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By Michael J. Haas, Senior Writer

In recent years, noninvasive techniques for imaging the response of tumors to therapy have moved upstream from diagnostic to drug development settings. However, commonly used techniques like MRI provide only structural information, such as tumor volume, which is not always an accurate readout of a compound's efficacy. Functional imaging techniques like fluorodeoxyglucose PET provide a more accurate readout of tumor response by tracking biochemical processes on or within tumor cells. But functional imaging agents are expensive to produce, which limits their use.

Researchers at **Vanderbilt University** and **Vanderbilt-Ingram Cancer Center** have identified a functional imaging agent that is easier to produce than existing agents and just as effective at monitoring the response of tumors to therapy, as reported in *Nature Medicine*. The research team described a seven-residue peptide biomarker that differentiated between tumors that did and did not respond to treatment with a VEGF tyrosine kinase inhibitor (TKI).¹

"We have not found a single VEGF TKI-responding cancer type that did not bind this peptide," said team leader Dennis Hallahan, professor of cancer research and chairman of radiation oncology at the university. "We studied cancer originating in the brain, lung, colon, skin, breast and prostate. The peptide was able to detect a response in each of these cancers," he told *SciBX*.

Using a phage display library owned by **The Scripps Research Institute**, Hallahan's team identified the peptide by screening for candidates that bound the vasculature of tumors responsive to VEGF tyrosine kinase inhibition. The peptide is known only by its sequence, HVGGSSV.

In mice with tumors, fluorescence images showed that fluorophore reporter-tagged HVGGSSV specifically bound to tumors responding to treatment with radiation and Sutent sunitinib, an inhibitor of multiple receptor tyrosine kinases. Sutent is marketed by **Pfizer Inc.** for renal cell carcinoma (RCC) and gastrointestinal stromal tumors.

The images were taken 24 hours after each injection of HVGGSSV.

Hallahan's team obtained similar results using three other VEGF TKIs: semaxanib, also from Pfizer, and PTK787 and AEE788, both from **Novartis AG**. Taken together, the results for all four compounds suggested that peptide binding was specific to the action of VEGF TKIs, not one particular compound.

In 2002 Pfizer terminated development of semaxanib, a small-molecule inhibitor of the VEGF receptor kinase insertion domain receptor, after it failed in a Phase II trial in advanced colorectal cancer.²



Science-Business eXchange

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SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Richard Hartgill, Chief Financial Officer, NPG.

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According to clinicaltrials.gov, Novartis has PTK787 in a Phase I trial in wet age-related macular degeneration and has AEE788 in two trials: a Phase I study in advanced cancer and a Phase I/II study in combination with the company's Certican everolimus mammalian target of rapamycin inhibitor (mTOR inhibitor) in recurrent or relapsed glioblastoma multiforme.

Histological analyses by the Vanderbilt team showed the peptide bound to the microvascular endothelia of tumors, leading the researchers to hypothesize in their paper that HVGSSV binds to a protein "that is unveiled during endothelial response to therapy" with TKIs.

"We are currently proving the hypothesis that this peptide binds to an endothelial surface receptor," Hallahan told *SciBX*. He declined to discuss the results of that experiment.

In the paper, Hallahan's team said HVGSSV is more easily synthesized than Annexin V (AnxV), a 319-amino-acid protein that binds to phosphatidylserine—which is highly expressed on the surface of cells undergoing apoptosis. AnxV has been used experimentally for the last 15 years to image how tumors respond to therapies.^{3,4}

The Vanderbilt researchers also said HVGSSV has faster clearance from the circulation than AnxV, which allows for more rapid imaging of tissues and organs. Hallahan told *SciBX* that HVGSSV clears quickly enough to allow imaging in about 24 hours.

However, Chris Reutelingsperger, associate professor of biochemistry at the **University Maastricht's** Cardiovascular Research Institute Maastricht, said the research team's statement about AnxV clearance "is rather subjective."

He pointed to a 2003 paper by Gerrit Kemerink and colleagues at **University Hospital Maastricht, University Hospital Gasthuisberg, the University of Leuven** and Theseus Imaging Corp., a subsidiary of **North American Scientific Inc.**, which showed, "The clearance from the circulation occurs with a half-life of about 24 minutes."⁵

Hallahan said the major obstacle to the use of AnxV is its synthesis. "The problem with GMP production of large proteins like Annexin V is that they are produced by cells in culture," he said. "In contrast, small peptides like HVGSSV can be synthesized [using] solid-state engineering," which should reduce production costs.

Picturing applications

Companies and institutions contacted by *SciBX* had mixed opinions on whether HVGSSV will have greater utility in clinical or preclinical research. However, the consensus is that the specific properties of the peptide require further study.

David Chang, VP of oncology therapeutics clinical development at **Amgen Inc.**, said the *Nature Medicine* paper described a "very preliminary but a very interesting finding. There is a lot of interest in this kind of imaging, but additional details need to be worked out—for instance, the specificity of the peptide to different cancer treatments and in other cancers."

He noted that the researchers have not yet demonstrated whether the peptide targets endothelial or tumor cells. "Having an agent that targets endothelial cells—regardless of tumor type—could have broad utility. But if the peptide is shown to target tumor cells, then its utility might be limited."

Chang also expressed reservations about the use of functional imaging agents like AnxV and HVGSSV in clinical and diagnostic settings.

“Ultimately techniques like this are interesting because it would be helpful to know whether a patient is responding to angiogenic agents—which requires that the patient be exposed to treatment,” he said. “But this approach is not as ideal as predicting whether a tumor will respond to treatment before exposing the patient to a drug.”

Nevertheless, he said the findings of Hal-lahan’s team “are the types of discoveries that Amgen would pay attention to” for potential use in its preclinical programs.

Amgen has two antiangiogenic compounds in clinical development. AMG 706, a VEGF receptor inhibitor, is in a Phase III trial for non-small cell lung cancer (NSCLC). AMG 386, a recombinant Fc peptide fusion protein targeting tyrosine kinase receptor 2 (Tie2), is in multiple Phase II trials for renal, ovarian, gastric and breast cancer tumors.

“Preclinical development of novel anticancer agents will benefit from such molecular imaging probes both by speeding up the process of development and increasing the probability of clinical success of experimental drugs,” said Reutelingsperger.

He said HVGGSV’s use would likely be limited to compounds that induce the expression or exposure of the peptide’s unknown target during treatment.

Binh Nguyen, CMO and VP of clinical development at **Tigris Pharmaceuticals Inc.**, said HVGGSV “would be a very useful technology for early preclinical research. If a company has a series of analogs of an anti-VEGF compound, it could screen that series with this technology to see which compounds are the most promising and most potent.”

Nguyen added: “It would be important to know the exact function of this HVGGSV peptide on the endothelial membrane proteins.”

Tigris has GFB-204, a calixarene-derived VEGF receptor inhibitor, in preclinical development to treat solid tumors.

Clive Wood, EVP of discovery research and CSO at **Dyax Corp.**, said it was “impressive” that a seven-residue peptide could achieve such a specific readout so quickly.

“It’s unusual to use this kind of imaging in preclinical work,” he said. “More effective and validated imaging endpoints could change the course of preclinical studies: experiments that now take weeks or months to give feedback could take as little as two or three days.”

He would like to see the peptide tested with other classes of anti-cancer drugs, “just to see what happens—in Avastin, for instance,” he said. “It would be very interesting to know what other drugs can work with this peptide.”

Wood also said the peptide could help determine how best to introduce a drug candidate into established anticancer regimens before entering clinical trials.

“You only get a few chances to get this right,” he said. “Imaging drug combinations in a preclinical setting could better predict effective combinations in a clinical setting, increasing the likelihood of success in development.”

As an example, Wood cited Dyax’s DX-2240, a human mAb that targets tyrosine kinase receptor 1 (Tie1) on tumor neovasculature. On its own, he said, the antibody has “modest to strong activity” in some

preclinical models, but in specific combination dosing regimens, DX-2240 increases the antitumor activity of other cancer therapies such as Avastin and Nexavar.

Last month, Dyax granted **sanofi-aventis Group** exclusive worldwide rights to develop and commercialize DX-2240. The compound is in preclinical development to treat cancer.⁶

Genentech Inc. markets Avastin bevacizumab, a humanized mAb against VEGF, in the U.S. for breast, non-small cell lung, colorectal and renal cancers. **Roche** markets the drug elsewhere.

