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By *Tim Fulmer, Senior Writer*

Australian and U.S. researchers have shown that a small molecule inhibitor of RNA polymerase I blocked tumor growth in mouse models of lymphoma.<sup>1</sup> **Cylene Pharmaceuticals Inc.** and the **Peter MacCallum Cancer Centre** plan to start a Phase I trial of the inhibitor in Australia this year.

During tumorigenesis, cancer cells produce abnormally high levels of rRNA to create the ribosomes necessary for rapid protein synthesis and cellular proliferation.<sup>2,3</sup> Because the enzyme RNA polymerase I (Pol I) drives the synthesis of rRNA, it has been hypothesized that inhibiting Pol I could be a way to indirectly block protein synthesis and prevent cancer cell proliferation.

The challenge has been figuring out how to target Pol I in cancer cells without impairing the function of the enzyme in healthy cells, in which it plays an essential role in normal protein synthesis.

In prior work, Cylene researchers used a cell-based screening assay to identify a small molecule that blocked rRNA synthesis by inhibiting Pol I.<sup>4</sup> In the new work, they tested *in vivo* whether the same Pol I inhibitor, CX-5461, could selectively kill hematological cancer cells, which often show dysregulation of rRNA synthesis and ribosome biogenesis.

In cultured lymphoma cells isolated from tumor-bearing mice, CX-5461 induced apoptosis and increased cell death compared with vehicle. Moreover, the killing effect was more pronounced in cells expressing wild-type p53 than in cells expressing mutant p53 or no p53 at all, suggesting CX-5461 required the downstream activity of wild-type p53.

Additional cell culture studies revealed a mechanism whereby the inhibition of Pol I by CX-5461 led to the buildup of ribosomal proteins and the activation of p53, which then upregulated apoptotic pathways to kill cancer cells (see **Figure 1, "Pol I inhibition in cancer"**).

Importantly, CX-5461 did not activate p53 and induce apoptosis in normal immune cells, confirming that the inhibitor's killing effects were selective for malignant cells.

In mice with established lymphoma expressing wild-type p53, a single dose of CX-5461 significantly decreased tumor burden in the lymph nodes compared with vehicle ( $p < 0.01$ ). In a separate group of the same lymphoma mice, three doses of CX-5461 significantly prolonged survival and restored white blood cell counts.

To translate the findings to human disease, the researchers next evaluated CX-5461 in a panel of cell lines derived from human hematological cancers. Consistent with the mouse data, the inhibitor

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induced apoptosis in cell lines expressing wild-type p53 much more potently than in cells expressing mutant p53.

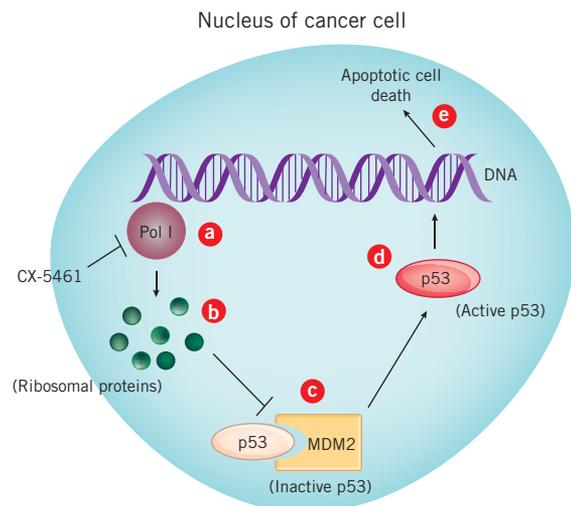
Finally, in mice transplanted with one of the human hematological cancer cell lines, once weekly CX-5461 decreased tumor volume compared with vehicle.

The team was led by Ross Hannan, associate professor of biochemistry and molecular biology at **The University of Melbourne** and head of the Oncogenic Signaling and Growth Control Program at Peter MacCallum, and Grant McArthur, cohead of the Cancer Therapeutics Program and director of the Melanoma & Skin Cancer Service at Peter MacCallum. Denis Drygin, Cylene VP of biology, and William Rice, Cylene president and CEO, were co-principal investigators on the study.

