cho, H. <i>et al. Nature</i>; published online March 29, 2012; doi:10.1038/nature11048 Contact: Ronald M. Evans, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: evans@salk.edu</p> <p>Solt, L.A. <i>et al. Nature</i>; published online March 29, 2012; doi:10.1038/nature11030 Contact: Thomas P. Burris, Scripps Florida, Jupiter, Fla. e-mail: tburris@scripps.edu</p>
Infectious disease				
HCV	HCV envelope glycoproteins	<p><i>In vitro</i> and mouse studies have identified mAbs binding to HCV envelope glycoproteins that could help treat or prevent infection. <i>In vitro</i> screening identified 73 mAbs that bound to 5 distinct clusters of HCV envelope epitopes. In a mouse model of HCV infection, two mAbs against two distinct epitopes given before viral challenge decreased infectivity of HCV genotypes 1 and 2 compared with control antibody. Next steps include conducting additional preclinical studies of these antibodies and using their binding epitopes to aid the design of HCV vaccines.</p> <p>Nabi Biopharmaceuticals' Civacir, a polyclonal antibody against HCV, is in Phase II trials to treat HCV infection.</p> <p>Massachusetts Biologic Laboratories has an HCV-neutralizing antibody against HCV E2 in Phase I/II testing to treat HCV infection.</p> <p>SciBX 5(16); doi:10.1038/scibx.2012.417 Published online April 19, 2012</p>	Patent application filed; available for licensing	<p>Gianga, E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 4, 2012; doi:10.1073/pnas.1114927109 Contact: Mansun Law, The Scripps Research Institute, La Jolla, Calif. e-mail: mlaw@scripps.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
HCV	HCV protease	<p>Rat and <i>in vitro</i> studies have identified macrocyclic urea-based HCV protease inhibitors that could help treat HCV infection. In HCV replicon assays, the compounds inhibited HCV replication with better potency than marketed and clinical-stage inhibitors. In rats, oral dosing of a lead inhibitor resulted in higher concentrations of the compound in the liver than oral dosing of two clinical-stage inhibitors. Researchers did not disclose next steps, which could include testing the lead inhibitor in animal models of HCV infection.</p> <p>GlaxoSmithKline plc did not disclose the status of the compounds, which were developed in collaboration with Anacor Pharmaceuticals Inc.</p> <p>Victrelis boceprevir, a small molecule HCV NS3/4A protease complex inhibitor from Merck & Co. Inc., is approved to treat HCV infection.</p> <p>Incivek telaprevir, a small molecule HCV NS3/4A protease complex inhibitor from Vertex Pharmaceuticals Inc., Johnson & Johnson and Mitsubishi Tanabe Pharma Corp., is marketed to treat HCV infection.</p> <p>At least 10 other companies have HCV protease inhibitors in Phase III trials or earlier development to treat HCV infection.</p> <p>SciBX 5(16); doi:10.1038/scibx.2012.418 Published online April 19, 2012</p>	Patented; available for licensing	<p>Kazmierski, W.M. <i>et al. J. Med. Chem.</i>; published online April 3, 2012; doi:10.1021/jm201278q Contact: Wieslaw M. Kazmierski, GlaxoSmithKline plc, Research Triangle Park, N.C. e-mail: wieslaw.m.kazmierski@gsk.com Contact: Maosheng Duan, same affiliation as above e-mail: duanmaosheng@hdbiosciences.com</p>
Influenza virus	Viral polymerase	<p><i>In vitro</i> studies have identified a small molecule inhibitor of influenza viral polymerase that could help treat influenza A and B infections. <i>In silico</i> screening identified six compounds that could disrupt interactions between influenza RNA polymerase subunits in a dose-dependent manner. In a panel of influenza A and B strains, a lead compound inhibited viral replication with IC₅₀ values below 25 nM and did not inhibit the replication of unrelated viruses. Next steps include designing, synthesizing and testing analogs of the most active compound to find more potent derivatives.</p> <p>Toyama Chemical Co. Ltd.'s favipiravir (T-705), a viral polymerase inhibitor, is in Phase III testing to treat seasonal influenza virus.</p> <p>Savira Pharmaceuticals GmbH has influenza viral polymerase inhibitors in preclinical development.</p> <p>SciBX 5(16); doi:10.1038/scibx.2012.419 Published online April 19, 2012</p>	Patent application filed; available for partnering	<p>Muratore, G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 2, 2012; doi:10.1073/pnas.1119817109 Contact: Arianna Loregian, University of Padua, Padua, Italy e-mail: arianna.loregian@unipd.it Contact: Giorgio Palu, same affiliation as above e-mail: giorgio.palu@unipd.it Contact: Gabriele Cruciani, University of Perugia, Perugia, Italy e-mail: gabri@chemiome.chm.unipg.it</p>