Nexavar sorafenib, from **Onyx Pharmaceuticals Inc.** and **Bayer AG**, is an inhibitor of multiple kinases, including VEGF receptors. It is approved in the U.S. and EU for the treatment

of both hepatocellular carcinoma and RCC.

Conversely, Dana Aftab, VP of translational research at **Exelixis Inc.**, said the preclinical utility of the peptide would be limited if it can only detect tumor response to VEGF kinase inhibitors.

“I don’t know of any companies that are still actively focused on the discovery and preclinical characterization of new compounds that target VEGF receptors for antiangiogenesis,” Aftab said. “In general, the majority of these compounds have already moved into the clinic. So many companies, including Exelixis, are now focused on developing drugs that target enzymes or pathways that are more directly involved in the proliferation and survival machinery within tumor cells, such as MET, RAF, MEK, PI3K and others.”

“More effective and validated imaging endpoints could change the course of preclinical studies: experiments that now take weeks or months to give feedback could take as little as two or three days.”

—Clive Wood, Dyax Corp.

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Aftab agreed with others that the peptide's utility may also depend on whether it binds a target on endothelial or tumor cells.

"If the peptide binds an endothelium-specific protein, then it may only be applicable to treatments that directly impact the tumor vasculature," he said. "If the peptide is recognizing a nonendothelial stromal or basement membrane component, or a tumor cell component resulting from cell death, it may be applicable to most tumors because these components are fairly well conserved."

Likewise, he said the peptide might have less utility if it bound a protein specific to only certain tumor cells. He doubted this was the case, but said it was unclear from the paper's supplemental data whether the peptide was detecting an endothelial protein or a tumor cell protein.

Aftab also was interested in seeing data obtained in a wider range of animal models. "In the paper, the peptide seemed to give the best response in the Lewis lung carcinoma mouse model, but this model is not derived from a human cancer," he said. "The researchers used a few human cancer models; these seemed to respond but not as robustly."

Data from a larger array of human tumor xenografts and genetic mouse models, and from a wider variety of therapeutic agents, would give a better picture of the specificity of the peptide, Aftab said.

"A fuller set of data would help to determine how broadly applicable the peptide is," he noted. "And those data would need to be characterized very carefully so that researchers could determine whether the peptide would work in their preferred models."

Aftab added: "I would need this kind of information before I could think about using the peptide preclinically."

Aftab said the peptide showed the most promise for clinical applications. "It would be a real benefit to have an imaging technique that could show a treatment effect after one or two weeks—instead of having to use traditional criteria that require generally two or more months of treatment," he said.

Exelixis has several anticancer drugs in clinical trials. The company's lead compound, XL647, which targets VEGF receptor, epidermal growth factor receptor (EGF receptor) and EGF receptor 2 (HER2), will enter Phase III trials for NSCLC this year.

XL184, which targets MET, RET and VEGF receptor, is in Phase I for medullary thyroid cancer and Phase I/II for lung cancer. The company will take XL184 into a pivotal study in medullary thyroid cancer later

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—Dana Aftab, *Exelixis Inc.*

this year and into a Phase II trial in glioblastoma in 2H08.

Hallahan said the team plans to take HVGGSSV into clinical trials but has not set a date to begin a Phase I study.

In the meantime, the team is experimenting with three radioisotopes of iodine, any of which could replace the fluorophore tag as a reporter on HVGGSSV. These radioiodine reporters are conjugated to the peptide by three tyrosine residues, an addition that Hallahan said does not affect the pharmacokinetic profile of the peptide.

He said the team is interested in using ¹³¹I for the clinical trials because it would deliver radiation to the tumor while imaging it.

Hallahan said that Vanderbilt University has applied for a provisional patent on the findings reported in *Nature Medicine* and is negotiating the licensing of development rights with **Cumberland Pharmaceuticals Inc.**

REFERENCES

1. Han, Z., *et al. Nat. Med.*; published online Feb. 24, 2008; doi:10.1038/nm1691
Contact: Dennis E. Hallahan, Vanderbilt University, Nashville, Tenn.
e-mail: dennis.hallahan@vanderbilt.edu
2. Maggos, C. *BioCentury* **13**(8) A8; Feb. 14 2005
3. Boersma, H. *et al. J. Nucl. Med.* **46**, 2035–2050 (2005)
4. Corsten, M. *et al. Cancer Res.* **66**, 1255–1260 (2006)
5. Kemerink, G. *et al. J. Nucl. Med.* **44**, 947–952 (2003)
6. Ward, M. *BioCentury* **16**(8) A11; Feb. 18 2008

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Schizophrenia develops a complex

By Tim Fulmer, Staff Writer

The general strategy for discovering compounds with antipsychotic activity has focused on identifying agonists or antagonists of a specific receptor class. This results in compounds that alleviate only a subset of schizophrenia symptoms without avoiding neurological side effects.

Researchers at the **Mount Sinai School of Medicine** have identified a serotonin/glutamate receptor complex in rodent brain that unites two pathways previously targeted individually to treat psychosis and other symptoms of schizophrenia.¹ Designing compounds or combination therapies that modulate the function of the complex rather than that of each receptor separately could be a strategy for generating a new class of antipsychotics.

First-generation typical antipsychotics like the generic haloperidol antagonize dopamine D2 receptors. Second-generation atypical antipsychotics like Zyprexa olanzapine from **Eli Lilly and Co.** antagonize the serotonin receptor (5-HT_{2A} receptor) in addition to showing moderate affinity for dopamine D2 receptors.

The third wave of approved drugs includes Abilify aripiprazole from **Bristol-Myers Squibb Co.** and **Otsuka Pharmaceutical Co. Ltd.** This small molecule is a partial agonist of the dopamine D2 and serotonin receptors and an antagonist of the 5-HT_{2A} receptor.

More recently, companies have been working on compounds that target metabotropic glutamate receptors (mGluRs). Last year saw the first Phase II data for mGluR agonists in schizophrenia. LY2140023, an oral prodrug of Lilly's LY404039 mGluR2/3 agonist, significantly improved schizophrenia symptoms compared with placebo in a Phase II trial in 97 patients ($p < 0.001$).^{2,3}

The mGluR space is clearly attracting the interest of pharma companies, as evidenced by a pair of deals in January. **Addex Pharmaceuticals S.A.** and **Merck & Co. Inc.** partnered to develop and market ADX63365 and other positive allosteric modulators of mGluR5 to treat schizophrenia and other undisclosed indications.⁴ ADX63365 is in preclinical development.

Also, **Pfizer Inc.** and **Taisho Pharmaceutical Co. Ltd.** partnered to develop and commercialize Taisho's TS-032, an mGluR agonist in preclinical testing to treat schizophrenia.

In their *Nature* paper, the Mount Sinai researchers used several methods, including coimmunoprecipitation and fluorescence resonance energy transfer, to show that 5-HT_{2A} and mGluR2 colocalize, interact and form functional complexes in mouse cortical neurons and in the human frontal cortex. Multiple hallucinogenic compounds, a glutamate receptor agonist and an atypical antipsychotic all influenced signaling through the complex.

Moreover, postmortem brain slices from untreated schizophrenia patients had higher 5-HT_{2A} receptor levels and lower mGluR2/3 levels than brain slices from controls with no history of psychiatric disorders.

The team of researchers, led by Javier Gonzalez-Maeso and Stuart Sealton, both professors in the Department of Neurology at Mount Sinai, hypothesized in the paper that “the 5-HT_{2A} receptor–mGluR2 complex integrates serotonin and glutamate signaling to regulate the sensory gating functions of the cortex, a process that is disrupted in psychosis.”

According to the group, the complex “is therefore a promising new target for the treatment of psychosis.”

Indeed, the receptor complex provides a target that could potentially combine the effects of two or more antipsychotics into a single therapeutic agent, Gonzalez-Maeso told *SciBX*.

However, John Krystal, professor of clinical pharmacology at **Yale University School of Medicine**, said the data also “raise the question as to whether mGluR2 agonists provide any benefits in addition to 5-HT_{2A} receptor blockade that is already provided by most antipsychotic medications.”

He added: “If mGluR2 receptor stimulation was simply an indirect way to reduce 5-HT_{2A} receptor function, then it might not produce a more effective new approach to the treatment of schizophrenia.”

Sealton said the group's next steps include investigating how sequence alteration of one or both of the receptors affects the function of the complex, as well as identifying mutations that disrupt or prevent formation of the complex but do not affect individual receptor function.