The findings were published in *Cancer Cell*.

“The field has known for a while that cancer cells become addicted to ribosomal biogenesis and protein synthesis for their survival and proliferation,” Davide Ruggero told SciBX. “This paper shows for the first time it is possible to directly target one of those processes without causing serious toxicity to healthy cells.”

In 2011, Ruggero, associate professor of urology at the **University of California, San Francisco**, published in *Cancer Cell* that the protein synthesis regulator eukaryotic translation initiation factor 4E binding protein 1 (eIF4EBP1) is a key mediator of cancer cell growth and progression.<sup>5</sup>



**Figure 1. Pol I inhibition in cancer.** Researchers from the **Peter MacCallum Research Centre** and **Cylene Pharmaceuticals Inc.** have published data in *Cancer Cell* showing that a small molecule inhibitor of RNA polymerase I (Pol I) reduced growth of hematological cancers in mice.

In lymphoma cells, the Pol I inhibitor CX-5461 blocked Pol I with low nanomolar potency [a], triggering a stress response involving the release of ribosomal proteins from the nucleolus [b], a sub-compartment of the nucleus. The ribosomal proteins then blocked interactions between p53 and the p53 inhibitory protein mdm2 p53 binding protein homolog (MDM2; HDM2) [c], which in turn activated p53 [d] and allowed it to upregulate expression of proapoptotic genes, killing the cancer cells [e].

Cylene and Peter MacCallum plan to start a Phase I trial of CX-5461 to treat hematological malignancies this year.

### Activating p53

The key advantage of CX-5461 is that it activates p53 through a downstream ribosomal stress pathway, which “doesn’t cause global DNA damage, and thus the side effects of the drug are significantly reduced compared to standard cytotoxic therapies and radiation,” said Hannan. In fact, CX-5461 is 300-fold more potent than nutlins at killing lymphoma cell lines, he added.

Nutlins, small molecule antagonists of mdm2 p53 binding protein homolog (MDM2; HDM2) that result in activation of p53, were developed by **Roche** and are in Phase I testing to treat various cancers. In preclinical studies, nutlins induced apoptosis in blood cancers including acute myelogenous leukemia (AML) and cutaneous T cell lymphoma (CTCL).<sup>6,7</sup> Roche declined to comment.

According to Klas Wiman, professor of oncology at the **Karolinska Institute** and cofounder of **Aprea AB**, the fact that CX-5461 works well in tumors that carry wild-type p53 but not so well in tumors that lack p53 or express mutant p53 is a potential limitation of the compound. “Targeting mutant p53-carrying tumors is a greater challenge, and here there is an urgent medical need, because mutant p53-carrying tumors are more resistant to conventional chemotherapy and have a worse prognosis,” said Wiman.

Aprea’s lead is PRIMA-1MET (APR-246), a small molecule that promotes the folding of mutant p53 into an active form. The compound is in Phase II testing to treat AML and chronic lymphocytic leukemia (CLL). In cultured cancer cells, PRIMA-1MET reactivated mutant p53 and triggered apoptotic cell death.<sup>8</sup>

CX-5461 “should be tested in a wider range of tumor types,” said Wiman. He added that “it should be tested in *ex vivo* primary patient tumor cells to study its differential effects on tumors carrying wild-type versus mutant p53.”

Cylene is continuing to look for genetic markers of sensitivity to CX-5461 in a wide variety of blood and solid cancers, Rice told *SciBX*.

Indeed, there is evidence that some solid tumors are sensitive to CX-5461, according to Hannan. “For example, preliminary studies have shown that a panel of ovarian cell lines exhibits a 1,000-fold range in sensitivity to CX-5461.”

Meanwhile, Cylene will focus mainly on hematological cancers,

**“The field has known for a while that cancer cells become addicted to ribosomal biogenesis and protein synthesis for their survival and proliferation. This paper shows for the first time it is possible to directly target one of those processes without causing serious toxicity to healthy cells.”**

—*Davide Ruggero,*  
*University of California,*  
*San Francisco*

which have a relatively low frequency of p53 mutations compared with many solid cancers (~13% vs. >40%).<sup>9,10</sup>

In the second half of this year, Cylene and Peter MacCallum researchers will start a Phase I trial of CX-5461 in Australia to treat hematological malignancies including advanced leukemia, lymphoma and multiple myeloma (MM).