Trypanosome	Not applicable	<p><i>In vitro</i> studies suggest terpenes from copaiba oils could help treat Chagas disease, which is caused by the <i>Trypanosoma cruzi</i> parasite. <i>In vitro</i>, various terpenes extracted from <i>Copaifera</i> tree oleoresin killed <i>T. cruzi</i> at different stages of its life cycle. Also <i>in vitro</i>, the terpenes serpene 3-hydroxycopalic acid and sesquiterpene β-caryophyllene acted synergistically to kill the parasite. Next steps could include testing the combination in animal models.</p> <p>SciBX 5(16); doi:10.1038/scibx.2012.420 Published online April 19, 2012</p>	Patent and licensing status unavailable	<p>Izumi, E. <i>et al. J. Med. Chem.</i>; published online March 22, 2012; doi:10.1021/jm201451h Contact: Celso Vataru Nakamura, State University of Maringá, Maringá, Brazil e-mail: cvnakamura@uem.br</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	β -Amyloid ($A\beta$)	Studies in mice suggest monomeric proanthocyanidin metabolites could help treat AD. In a mouse model of AD, dietary supplementation with monomeric and polymeric proanthocyanidin metabolites increased cognitive performance compared with no treatment. In the mouse model, the monomeric metabolites decreased $A\beta$ oligomer levels in the brain compared with no treatment, whereas polymeric metabolites had no effect. Next steps include testing the efficacy of the monomeric metabolites when delivered via different routes. SciBX 5(16); doi:10.1038/scibx.2012.421 Published online April 19, 2012	Patent and licensing status undisclosed	Wang, J. <i>et al. J. Neurosci.</i> ; published online April 11, 2012; doi:10.1523/JNEUROSCI.6437-11.2012 Contact: Giulio M. Pasinetti, Mount Sinai School of Medicine, New York, N.Y. e-mail: giulio.pasinetti@mssm.edu
Alzheimer's disease (AD)	β -Site APP-cleaving enzyme 1 (BACE1)	Cell culture studies suggest spiropyrolidine-based compounds could help treat AD. <i>In vitro</i> , optimized spiropyrolidine derivatives inhibited the AD target BACE1 with micromolar IC_{50} values and showed properties associated with good brain penetration. Researchers did not disclose next steps, which could include testing the lead BACE1 inhibitors in animal models of AD. Pfizer Inc. did not disclose the status of its lead BACE1 inhibitor. At least five other companies have BACE1 inhibitors in preclinical or Phase I testing for AD. SciBX 5(16); doi:10.1038/scibx.2012.422 Published online April 19, 2012	Patent and licensing status undisclosed	Efremov, I.V. <i>et al. J. Med. Chem.</i> ; published online April 2, 2012; doi:10.1021/jm201715d Contact: Felix F. Vajdos, Pfizer Worldwide Research, Groton, Conn. e-mail: felix.vajdos@pfizer.com Contact: Ivan V. Efremov, same affiliation as above e-mail: ivan.efremov@pfizer.com
Alzheimer's disease (AD)	Insulin receptor substrate 1 (IRS1)	<i>In vitro</i> , mouse and nonhuman primate studies suggest improving insulin sensitivity could help treat AD. In neurons from AD patients without diabetes, insulin signaling pathways, including the IRS1 pathway, showed less insulin responsiveness than those in neurons from controls without cognitive impairment. In samples from patients with AD or mild cognitive impairment, levels of serine-phosphorylated IRS1, which is involved in insulin insensitivity, were greater than those in samples from controls without cognitive impairment. In cynomolgus monkeys, intracerebroventricular delivery of β -amyloid ($A\beta$) oligomers increased neuronal IRS1 levels compared with those seen in sham-operated controls. In a mouse model of AD, insulin plus the insulin sensitizer Byetta exenatide prevented IRS1 phosphorylation in neurons and increased memory retention and decreased $A\beta$ plaque size compared with saline. Next steps include determining whether insulin resistance could help diagnose the early stages of AD. Byetta, a synthetic exendin-4 from Amylin Pharmaceuticals Inc. and Eli Lilly and Co., is marketed to treat type 2 diabetes. SciBX 5(16); doi:10.1038/scibx.2012.423 Published online April 19, 2012	Findings from first study unpatented; unlicensed Findings from second study unpatented; unavailable for licensing	Talbot, K. <i>et al. J. Clin. Invest.