Generating mGluR2 and 5-HT_{2A} receptor knockout mice or knockin mice that express chimeric receptors also would be useful to gain a better understanding of how the complex functions and affects downstream signaling pathways, Gonzalez-Maeso told *SciBX*.

David Bredt, VP of neuroscience research and clinical development at Eli Lilly, told *SciBX* that

“while this is the first evidence of a direct interaction between these two receptors,” the paper's findings were also consistent with the previous work of the company's scientists that showed behavioral evidence of interactions between hallucinogenic compounds and mGluR2/3 receptors. In mice, mGluR2/3 agonists such as LY354740 or LY379268 blocked the behavioral effects of 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI), a hallucinogenic compound that acts through the 5-HT_{2A} receptor.⁵

Previous work by the Mount Sinai group showed that a specific activation pattern of serotonin receptor pathways in the mouse cortex is necessary for the psychoactive effects of hallucinogenic compounds such as lysergic acid diethylamide (LSD).⁶

Bredt thinks future research could examine whether 5-HT_{2A} or mGluR2 receptors “form complexes with other receptors expressed on the surface of neurons, including other groups of metabotropic glutamate receptors. Future studies would also be useful to determine how the formation of these complexes might vary with progression of schizophrenia.”

Research already suggests that interactions exist between mGluR2 and other glutamate receptors in animal models and humans.^{7,8} Krystal told *SciBX* his research team discovered that LY354740 reduced the disruption of working memory caused by the ionotropic NMDA glutamate receptor antagonist ketamine in healthy volunteers. Deficits in working memory,

(Continues on p. 6)

“At least in some situations, combining antipsychotic compounds could produce a synergistic effect that might treat multiple symptoms of schizophrenia.”

— Vincent Mutel,
Addex Pharmaceuticals S.A.

Uncloaking IL-7

By Matthew Mikulski, Staff Writer

Despite the fact that the cytokine interleukin-7 (IL-7) is known to be involved in autoimmune diseases, no companies are pursuing IL-7 antagonists, and only one company—**Cytheris S.A.**—is using IL-7 itself as a therapeutic to boost patients' immune systems. One reason is that IL-7's specific role in autoimmune disease is unknown. In a paper in the *Proceedings of the National Academy of Sciences*, Canadian researchers have now shown that IL-7 initiates disease in an animal model of type 2 diabetes.¹

The results also suggest that IL-7 could be involved in the pathology of other autoimmune diseases. However, at least one company thinks that such diseases would be better addressed by hitting other autoimmune targets due to potential immunosuppression issues.

The researchers' model of diabetes consisted of a transgenic viral antigen expressed specifically on β -islet cells, which could then serve as a target for T cells that had been primed either *in vivo* or *in vitro* to simulate self-reactivity.

They first found that mice with antigen-primed CD8⁺ T cells alone did not spontaneously develop diabetes, even after a toll-like receptor 9 (TLR9) ligand stimulated an immune response. Similar to previous observations,² the addition of primed CD4⁺ T cells to the CD8⁺ T cells was sufficient for development of diabetes.

Mice with primed CD4⁺ cells alone developed diabetes very infrequently, although treatment with the lymphocyte-depleting agent cyclophosphamide restored diabetes incidence to 100%.

The researchers next sought to identify whether the addition of IL-7 to treatment with primed CD4⁺ T cells was sufficient to stimulate autoimmunity. Overexpression of IL-7 has previously been shown to result

“Our studies strongly support a role for IL-7 in the induction and perhaps maintenance of at least some autoimmune diseases.”

*—Tak W. Mak and colleagues,
The Campbell Family Institute for
Breast Cancer Research*

in severe autoimmune disease, and the protein has been implicated in rheumatoid arthritis (RA) as well as atherosclerosis.

Addition of IL-7 restored diabetes incidence to nearly 100%. Furthermore, an antibody against the IL-7 receptor α -chain protected mice against the increase in diabetes that followed cyclophosphamide-induced lymphopenia. According to the researchers, lymphopenia results in higher levels of IL-7 and other cytokines than is considered normal.

Thus, the researchers from **The Campbell Family Institute for Breast Cancer Research** wrote, “Our studies strongly support a role for IL-7 in the induction and perhaps maintenance of at least some autoimmune diseases.”

The group also suggested “IL-7 and its receptor may be promising targets for biological agents in the treatment of autoimmunity.”

Nevertheless, companies are not pursuing development of IL-7 antagonists. Part of the problem, said Michel Morre, CEO of immunomodulatory therapeutics company Cytheris, is that because IL-7 has a central role in lymphocyte homeostasis, blocking the protein may lead to general immunosuppression. That, he said, would “likely lead to opportunistic infections.”

Morre noted that IL-7 knockout mice exhibit severe immunodeficiency, a phenotype that anti-IL-7 antibodies reproduce.³

Cytheris owns IP covering antibody-based inhibition of IL-7 but has elected instead to develop recombinant IL-7 to boost the immune system. The program is in Phase I/II testing in HIV and HCV and is in Phase I testing for cancer.

Instead of anti-IL-7 therapeutics for autoimmune diseases, Morre thinks a better option would be molecules that preferentially inhibit the activity of autoreactive T cells, such as cytotoxic T lymphocyte antigen 4 (CTLA-4).

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which is a cognitive function, have been reported in some schizophrenia patients, he said.

Vincent Mutel, CEO of Addex, told *SciBX* that the paper “does point out how the various signaling pathways linked to schizophrenia may in fact be closely integrated—which would suggest that, at least in some situations, combining antipsychotic compounds could produce a synergistic effect that might treat multiple symptoms of schizophrenia.”

Nevertheless, he added that the publication will not alter Addex's general strategy of targeting specific receptors associated with schizophrenia.

“There is evidence in animal models that targeting mGluR5 could treat both positive symptoms of schizophrenia like hallucination as well as cognitive impairment,” Mutel said. “This is important because although marketed antipsychotics that act on 5-HT_{2A} reduce hallucination, their ability to treat negative symptoms is much less clear. Thus, it's of the highest priority to develop compounds that treat cognitive deficits associated with schizophrenia.”

REFERENCES

- Gonzalez-Maeso, J. *et al. Nature*; published online Feb. 24, 2008; doi:10.1038/nature06612
Contact: Stuart Sealfon, Mount Sinai School of Medicine, New York, N.Y. e-mail: Stuart.Sealfon@mssm.edu
- Patil, S. *et al. Nat. Med.* **13**, 1102–1107 (2007)
- Mujtaba, U. *BioCentury* **15**(40), A11; Sept. 10, 2007
- Hansen, S. *BioCentury* **16**(2), A26; Jan. 7, 2008
- Gewirtz, J.C. & Marek, G.J. *Neuropsychopharmacology* **23**, 569–576 (2000)
- Gonzalez-Maeso, J. *et al. Neuron* **53**, 439–452 (2007)
- Moghaddam, B. & Adams, B. *Science* **281**, 1349–1352 (1998)
- Krystal, J. *et al. Psychopharmacology* **179**, 303–309 (2005)

COMPANIES AND INSTITUTIONS MENTIONED

- Addex Pharmaceuticals S.A.** (SWX:ADXN), Geneva, Switzerland
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- Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.
- Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.
- Mount Sinai School of Medicine**, New York, N.Y.
- Otsuka Pharmaceutical Co. Ltd.** (Tokyo:4768), Tokyo, Japan
- Pfizer Inc.** (NYSE:PFE), New York, N.Y.
- Taisho Pharmaceutical Co. Ltd.**, Tokyo, Japan
- Yale University School of Medicine**, New Haven, Conn.

Anemia's Gas6 pedal

By Linda A. Goldstein, Senior Writer

A relatively large percentage of anemic patients who receive therapy with erythropoiesis-stimulating agents are either hyporesponsive or resistant to erythropoietin. Researchers at the **University Hospital Center** and **University of Lausanne** may have found a new way of treating these patients' anemia using a protein called growth arrest-specific gene 6, but much work still needs to be done to see if it avoids the problems caused by erythropoiesis-stimulating agents.

Until now, hyporesponsive or resistant patients have typically been treated with higher doses of erythropoiesis-stimulating agents (ESAs), which can raise the risk of mortality and cardiovascular events. Over the past 12 months, an increasing amount of clinical data have shown the problems with this strategy.¹⁻³ As a result, the FDA and the Centers for Medicare and Medicaid Services have moved to limit the use of ESAs.