The initial dose-escalation phase of the trial will include patients with any relapsed or refractory hematological malignancy, whereas the second phase will enrich for patients whose disease is wild type for p53, such as mixed-lineage leukemia, said Hannan.

Cylene has patents covering CX-5461 and the *Cancer Cell* findings that are available for licensing. Hannan did not disclose if Peter MacCallum has IP associated with any of the findings.

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### COMPANIES AND INSTITUTIONS MENTIONED

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# AZ goes APOE

By Lev Osherovich, Senior Writer

**AstraZeneca plc** has assembled an academia-industry consortium to unravel the role of apolipoprotein E in Alzheimer's disease. The team, dubbed the A5 alliance, hopes to uncover basic mechanisms about how apolipoprotein E drives the disease process and to discover therapeutics tailored for carriers of the Alzheimer's disease-associated *apolipoprotein E4* allele.

Even though apolipoprotein E (APOE)'s contribution to AD risk has been known since the early 1990s, the underlying mechanism remains a mystery. APOE pathophysiology has proven hard to study because the protein plays multiple roles in cholesterol transport, cardiovascular function and inflammation, all of which are thought to affect AD.<sup>1</sup>

AstraZeneca's Neuroscience Innovative Medicines Unit (iMed) will provide drug screening expertise and \$5 million over 4 years to fund work by academic teams at **Weill Cornell Medical College, Washington University in St. Louis, The Feinstein Institute for Medical Research** and **The University of British Columbia**.

AstraZeneca's ultimate aim is to seed development of a new AD therapeutic class that modulates the activity of APOE itself. Such an approach is fundamentally different from existing symptomatic therapies or drug candidates that hit another key AD target,  $\beta$ -amyloid (A $\beta$ ).

APOE is a component of the lipoprotein particles that transport cholesterol in the bloodstream. In the brain, APOE is thought to affect the activity of microglia and astrocytes, which are glial cells that help maintain the environment around neurons.

In AD, that environment goes awry, leading to a cascade of malfunctioning brain circuitry, protein aggregation and neuronal death. In *APOE4* carriers, this disease process occurs more quickly than it does in individuals with the disease-neutral *APOE3* allele.

The A5 alliance is "focused on the biology of the genetic predisposition for AD by *APOE4*," said Michael Wood, project leader of AstraZeneca's iMed. "We don't understand the underlying contribution of APOE to pathology."

The A5 alliance hopes to crack this hard nut using new cell culture, genetic and imaging assays developed in academic laboratories as well as pharmacological tools from the AstraZeneca side.

## The problem

Human genetic evidence suggests *APOE4* is a major player in AD disease risk, "dwarfing the effect of other risk genes," said Andrew Saykin, professor of medical and molecular genetics and radiology and director of the Center for Neuroimaging at the **Indiana University School of Medicine**. Saykin is not a member of the A5 alliance.

Saykin said that the presence of *APOE4* likely contributes to the majority of cases of late-onset AD, the most prevalent form of the disease.

"In the general population, maybe 25% of Caucasians carry one or more copies of *APOE4*," said Saykin. "But if you take a clinical sample of patients with AD, often as many as 40%–65% of patients have *APOE4*."

"Inheriting one copy of *APOE4* increases your risk of AD by a third, but inheriting two copies increases your risk by an astonishing 15-fold in contrast to the so-called wild-type *APOE3* allele," said A5 alliance leader Steven Paul.

Paul is professor of neuroscience and psychiatry and director of the Helen and Robert Appel Alzheimer's Disease Research Institute at Weill Cornell and a venture partner at **Third Rock Ventures**. Paul was previously EVP of science and technology and president of the Lilly Research Laboratories unit of **Eli Lilly and Co**.

Most patients with AD carry *APOE4*, and the outlook for these patients with therapies currently in late-stage development is poor.

Because of the aggressive course of disease caused by *APOE4*, current AD trials typically segregate carriers and noncarriers into separate arms. Such stratified trials have so far suggested that therapeutics aimed at reducing levels of aggregated A $\beta$  are less effective in *APOE4* carriers than in noncarriers.