</i> ; published online March 26, 2012; doi:10.1172/JCI59903 Contact: Konrad Talbot, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: talbotk2@mail.med.upenn.edu Bomfim, T.R. <i>et al. J. Clin. Invest.</i> ; published online March 26, 2012; doi:10.1172/JCI57256 Contact: Fernanda G. De Felice, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil e-mail: felice@bioqmed.ufrj.br

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Anxiety; depression	Histone deacetylase 6 (HDAC6)	Mouse studies suggest inhibiting HDAC6 could help treat stress-related neurological disorders. In a mouse model of social defeat, Hdac6 expression in serotonin (5-HT) neurons was lower in stress-resistant mice than vulnerable mice. In this model, deletion of Hdac6 in 5-HT receptor-expressing neurons decreased social avoidance compared with wild-type Hdac6 expression and prevented neuron hypertrophy. Next steps include collaborating with Acetylon Pharmaceuticals Inc. to test brain-penetrant HDAC6 inhibitors in animal models. ACY-1215, an HDAC6 inhibitor from Acetylon, is in Phase I/II testing to treat multiple myeloma.	Patent and licensing status undisclosed	Espallergues, J. <i>et al. J. Neurosci.</i> ; published online March 28, 2012; doi:10.1523/JNEUROSCI.5634-11.2012 Contact: Olivier Berton, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: bertonol@upenn.edu
		SciBX 5(16); doi:10.1038/scibx.2012.424 Published online April 19, 2012		
Autism	<i>Moesin pseudogene 1 antisense (MSNPIAS)</i>	Studies in human tissue and in cell culture suggest antagonizing <i>MSNPIAS</i> expression could help treat autism. Previous genome-wide association studies had identified a chromosomal region containing the noncoding <i>moesin pseudogene 1 (MSNPI)</i> as an autism risk factor. In postmortem brain samples from patients with autism, levels of <i>MSNPIAS</i> , a newly identified antisense transcript encoded at the <i>MSNPI</i> locus, were higher than those in healthy controls. In cell culture, <i>MSNPIAS</i> overexpression decreased levels of moesin, a protein involved in synaptic structure, compared with normal <i>MSNPIAS</i> expression. Next steps include testing the effect of <i>MSNPIAS</i> in mouse models of autism.	Unpatented; licensing status not applicable	Kerin, T. <i>et al. Sci. Transl. Med.</i> ; published online April 4, 2012; doi:10.1126/scitranslmed.3003479 Contact: Daniel B. Campbell, University of Southern California, Los Angeles, Calif. e-mail: dbcampbe@usc.edu
		SciBX 5(16); doi:10.1038/scibx.2012.425 Published online April 19, 2012		
Pain	Opioid receptor $\delta 1$ (OPRD1; DOR)	Mouse studies suggest DOR agonists that also promote DOR recycling could help treat pain without causing opioid addiction and tolerance. In a mouse model of neuropathic pain, a DOR agonist that did not promote receptor recycling decreased pain sensitivity compared with vehicle but also induced an acute opioid tolerance response. In the same model, a DOR agonist that promoted receptor recycling lowered pain sensitivity compared with vehicle but did not cause an acute tolerance response. Next steps include screening for drug-like DOR agonists that promote receptor recycling. Cubist Pharmaceuticals Inc. has the DOR agonist ADL5747 in Phase II testing for pain.	Patent status undisclosed; available for partnering and collaborations	Audet, N. <i>et al. J. Neurosci.</i> ; published online April 4, 2012; doi:10.1523/JNEUROSCI.3734-11.2012 Contact: Graciela Pineyro, Sainte-Justine University Hospital Center Research Center, Montreal, Quebec, Canada e-mail: graciela.pineyro.filpo@umontreal.ca
		SciBX 5(16); doi:10.1038/scibx.2012.426 Published online April 19, 2012		
Ophthalmic disease				