(Continued from "Uncloaking IL-7," p. 6)

Antibodies against CTLA-4 work by inhibiting the activity of CD28, a co-stimulatory receptor located on the surface of T cells. **Bristol-Myers Squibb Co.**'s Orenia abatacept, a fusion protein containing CTLA-4 and immunoglobulin that functions as a soluble CTLA-4 receptor, is marketed to treat RA.

Bristol-Myers is developing a follow-on product that targets CTLA-4 but uses a slightly different binding sequence. That product, belatacept (BMS-224818), is in Phase III testing to prevent organ transplant rejection.⁴

Although Morre thinks an anti-IL-7 therapy would have an uphill struggle in the clinic, he suggested it might be possible to use such an approach to treat an autoimmune disease that is not manifested systemically, such as ulcerative colitis.

Results published by Japanese researchers a decade ago showed that mice overexpressing IL-7 in the colonic mucosa developed chronic colitis.⁵ Studies published in 2004 and coauthored by some of the same Japanese researchers revealed that IL-7 exacerbates chronic colitis by accelerating the expansion of mucosal CD4⁺ T cells that express high levels of IL-7 receptor.⁶

The key, Morre said, would be delivering blocking antibody or inhibitory peptide specifically to the gastrointestinal tract.

Alan Solinger, VP of clinical immunology at autoimmune and cancer antibody company **Xoma Ltd.**, believes gastrointestinal tract delivery would be one of the more difficult local routes of administration. Instead, he thinks treating autoimmune-related thyroid disease might be feasible.

"If someone has an inflamed thyroid and a doctor believes it to be autoimmune related," a local injection of an anti-IL-7 therapeutic would be possible, he said.

Solinger told *SciBX* that the lack of interest in developing anti-IL-7 therapies is likely due to several factors, including that knockout and antibody data suggest blocking the target is unsafe, it is a poorly under-

Indeed, in 2007, sales of **Amgen Inc.**'s Aranesp darbepoetin alfa fell 12% compared to 2006, including a 23% decline in U.S. sales. U.S. sales of Amgen's Epogen epoetin alpha were down 1%. **Johnson & Johnson's** full-year 2007 earnings showed a 12.3% drop in worldwide sales of its Procrit/Epex epoetin, including an 18.2% slide in the United States.

"People are a little scared to use ESAs, rightly or wrongly, and there's an interest in looking elsewhere to combat anemia," said David Steensma, professor of hematology and oncology at the **Mayo Clinic**.

Enter growth arrest-specific gene 6 (Gas6). The soluble, vitamin K-dependent protein was discovered by an Italian research group in 1993.⁴ Since then, Gas6 has been studied extensively and shown to be important in the proliferation, survival, migration and adhesion of different cell types in diverse organ tissues.

Most recently, Anne Angelillo-Scherrer and colleagues at the University Hospital Center and University of Lausanne published a paper (Continues on p. 8)

stood mechanism of action and there is greater interest in other disease targets.

Solinger noted that mouse and human IL-7 have only about 60% similarity, meaning studies in animal models of autoimmune diseases could easily mislead on safety, efficacy or both in humans.

What is known, he said, is that IL-7 in humans seems to have a greater effect on T cells than it does in mice, where its effects seem to be spread over both T cells and B cells. Until a blocking therapeutic is tested in humans, he continued, "you don't know."

Solinger did suggest that the tissue-specific autoimmune model used by the authors could be adapted to model other tissue-localized autoimmune diseases such as lupus, as well as certain niche autoimmune diseases of the thyroid and gut. "This sort of model would be useful in helping to pick apart the mechanisms of disease," he said.

Solinger said he would be interested in talking with his business development team about the possibility of collaborating with the researchers.

REFERENCES

1. Calzascia, T. *et al. Proc. Natl. Acad. Sci. USA*; published online Feb. 14, 2007; doi:10.1073/pnas.0712135105
Contact: Tak W. Mak, The Campbell Family Institute for Breast Cancer Research, University Health Network, Toronto, Canada
e-mail: tmak@uhnresearch.ca
2. Kurts, C. *et al. J. Exp. Med.* **186**, 2057-2062 (1997)
3. Bhatia, S. *et al. J. Exp. Med.* **181**, 1399-1409 (1995)
4. BCiQ: BioCentury Online Intelligence
5. Watanabe, M. *et al. J. Exp. Med.* **187**, 389-402 (1998)
6. Okada, E. *et al. Am. J. Physiol. Gastrointest. Liver Physiol.* **288**, G745-G754 (2005)

COMPANIES AND INSTITUTIONS MENTIONED

- Bristol-Myers Squibb Co.** (NYSE: BMY), New York, N.Y.
- The Campbell Family Institute for Breast Cancer Research**, Princess Margaret Hospital, Toronto, Ontario, Canada
- Cytheris S.A.**, Paris, France
- Xoma Ltd.** (NASDAQ: XOMA), Berkeley, Calif.

in the *Journal of Clinical Investigation* describing the results of a series of preclinical experiments exploring the role of Gas6 in erythropoiesis and anemia.⁵

The key finding is that Gas6 plays a critical role in the generation of erythroid progenitors and erythroblasts, at least in part by enhancing their survival response to erythropoietin (EPO).

In mice lacking Gas6, the erythropoietic response to EPO was reduced, and when anemia was induced in the animals, hematocrit recovery was impaired. By contrast, in wild-type mice, treatment with Gas6 protected against the development of anemia and facilitated hematocrit recovery.

In additional mouse models of EPO resistance and insufficiency, Gas6 amplified EPO's effect of increasing hematocrit levels after induction of both acute and chronic anemia.

The authors concluded that Gas6 plays a role in erythropoiesis and therefore might have the potential to treat anemic patients who are hyporesponsive or resistant to ESA treatment.

In terms of the predictive value of the results from murine models, "erythropoiesis in mice follows the same rules [as] in humans; most pathways are shared among species, and even single components are quite preserved across evolution," Antonio Risitano, from the Division of Hematology, **Federico II University of Naples**, told *SciBX*.

Although primates would be the best animal model, Risitano thinks that mice may be a good surrogate. "In my opinion, the mouse model is very important and may give pivotal information." Even so, Risitano cautioned that "...humans are quite different, and interpretations from the animal models have to be drawn very carefully."

In humans, the erythropoietic response to anemia is induced in the spleen and bone marrow. In mice, the response occurs primarily in the spleen. Nevertheless, Angelillo-Scherrer and colleagues replicated their genetic results in splenectomized animals with induced anemia.

According to Risitano, one of the next steps is to develop a model that will "match [the anemia] affecting humans as a direct consequence of the defect or shared pathogenic pathways. Once you have this information, the model may be also suitable to test the potential efficacy of drugs or any other therapeutic strategy."

A key unanswered question is whether Gas6-based therapeutics would circumvent the safety issues associated with the marketed ESAs. According to Steensma, "there is a suggestion that the signaling [of Gas6]

overlaps substantially with EPO, so it's not clear that they would be able to get away from the safety concerns that have been raised with EPO."

Research also has shown that Gas6 promotes platelet aggregation and the stabilization of platelet aggregation.⁶ "We know that ESAs have a thrombosis risk, so the question is: if you give ESA plus something that increases Gas6, would there be a lot of blood clots?" noted Steensma. "If this moves forward clinically, we'd have to follow it very closely."

Peter Young, VP of research at **Affymax Inc.**, thought the *JCI* article was "intriguing in that it provides another potential player in how erythropoiesis is driven in mammals. It may play into the hyporesponder side of things, but that would have to be further evaluated in humans. It's an excellent study, but it's in mice, so obviously it's very early in terms of understanding how this molecule plays a role in human anemia."

Affymax's Hematide is in Phase III testing to treat anemia associated with chronic renal failure and in Phase II testing to treat anemia in patients with cancer. The compound is a peptide agonist with an amino acid sequence that is unrelated to naturally occurring EPO.

The other late-stage ESA in development is FG-2216 from **FibroGen Inc.** The small-molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH) is in Phase II trials to treat anemia in chronic renal failure patients.

The other late-stage ESA in development is FG-2216 from **FibroGen Inc.** The small-molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH) is in Phase II trials to treat anemia in chronic renal failure patients.