As an example, **Pfizer Inc.** and **Johnson & Johnson** reported on July 26 that bapineuzumab (AAB-001), a mAb targeting A $\beta$ , did not meet endpoints in a Phase III trial in patients with mild to moderate AD who carry *APOE4*. Data from ongoing trials of bapineuzumab in noncarriers are expected next year.

**"One of the goals of this alliance is to sort out exactly whether you want to increase or decrease APOE levels. Even though we're not sure whether increasing or decreasing APOE levels is better, we have the models to test the effect of both treatments."**

— Steven Paul,  
Weill Cornell Medical College

## Less or more?

The A5 alliance plans to tackle the mechanism of APOE using cell culture, mouse models and imaging techniques. The central premise of the consortium is that APOE affects production or activity of A $\beta$  and that *APOE4* performs this function poorly compared with *APOE3*. If so, raising levels of *APOE4* would presumably ameliorate AD.

Along these lines, a team led by Gary Landreth, professor of neuroscience at **Case Western Reserve University School of Medicine**, reported earlier this year that a retinoid X receptor (RXR) agonist that upregulates expression of APOE had a beneficial effect in a mouse model of AD.<sup>2</sup>

That technology has been licensed to **ReXceptor Inc.**, which plans to start a Phase I AD trial this year.

On the other hand, other researchers believe that *APOE4* has a distinct toxic effect in neurons. If that were the case, it would be best to reduce levels of *APOE4*.

Indeed, **Merck & Co. Inc.** and researchers at the **Gladstone Institute of Neurological Disease** looked into the potential toxic effects of *APOE4* on mitochondrial function and screened for compounds to prevent this toxicity.

That project was terminated by Merck in 2011, and preclinical compounds arising from the collaboration were out-licensed to **ApoBiopharma Inc.**<sup>3</sup>

Altogether, the existing data on APOE's role in AD paint a complex and seemingly contradictory picture, making it hard for pharmas to decide how to tackle the target.

“The bulk of the evidence generated in preclinical models points toward APOE playing a role in clearing A $\beta$ , thereby probably reducing amyloid burden,” said Wood. “But there has been a long-standing hypothesis that there’s a toxic gain of function in APOE4. That’s something we want to sort out.”

Paul and Wood believe that academic members of the A5 alliance have lined up the tools and techniques to clear the air about how to hit APOE.

Prior mouse studies by Paul and fellow A5 alliance member David Holtzman suggest that the APOE genotype affects clearance of A $\beta$  in the brain.<sup>4</sup>

Holtzman is professor of neurology and developmental biology and associate director of the Alzheimer’s Disease Research Center at Washington University in St. Louis.

Holtzman’s team has created AD mice in which the murine version of *ApoE* has been replaced with human APOE variants, including APOE4, APOE3 and APOE2, a rare variant that actually reduces AD risk.

“I’m a strong believer in our work with Holtzman that suggests that APOE influences how much amyloid develops in the brain,” said Paul. In mice, “APOE4 carriers have more amyloid than APOE3, and in turn APOE3 carriers have more than APOE2. This has been substantiated in human imaging studies.”

What is still unknown is which specific step in A $\beta$  production is affected by APOE and how the three human variants of APOE differ with respect to that activity. Answering these questions will require using cell culture assays.

Paul said the biggest unanswered question about APOE in AD is whether it is better to have more or less of it. The consortium will address this with mouse genetics and *in vivo* imaging studies in mice.

“One of the goals of this alliance is to sort out exactly whether you want to increase or decrease APOE levels,” said Paul. “Even though we’re not sure whether increasing or decreasing APOE levels is better, we have the models to test the effect of both treatments.”

“We want to establish a model that we think is representative of Alzheimer’s disease and then alter the expression of different APOE proteins,” said Wood. “This will help to guide subsequent drug discovery and development.”

Paul mentioned the possibility that APOE3 and APOE4 might have different effects in disease and would thus require different types of intervention.

“There’s still the question of whether treating disease in E4 is the same as treating it in E3 carriers,” he noted.