Glaucoma	Glycosylation dependent cell adhesion molecule 1 (GLYCAM1)	Mouse studies suggest localized X-ray radiation could help prevent glaucoma by blocking neuroinflammation. In a mouse model of glaucoma, locally administered X-ray radiation prevented the development of glaucoma ($p=1.8 \times 10^{-32}$). In the model, radiation treatment increased Glycam1 expression and decreased monocyte infiltration into the retina compared with no treatment. Next steps include testing nonradiation methods to block monocyte infiltration into the retina.	Patent application filed; available for licensing	Howell, G.R. <i>et al. J. Clin. Invest.</i> ; published online March 19, 2012; doi:10.1172/JCI61135 Contact: Simon W.M. John, The Jackson Laboratory, Bar Harbor, Maine e-mail: simon.john@jax.org
		SciBX 5(16); doi:10.1038/scibx.2012.427 Published online April 19, 2012		

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			
RNA-based molecular diagnostic of infectious diseases	Real-time RNA expression profiling of pathogens could provide a rapid diagnostic of infectious diseases. In cell culture, oligonucleotide probes targeting mRNA molecules unique to three different Gram-negative bacteria and <i>Mycobacterium tuberculosis</i> detected the pathogens in pure samples and in complex mixtures. Also in cell culture, the probes detected mRNA expression profiles that distinguished antibiotic-sensitive and antibiotic-resistant bacterial strains. In urine samples from patients testing positive for urinary tract infections, the mRNA probes identified <i>Escherichia coli</i> strains that were responsive to the generic antibiotic ciprofloxacin. Next steps include generating a large library of mRNA expression signatures that differentiate a range of drug-sensitive and drug-resistant bacterial pathogens (see RNA profiling pathogens , page 8).	Patented; available for licensing from the Broad Institute of MIT and Harvard	Barczak, A.K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 2, 2012; doi:10.1073/pnas.1119540109 Contact: Deborah T. Hung, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: hung@molbio.mgh.harvard.edu
Drug platforms			
RNA-based inhibitors of endogenous antisense transcripts for locus-specific gene upregulation	Mouse and cell culture studies have shown that knockdown of endogenous antisense transcripts could enable targeted upregulation of specific gene loci. In cultured human and mouse cell lines, small interfering RNA against an antisense transcript that targets <i>brain-derived neurotrophic factor (BDNF)</i> led to upregulation of <i>BDNF</i> . In mice, intracerebroventricular delivery of an oligonucleotide antagonist of the <i>Bdnf</i> antisense transcript led to greater <i>Bdnf</i> expression, neuronal survival and neuronal proliferation than delivery of control oligonucleotide. Next steps include testing this approach in mouse models of disease. RaNA Therapeutics Inc. has oligonucleotide inhibitors of long noncoding RNA in preclinical development to induce locus-specific gene expression.	Patented; licensed to Curna Inc., which was acquired by Opko Health Inc.; available for partnering	Modarresi, F. <i>et al. Nat. Biotechnol.</i> ; published online March 25, 2012; doi:10.1038/nbt.2158 Contact: Claes Wahlestedt, University of Miami Miller School of Medicine, Miami, Fla. e-mail: cwahlestedt@med.miami.edu
Imaging			
MRI contrast agent targeting vascular cell adhesion molecule-1 (VCAM-1) for detection of early brain metastases	VCAM-1-targeting MRI contrast agents could help detect early brain metastases and enable early therapeutic intervention. In two mouse models of brain metastasis and in human postmortem brain tissue containing metastatic lesions, VCAM-1 was upregulated on tumor-associated blood vessels but not on normal blood vessels. In the two mouse models of brain metastasis, i.v. injection of VCAM-1-targeting microparticles of iron oxide resulted in more sensitive MRI visualization of metastases, including tumors of <1,000 cells, compared with injection of a clinically used gadolinium-based MRI contrast agent. Ongoing work includes developing a form of the agent for human use and establishing a spinout company for clinical translation of the imaging agents.	Unpatented; licensing status not applicable	Serres, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 26, 2012; doi:10.1073/pnas.1117412109 Contact: Nicola R. Sibson, University of Oxford, Oxford, U.K. e-mail: nicola.sibson@oncology.ox.ac.uk

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