REFERENCES

1. Edelson, S. *BioCentury* **15**(12), A1; March 12, 2007
2. Usdin, S. *BioCentury* **15**(22), A1; May 14, 2007
3. Usdin, S. *BioCentury* **15**(50), A11; Nov. 12, 2007
4. Manfioletti, G. *et al. Mol. Cell Biol.* **13**, 4976-4985 (1993)
5. Angelillo-Scherrer, A. *et al. J. Clin. Invest.*; published online Jan. 10, 2008; doi:10.1172/JCI30375
Contact: Anne Angelillo-Scherrer, University Hospital Center and University of Lausanne, Lausanne, Switzerland
e-mail: Anne.Angelillo-Scherrer@chuv.ch
6. Angelillo-Scherrer, A. *et al. J. Clin. Invest.* **115**, 237-246 (2005)

COMPANIES AND RESEARCH INSTITUTIONS MENTIONED

- Affymax Inc.** (NASDAQ:AFFY), Palo Alto, Calif.
- Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.
- Federico II University of Naples**, Naples, Italy
- FibroGen Inc.**, South San Francisco, Calif.
- Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.
- Mayo Clinic**, Rochester, Minn.
- University Hospital Center**, Lausanne, Switzerland
- University of Lausanne**, Lausanne, Switzerland

"People are a little scared to use ESAs, rightly or wrongly, and there's an interest in looking elsewhere to combat anemia."

—David Steensma, Mayo Clinic

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mTOR caveats

By Michael J. Haas, Senior Writer

In many tumor types, rapamycin is thought to inhibit mammalian target of rapamycin's regulation of a key transcription factor—hypoxia-inducible factor-1 α —that is involved in tumor cell growth and proliferation. A widely used biomarker therefore relies on suppression of this factor as a proxy for mammalian target of rapamycin inhibition. However, a recent report in *Current Biology* questions whether that particular biomarker is appropriate in all tumor types.

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates cell growth, proliferation and survival as well as protein synthesis and transcription. Hypoxia-inducible factor-1 α (HIF-1 α), an oxygen-sensitive transcription factor, sits downstream of and is regulated by mTOR. HIF-1 α is highly expressed in many tumor types and is known to regulate the expression of genes involved in tumor angiogenesis, metabolism and invasion.

Suppression of HIF-1 α in turn suppresses *GLUT1*, a glucose transport gene that regulates uptake of fluorodeoxyglucose (FDG). As a result, mTOR-induced suppression of HIF-1 α can be quantitated by monitoring the uptake of radiolabeled FDG with PET.

In the Jan. 8 issue of *Current Biology*, a research team led by Karen Cichowski found that in neurofibromatosis type 1 (NF1)-related tumors, rapamycin suppressed tumor growth without suppressing HIF-1 α expression—raising questions about the general relevance of HIF-1 α as a biomarker of mTOR inhibition.¹ Cichowski is an assistant professor of medicine at **Brigham and Women's Hospital's** Department of Medicine and at **Harvard Medical School**. Other researchers on the paper were from the **Dana-Farber Cancer Institute, Massachusetts General Hospital and Children's Hospital Boston**.

Rapamycin, also called sirolimus, is a potent immunosuppressor that inhibits interleukin-2 (IL-2) activation of B cells and T cells. Rapamune sirolimus is marketed by **Wyeth** as an immunosuppressant to prevent organ transplant rejection.

NF1 is a genetic disease characterized by the development of malignant peripheral nerve sheath tumors (MPNSTs). Cichowski and others had already demonstrated that NF1 inactivation led to aberrant activation of mTOR pathways, suggesting that MPNSTs depend on increased mTOR signaling for growth.^{2,3} Thus, Cichowski's team sought to identify the effectors that mTOR activated for MPNST development.

The research team used a genetically engineered, spontaneous tumor model of NF1 in which mice deficient in both NF1 and p53 were treated with rapamycin. The scientists found that rapamycin did indeed suppress MPNST growth, but that it had no effect on the expression of HIF-1 α or its transcripts. Instead, results showed that rapamycin suppressed tumor growth via suppression of mTOR complex-1 (TORC1), a cluster of three proteins—including mTOR—that functions as a nutrient and energy sensor to control protein synthesis.

The researchers looked for other activators of mTOR in MPNSTs among known mTOR targets: cyclin D1 (CCND1), programmed cell

death-4 (PDCD4), c-myc, p27 and p21. Of these, rapamycin suppressed only CCND1 expression.

CCND1 is a member of the cyclin family, which regulate cyclin-dependent kinases. Mutations in the *CCND1* gene have been observed in many tumors and are thought to contribute to tumorigenesis.

Additional *in vitro* experiments by Cichowski's team demonstrated that NF1 inactivation enhanced CCND1 expression, a finding that correlated with findings reported by other researchers.⁴

Taken together, these results indicated that CCND1 was a critical target of rapamycin in MPNSTs *in vivo*. This led Cichowski's team to conclude that CCND1 expression might be a better biomarker than HIF-1 α suppression for mTOR inhibition in those tumors.

But the team, noting that CCND1 had been implicated as a critical rapamycin target in mantle cell lymphoma, also suggested CCND1 as a general target of mTOR—and a biomarker of mTOR inhibition—in tumorigenesis.

Henrik Oerum, CSO of **Santaris Pharma A/S**, said the *Current Biology* study “underpins what is probably not a big surprise to most researchers: one cannot automatically assume that a particular drug elicits its effect in different cell types by exactly the same mechanism

of action. In the case of MPNSTs, the study suggests that cyclin D1 could be an appropriate biomarker. However, much work remains to consolidate this observation, including target-disease association studies in human MPNST tumors.”

Santaris and partner **Enzon Pharmaceuticals Inc.** are developing EZN-2968, a HIF-1 α antagonist in Phase I testing to treat lymphoma and solid tumors. “Clinical indications chosen for this drug candidate are all selected on the basis of scientific and medical data that links elevated levels of HIF-1 α to the pathology of the disease,” Oerum said.

John Lyons, VP of translational biology at **Astex Therapeutics Ltd.**, told *SciBX* that the paper supports “the need for a thorough, intimate understanding of the signaling networks in the target cell types. Without this information, costly clinical trials might prove ineffective and, more importantly, patients with MPNSTs and other cancers will not receive the targeted therapy that they deserve.”

Last year, Astex completed a Phase I trial of its AT7519 CDK inhibitor in solid tumors. The company is considering whether to develop the compound for chronic lymphocytic leukemia.

Behind AT7519, Astex has its AT9311 CDK inhibitor in preclinical development for multiple myeloma. AT9311 is partnered with **Novartis AG**.

Lyons suggested the findings “will certainly lead clinicians to put forward a case for testing new signal transduction inhibitors in patients with NF1-associated malignancies,” including rapamycin analogs and CDK1, CDK2 and CDK4 inhibitors.

Although the question of which mTOR biomarker is suitable for which cancer will take time to sort out, another finding in Cichowski's paper could have more near-term implications. The researchers suggested that genetically engineered mouse models make better preclinical predictors of therapeutic responses to mTOR inhibitors in human tumors than xenograft tumor models.

“One cannot automatically assume that a particular drug elicits its effect in different cell types by exactly the same mechanism of action.”

—Henrik Oerum,
Santaris Pharma A/S

In xenografts, mTOR inhibitors have been found to suppress tumors by rapidly disrupting tumor microvasculature—often leading to tumor regression. But in genetically engineered models, Cichowski and her team obtained very different results: after eight days of treatment with rapamycin, tumor growth was suppressed but the tumors still had clearly defined microvasculature. Rapamycin had no observable effect on the density of microvasculature until day 14 and beyond.

The researchers attributed the discrepancy to differences in signaling that give spontaneously arising tumors more stable microvasculature.

Oerum agreed that this was probably the case. “The effect of rapamycin on tumor vasculature is likely to be better portrayed in the engineered mouse,” he said.

Oerum said the formation of a xenograft tumor involves the rapid development of crude vasculature that ties the tumor into the host’s circulatory system and allows the xenograft to survive. Such “emergency vascularization,” he said, might be highly susceptible to disruption by a drug.

A spontaneously arising tumor—such as that in a genetically engineered mouse or a human patient with NF1—develops vasculature over time, as the tumor grows in the host. Such a tumor is likely to have more stable and less readily disrupted vasculature than a xenograft.

“We used various xenografts for our HIF-1 α work,” Oerum told

SciBX. “We would have loved, though, to use genetically engineered models if they had been available to us.”

Lyons agreed. “Xenograft models are the workhorses of the cancer therapy development field,” he said. “But the transgenic models of knockouts and knockins are much more relevant to a patient’s disease.”

Cichowski was unable to respond to requests for an interview.

REFERENCES

1. Johannessen, C. *et al. Curr. Biol.*; published online Dec. 27, 2007; doi:10.1016/j.cub.2007.11.066
Contact: Karen Cichowski, Genetics Division, Department of Medicine, Brigham and Women’s Hospital, Boston, Mass.
e-mail: kcichowski@rics.bwh.harvard.edu
2. Dasgupta, B. *et al. Cancer Res.* **65**, 2755–2760 (2005)
3. Johannessen, C. *et al. Proc. Natl. Acad. Sci. USA* **102**, 8573–8578 (2005)
4. Kim, H. *et al. J. Neurosci.* **21**, 1110–1116 (2001)

COMPANIES AND INSTITUTIONS MENTIONED

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Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
Novartis AG (NYSE:NVS; SWX:NOVN), Basel, Switzerland
Santaris Pharma A/S, Horsholm, Denmark
Wyeth (NYSE:WYE), Madison, N.J.



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This week in therapeutics

THE DISTILLERY brings you this week's most essential scientific findings in therapeutics, distilled by *SciBX* editors from a weekly review of more than 400 papers in 37 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Breast cancer	Aromatase	An SAR study identified a series of nimesulide derivatives (sulfonanilides) that inhibited aromatase and could potentially treat estrogen-dependent breast cancer. Nimesulide is a nonsteroidal anti-inflammatory drug that inhibits aromatase, a key enzyme in the biosynthesis of estrogen that is required for tumor growth in a majority of breast cancers. Ten of the nimesulide derivatives had IC_{50} values of $<0.4 \mu\text{M}$ in SK-BR-3 breast cancer cells and showed greater <i>in vitro</i> activity against aromatase than the parent compound. Next steps include testing the derivatives for aromatase inhibitory activity <i>in vivo</i> . Helsinn Healthcare S.A. markets nimesulide in Europe and other ex-U.S. territories to treat acute pain, osteoarthritis and dysmenorrhea.	U.S. patent application filed covering composition of matter on more than 200 sulfonanilides; available for licensing	Su, B. <i>et al. J. Med. Chem.</i> ; published online Feb. 14, 2008; doi:10.1021/jm701107h Contact: Robert W. Brueggemeier, College of Pharmacy, The Ohio State University, Columbus, Ohio e-mail: brueggemeier.1@osu.edu
Cancer	Nitric oxide (NO) synthase	A study in cancer cell lines and mice suggests that antagonizing NO synthase could improve tumor oxygenation and make tumors more responsive to radiation therapy. In the U87MG human glioma cell line, silencing neuronal NO synthase with short hairpin RNA or inhibiting the enzyme with the small molecule L-NPA improved blood vessel density and vascular permeability compared with untreated controls and subsequently increased tumor tissue oxygenation. Xenograft mice with NO synthase-silenced human glioma tumors showed suppressed and delayed tumor growth and increased survival time after radiation treatment compared with xenograft mice with control human glioma tumors. The authors said that next steps include improving the safety and efficacy of compounds and methods that modulate NO signaling.	Patent application filed for modulation of NO signaling to normalize tumor vasculature; available for licensing	Kashiwagi, S. <i>et al. Nat. Med.</i> ; published online Feb. 17, 2008; doi:10.1038/nm1730 Contact: Dai Fukumura, Massachusetts General Hospital and Harvard Medical School, Boston, Mass. e-mail: dai@stele.mgh.harvard.edu
Cancer	Prokineticin 2 (PROK2; Bv8)	A study in mice suggests that antagonizing Bv8 could be useful for treating early-stage cancers. In a mouse model of multistage pancreatic cancer, anti-Bv8 antibodies reduced early-stage hyperplasia and tumor angiogenesis compared with a control antibody. However, anti-Bv8 treatment had no effect on vascularization at later stages of tumor progression. The results support previous data suggesting that Bv8 plays a role in the initial homing of neutrophils to the site of developing tumors (<i>See Mikulski, M. SciBX 1(2), 6; Feb. 7, 2008</i>). Next steps should examine the role of anti-Bv8 antibodies in other cancers.	Patented by Genentech Inc.; licensing status undisclosed	Shojaei, F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 4, 2008; doi:10.1073/pnas.0712185105 Contact: Napoleone Ferrara, Genentech Inc., South San Francisco, Calif. e-mail: ferrara.napoleone@gene.com
Cardiovascular disease				
Arterial thrombosis	Kindlin-3	<i>Ex vivo</i> and <i>in vivo</i> studies suggest that antagonizing the adhesion plaque protein kindlin-3 could help prevent arterial thrombosis and subsequent heart attacks or strokes. In <i>ex vivo</i> platelet aggregation assays, platelet-specific knockout of murine kindlin-3 blocked integrin-mediated platelet adhesion. Mice with kindlin-3-deficient platelets developed no thrombi and maintained blood flow in all vessels 40 minutes after mesenteric arteriole injury, whereas all wild-type animals had occluded vessels within 18–39 minutes. Next steps include investigating the structure of the kindlin-3-integrin complex to examine the relative roles of kindlin-3 and Talin, a known mediator of cell adhesion, in the activation of integrins.	U.S. patent application filed for antithrombotic applications; unlicensed	Moser, M. <i>et al. Nat. Med.</i> ; published online Feb. 17, 2008; doi:10.1038/nm1722 Contact: Reinhard Fässler, Max Planck Institute of Biochemistry, Martinsried, Germany e-mail: faessler@biochem.mpg.de

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Atherosclerosis	Interleukin-33 (IL-33; NF-HEV)	A study in mice suggests that targeting the IL-33 pathway could help treat atherosclerosis. Fat-fed ApoE-deficient mice that received IL-33 had lower inflammation, lower atherosclerotic plaque formation in the aortic sinus and higher levels of antioxidantized low-density lipoprotein (ox-LDL) antibodies than mice that received saline. In addition, <i>ApoE</i> -deficient mice treated with an IL-33 decoy receptor developed larger plaques in the aortic sinus than animals that received IgG control. Treatment of mice with both an anti-IL-5 antibody and IL-33 prevented reduction of plaque size and reduced the amount of ox-LDL antibodies, suggesting that IL-5 plays a role in mediating the effects of IL-33. Next steps include determining the maximum tolerated dose of IL-33.	No patent application filed; licensing status undisclosed	Miller, A. <i>et al. J. Exp. Med.</i> ; published online Feb. 11, 2008; doi:10.1084/jem.20071868 Contact: Foo Y. Liew, Glasgow Biomedical Research Centre and British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, U.K. e-mail: f.y.liew@clinmed.gla.ac.uk Contact: Damo Xu, same affiliation as above e-mail: d.xu@clinmed.gla.ac.uk
Atherosclerosis	Renin; renin-angiotensin system (RAS)	A study in mice suggests that inhibiting renin could be useful for treating atherosclerosis. In low-density lipoprotein-deficient mice fed a fat-supplemented diet, the renin inhibitor aliskiren reduced atherosclerotic lesion size in both the aortic arch and aortic root compared with vehicle-treated controls. Next steps could include investigating the role of endothelial cells in atherosclerosis-associated RAS as well as examining renin inhibition in other animal models of cardiovascular disease. Aliskiren from partners Novartis AG and Speedel is marketed in the U.S. as Tekturna and in the EU as Rasilez to treat hypertension.	No patent applications filed by researchers; data owned by Novartis AG, which partially funded the research; licensing status undisclosed	Lu, H. <i>et al. J. Clin. Invest.</i> ; published online Feb. 14, 2008; doi:10.1172/JCI32970 Contact: Alan Daugherty, University of Kentucky, Lexington, Ky. e-mail: Alan.Daugherty@uky.edu Contact: Lisa A. Cassis, same affiliation as above e-mail: Lcassis@uky.edu
Thrombosis	AMPA-type glutamate receptor (AMPA)	A study in cell culture and mice suggests that antagonizing AMPAR could reduce platelet activation and potentially treat or prevent thrombosis. Analysis of human plasma showed that platelets expressed AMPARs and that the binding of glutamate to AMPARs increased platelet activation. Also, platelets treated with an AMPAR antagonist or derived from mice deficient in an AMPAR subunit were more resistant to AMPAR activation than untreated or wild-type platelets. Mice that lacked the receptor subunit had longer time to thrombosis than wild-type mice. Next steps include testing AMPAR antagonists <i>in vitro</i> and in animal models of thrombosis. No fewer than seven companies have compounds targeting the AMPA receptor in preclinical and clinical testing for multiple neurological indications.	Patent application filed for glutamate receptor antagonists; licensing status undisclosed	Morrell, C. <i>et al. J. Exp. Med.</i> ; published online Feb. 18, 2008; doi:10.1084/jem.20071474 Contact: Craig Morrell, Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: cmorrell@jhmi.edu

Endocrine disease

Diabetes	Not applicable	Pancreatic endoderm derived from human embryonic stem cells (hESCs) could be a useful cell therapy for diabetes. hESC-derived pancreatic endoderm generated glucose-responsive endocrine cells after implantation into mice. Glucose-regulated human insulin and C-peptide levels were comparable to those in mice transplanted with about 3,000 adult human islet cells. The pancreatic endoderm implants also protected against streptozotocin-induced hyperglycemia. Next steps include improving endodermal cell-selection techniques. Novocell Inc. has implantable polyethylene glycol-encapsulated human pancreatic islet cells in Phase I/II testing for type 1 diabetes. MicroIslet Inc.'s MicroIslet-P, a suspension of microencapsulated porcine islets for injection into the abdominal cavity, is in preclinical testing to treat type 1 diabetes.	Multiple U.S. and international patent applications filed covering <i>in vivo</i> differentiation of hESCs and other related technologies; available for licensing	Kroom, E. <i>et al. Nat. Biotechnol.</i> ; published online Feb. 20, 2008; doi:10.1038/nbt1393 Contact: Emmanuel Baetge, Novocell Inc., San Diego, Calif. e-mail: ebaetge@novocell.com
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This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Type 2 diabetes; obesity	Mitogen-activated protein kinase phosphatase-4 (MKP-4)	A study in cell lines and mice suggests that increasing the activity of MKP-4 could be useful for treating type 2 diabetes and obesity. Overexpression of MKP-4 in insulin-sensitive cell lines inhibited the phosphorylation of ERK and Jun N-terminal kinase (JNK) and consequently protected against stress-induced insulin resistance. In leptin-deficient mice, adenoviral delivery of MKP-4 to the liver decreased ERK and JNK phosphorylation and led to reductions in glycemia, improved glucose tolerance and reduced fatty liver compared with leptin-deficient mice that received green fluorescent protein as a control. Next steps include clarifying the mechanisms that regulate the activity and expression of MKP-4 in insulin-sensitive tissues.	Not patented; unlicensed	Emanuelli, B. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 18, 2008; doi:10.1073/pnas.0712275105 Contact: C. Ronald Kahn, Joslin Diabetes Center, Boston, Mass. e-mail: c.ronald.kahn@joslin.harvard.edu
Infectious disease				
Sepsis	Thrombin; protease-activated receptor 1 (PAR1); sphingosine kinase; sphingosine 1-phosphate receptor (S1P receptor)	A study in mice suggests that proteins involved in coagulation and S1P signaling could be targets for sepsis therapeutics. Mice that received pharmacological inhibitors or mice with genetic disruption of thrombin, PAR1, sphingosine kinase or S1P had lower levels of sepsis-associated cytokines and improved survival compared with untreated or wild-type controls, respectively. These treatments lowered S1P production by dendritic cells, which normally boost inflammation through S1P-driven migration, sometimes leading to sepsis. Next steps include repurposing drugs that target the PAR1-S1P pathway to treat sepsis and developing dose regimens that block sepsis without compromising immunity.	Not patented; licensing status undisclosed	Niessen, F. <i>et al. Nature</i> ; published online Feb. 27, 2008; doi:10.1038/nature06663 Contact: Wolfram Ruf, Department of Immunology, The Scripps Research Institute, La Jolla, Calif. e-mail: ruf@scripps.edu
Staphylococcus	Calprotectin; Manganese ions; zinc ions	A study in cell culture and mice suggests that metal-chelating peptides could be useful for treating <i>Staphylococcus aureus</i> infection. Calprotectin, an S100 calcium-binding protein, localized to <i>S. aureus</i> abscesses in mice, where it chelated zinc and manganese ions, preventing nutrient uptake and thus <i>S. aureus</i> growth. In calprotectin-deficient mice, levels of the two metal ions were higher and staphylococcal proliferation was greater in <i>S. aureus</i> abscesses than in wild-type mice. The researchers are now looking for recombinant peptides with metal-chelating properties.	International patent application filed covering methods of treating microbial infections using metal ion chelators, including calprotectin; available for licensing	Corbin, B. <i>et al. Science</i> ; published online Feb. 14, 2008; doi:10.1126/science.1152449 Contact: Eric P. Skaar, Vanderbilt University Medical Center, Nashville, Tenn. e-mail: eric.skaar@vanderbilt.edu
Staphylococcus	<i>Staphylococcus aureus</i> dehydrosqualene synthase	<i>In vitro</i> and <i>in vivo</i> studies suggest that inhibitors of <i>S. aureus</i> dehydrosqualene synthase could be useful for treating <i>S. aureus</i> infections. Dehydrosqualene synthase plays a role in the biosynthesis of staphyloxanthin, a bacterial virulence factor that promotes resistance to neutrophils. A screen of nine inhibitors of human squalene synthase identified several compounds that also inhibited <i>S. aureus</i> dehydrosqualene synthase. One inhibitor, BPH-652, blocked staphyloxanthin synthesis <i>in vitro</i> and had an IC ₅₀ value of about 100 nM. Mice treated with BPH-652 had significantly lower <i>S. aureus</i> bacterial counts in their kidneys than untreated controls at 72 hours postinfection ($p < 0.001$). Next steps include clinical studies of BPH-652 to treat complicated <i>S. aureus</i> skin and soft tissue infections. Takeda Pharmaceutical Co. Ltd.'s lapaquistat (TAK-475), a squalene synthase inhibitor, is in Phase III testing to treat hypercholesterolemia.	Patent application filed; unavailable for licensing	Liu, C. <i>et al. Science</i> ; published online Feb. 14, 2008; doi:10.1126/science.1153018 Contact: Eric Oldfield, University of Illinois, Urbana, Ill. e-mail: eo@chad.scs.uiuc.edu Contact: Andrew H.-J. Wang, Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei, Taiwan e-mail: ahjwang@gate.sinica.edu.tw Contact: Victor Nizet, University of California, San Diego, La Jolla, Calif. e-mail: vnizet@ucsd.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Neurology				
Psychosis	Metabotropic glutamate receptor subtype 2/3 (mGluR2/3); serotonin receptor (5-HT _{2A} receptor)	<p>A study in mice and postmortem human brain showed that the 5-HT_{2A} receptor and mGluR2 form a complex that might be targeted to treat psychosis associated with schizophrenia. Multiple methods, including coimmunoprecipitation and fluorescence resonance energy transfer, showed that the two receptors colocalized, interacted and formed functional complexes in mouse cortical neurons and human brain slices. Hallucinogenic compounds such as lysergic acid diethylamide (LSD), a glutamate receptor agonist and an atypical antipsychotic all influenced signaling through the complex. Moreover, postmortem brain slices from schizophrenia patients had greater 5-HT_{2A} receptor levels and lower mGluR2 levels than brain slices from subjects with no record of psychiatric illness. Next steps include investigating how cross-talk between the two receptors might influence the activity of hallucinogenic compounds. No fewer than five companies are developing or marketing compounds that target the 5-HT_{2A} receptor to treat psychosis and schizophrenia.</p> <p>LY2140023, an oral prodrug form of LY404039, a mGluR2/3 agonist from Eli Lilly and Co., completed a Phase II trial to treat schizophrenia last year.</p> <p>Addex Pharmaceuticals S.A. and partner Merck & Co. Inc. are developing the biotech's ADX63365, a positive allosteric modulator of mGluR5 that is in preclinical development.</p> <p>Pfizer Inc. and Taisho Pharmaceutical Co. Ltd. partnered in January to develop and commercialize Taisho's TS-032, an mGluR agonist that is in preclinical testing to treat schizophrenia. (See Schizophrenia develops a complex, page 5.)</p>	Provisional patent application filed for the complex; available for licensing	<p>Gonzalez-Maeso, J. <i>et al. Nature</i>; published online Feb. 24, 2008; doi:10.1038/nature06612</p> <p>Contact: Stuart Sealfon, Mount Sinai School of Medicine, New York, N.Y.</p> <p>e-mail: Stuart.Sealfon@mssm.edu</p>
Ophthalmic disease				
Glaucoma	Secreted frizzled-related protein-1 (sFRP-1)	<p>Studies in mice suggest that antagonizing sFRP-1 could help alleviate elevated intraocular pressure (IOP) associated with glaucoma. In glaucoma patients, sFRP-1 is a Wnt signaling pathway antagonist that is overexpressed in the trabecular meshwork of the eye. Addition of recombinant sFRP-1 to <i>ex vivo</i>-cultured human eyes reduced levels of the Wnt pathway mediator β-catenin in the trabecular meshwork and also decreased ocular outflow velocity. Moreover, intravitreal injection of human sFRP-1 into mice increased IOP compared with untreated controls. Finally, local treatment of ocular hypertensive rodents with an inhibitor of glycogen synthase kinase-3 (GSK-3), a downstream suppressor of Wnt signaling, reduced sFRP-1-induced IOP compared with vehicle-treated controls. Next steps include testing the inhibitors in glaucoma patients.</p> <p>No fewer than eight companies have compounds in preclinical and clinical development to reduce IOP associated with glaucoma.</p>	Patent application filed for the research; unavailable for licensing	<p>Wang, W. <i>et al. J. Clin. Invest.</i>; published online Feb. 14, 2008; doi:10.1172/JCI33871</p> <p>Contact: Abbot F. Clark, Alcon Research Ltd., Fort Worth, Texas</p> <p>e-mail: abe.clark@alconlabs.com</p>

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 37 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
An RNA transcript-based method for measuring transcription factor activity	A reporter system that measures the activity of multiple transcription factors could be useful for screening therapeutics and identifying transcriptional profiles that are prognostic of disease. The method uses DNA reporter sequences that generate nearly identical reporter transcripts. After processing, the transcripts produce distinct DNA fragments that can be quantitatively evaluated. <i>In vitro</i> proof-of-concept studies with a panel of 43 reporter sequences distinguished cancer cell lines according to their transcription factor (TF) activity profiles. The group is designing a similar system that works <i>in vivo</i> . Attagene Inc., which already offers services using the Factorial TF profiling system, plans to soon launch a reagent kit for researchers to use in the lab.	Three international patent applications filed covering the use of homogenous RNA reporter transcripts to measure transcriptional activity; patents owned by Attagene and unavailable for licensing	Romanov, S. <i>et al. Nat. Methods</i> ; published online Feb. 24, 2008; doi:10.1038/nmeth.1186 Contact: Sergei Makarov, Attagene Inc., Research Triangle Park, N.C. e-mail: smak@attagene.com
Biocompatible and biodegradable tissue adhesives for surgery and other medical applications	Biodegradable and biocompatible poly(glycerol-co-sebacate acrylate) polymer films with nanoscale patterning that mimics the nanotopography of gecko feet could be useful for drug delivery and dressing or sealing wounds. Thin tapes of the material showed strong adhesion to porcine intestinal tissue <i>ex vivo</i> as well as adhesion and biocompatibility in rat abdominal tissues <i>in vivo</i> . Next steps include developing the adhesive tapes for medical applications including suture replacement, drug or growth factor delivery and leak prevention in gastric bypass surgery or hernia repair.	Massachusetts Institute of Technology has filed a provisional patent application for medical applications of the tissue adhesive and has a patent issued and a patent pending for the material; available for licensing for a variety of medical applications	Mahdavi, A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 18, 2008; doi:10.1073/pnas.0712117105 Contact: Jeffrey M. Karp, Center for Biomedical Engineering, Brigham and Women's Hospital, Boston, Mass. e-mail: jkarp@rics.bwh.harvard.edu Contact: Robert Langer, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: rlanger@mit.edu
Cationic amino acid motifs for improving cell penetration of protein therapeutics	Engineering as few as five arginine residues into a protein α -helix could be sufficient to allow protein therapeutics to effectively cross the host cell membrane. Substitution of 4, 5 or 6 arginine residues into the α -helix of the 36-residue avian pancreatic polypeptide resulted in three variants with minimal loss of structural stability compared with wild-type protein. Moreover, microscopy revealed that all variants penetrated HeLa cells, some with rates of uptake superior to those of a known oligoarginine protein carrier. The authors did not disclose their next steps.	Yale University has a patent portfolio covering compositions and uses of miniature proteins; available for licensing	Smith, B. <i>et al. J. Am. Chem. Soc.</i> ; published online Feb. 14, 2008; doi:10.1021/ja800074v Contact: Alanna Schepartz, Yale University, New Haven, Conn. e-mail: alanna.schepartz@yale.edu
Contrast-enhanced MRI for the early detection of platelet aggregation	An imaging study suggests that a contrast agent specific for activated platelets might help standard MRI detect early platelet aggregation events associated with cerebral malaria, stroke and other diseases with cerebral pathology. The contrast agent consisted of iron oxide microparticles that were conjugated to antibodies that bind activated platelets. In rodents infected with cerebral malaria, the contrast agent showed greater binding in various regions of the cortex than in rodents receiving sham microparticles, where no such binding occurred. The contrast agent was also used to identify tumor necrosis factor as a promoter of platelet adhesion. Future work will seek to improve the safety and efficacy of the contrast agent.	Two international patent applications filed covering the use of iron-sugar colloidal particles and multimeric iron oxide particles as contrast agents in medical imaging; available for licensing	von sur Muhlen, C. <i>et al. J. Clin. Invest.</i> ; published online Feb. 14, 2008; doi:10.1172/JCI33314 Contact: Daniel C. Anthony, University of Oxford, Oxford, U.K. e-mail: daniel.anthony@pharm.ox.ac.uk

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Generating dopaminergic neurons from human embryonic stem cells (hESCs) to treat Parkinson's disease (PD)	A method for generating dopaminergic neurons derived from hESCs could be useful for treating PD. The technique generates homogeneous spherical neural masses that subsequently produce a large number of neurons within a relatively short time. Moreover, these neural masses can be expanded over long periods of time without losing the capacity to differentiate into dopaminergic neurons. In a rat model of PD, transplanted hESC-derived dopaminergic neurons reduced motor deficits in all three behavioral tests commonly used to measure the efficacy of PD therapeutics. Next steps include improving the purity of the dopaminergic neurons.	Patent application filed; licensing status undisclosed	Cho, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 25, 2008; doi:10.1073/pnas.0712359105 Contact: Dong-Wook Kim, Yonsei University College of Medicine, Seoul, South Korea e-mail: dwkim2@yuhs.ac
Immunoassay to detect cancer biomarkers	A single-step immunoassay that uses gold nanoparticle probes in combination with dynamic light scattering could offer greater sensitivity and efficiency than multistep immunoassays for detecting cancer biomarkers. The method detected free prostate-specific antigen (f-PSA), a biomarker of prostate cancer, in a protein matrix solution. Next steps include testing the immunoassay on human blood samples.	Provisional patent application filed for the immunoassay design; available for licensing	Liu, X. <i>et al. J. Am. Chem. Soc.</i> ; published online Feb. 8, 2008; doi:10.1021/ja711298b Contact: Qun Huo, Nanoscience Technology Center, University of Central Florida, Orlando, Fla. e-mail: qhho@mail.ucf.edu
Noninvasive imaging of tumors	<i>In vivo</i> , noninvasive imaging of a simple peptide biomarker could offer a cost-effective method for distinguishing responding from nonresponding cancers. Daily injection and imaging of the fluorophore-tagged HVGSSV peptide revealed that HVGSSV bound tumors that were responding to VEGF tyrosine kinase inhibitor (TKI) treatment but did not bind to tumors treated with radiation alone or those known to be unresponsive to VEGF TKIs. Ongoing work will identify the protein that the peptide binds and evaluate the pharmacokinetic and imaging properties of the radioiodine-tagged peptide. (See Watching cancer glow away , page 1.)	Provisional patent application submitted; currently negotiating licensing	Han, Z. <i>et al. Nat. Med.</i> ; published online February 24, 2008; doi:10.1038/nm1691 Contact: Dennis E. Hallahan, Vanderbilt University, Nashville, Tenn. e-mail: dennis.hallahan@vanderbilt.edu

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