Paul said that once the question of whether to agonize or antagonize APOE is resolved, the consortium will launch drug screening efforts with the help of AstraZeneca’s compound libraries and medicinal chemistry expertise. AstraZeneca will retain rights to the company’s compounds. Terms of ownership of new patents emerging from the collaboration are undisclosed.

**“Even though we have closed our neuroscience-focused laboratories, we still have a lot of internal drug discovery capabilities. We’re looking toward this collaboration as a way to guide discovery efforts to identify a treatment for AD.”**

—Michael Wood, AstraZeneca plc

### Shrunken heads

The A5 alliance is an example of how AstraZeneca hopes to replenish its early discovery pipeline with compounds from external collaborators. Last year, the pharma shrank its internal neuroscience discovery unit down to 40–50 people focused on external partnering.<sup>5</sup>

AstraZeneca has only three compounds in clinical development for AD, all of which aim to relieve AD symptoms but do not halt the disease process.

Those compounds are AZD3480 (TC-1734) and AZD1446, neuronal nicotinic acetylcholine receptor  $\alpha_4\beta_2$  agonists partnered with **Targacept Inc.** that are respectively in Phase II and Phase I testing for AD; and AZD5213, a histamine H3 receptor (HRH3) antagonist in Phase II trials.

“Even though we have closed our neuroscience-focused laboratories, we still have a lot of internal drug discovery capabilities,” said Wood. “We’re looking toward this collaboration as a way to guide discovery efforts to identify a treatment for AD.”

Despite the A5 alliance’s focus on APOE, Wood said AstraZeneca is open to other targets for next-generation AD therapeutics. He noted that the ultimate yardstick for a disease-modifying agent in AD will be its effect on A $\beta$ .

“We still believe that amyloid is a key component of AD. You have to have amyloid plaques to be considered an AD patient,” said Wood.

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### COMPANIES AND INSTITUTIONS MENTIONED

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# New options for NEC

By Tracey Baas, Senior Editor

A team from the **University of Pittsburgh School of Medicine** has mouse data showing that amniotic fluid can decrease the severity of necrotizing enterocolitis, a GI disease primarily seen in premature infants.<sup>1</sup> An important next step will be exploring in greater detail the precise factors in amniotic fluid that underlie the beneficial effect and turning those factors into medicines.

The effects of necrotizing enterocolitis (NEC) range from mucosal injury to necrosis and perforation. It is the leading cause of death from GI disease in premature infants and is thought to develop due to an abnormal response to the microbial flora that colonizes the GI tract.

Standard care has not changed much over the past 30 years and involves intensive antibiotic regimens, food withdrawal, fluid control, peritoneal drainage and potentially surgery and resection of the affected intestine. In cases in which the infant requires surgery, the survival rate is about 50%.<sup>2</sup>

The mechanistic details of how NEC develops remain unclear, although recent studies have suggested activation of toll-like receptor 4 (TLR4) within the intestinal epithelium leads to mucosal injury by way of increased enterocyte apoptosis and decreased intestinal healing.<sup>2</sup> TLR4 is the receptor for lipopolysaccharide (LPS).

Because the premature intestine is bathed in amniotic fluid that is lost at early delivery, the Pittsburgh team hypothesized that the fluid might exert a restraining influence on TLR4 signaling. If so, they wanted to identify the specific factors within the fluid providing protection to the intestinal epithelium.

In fetal mice, injection of amniotic fluid plus LPS into the GI tract decreased activation of TLR4 and proinflammatory cytokine expression compared with injection of LPS alone. In fetal mice injected with amniotic fluid and LPS, the epidermal growth factor receptor (EGFR) inhibitor Erbitux cetuximab reversed the inhibitory effects of the amniotic fluid, suggesting amniotic fluid inhibits TLR4 signaling through EGFR.

In a newborn mouse model of NEC, daily enteral delivery of amniotic fluid significantly decreased NEC severity compared with no treatment ( $p < 0.05$ ). Protection was lost if mice were pretreated with Erbitux or received EGF-depleted amniotic fluid. EGFR is found on the cells in the intestine. EGF is found in the liquids that bathe the intestine, such as amniotic fluid.

Next, the researchers wanted to see whether decreased intestinal EGFR levels in the intestinal epithelium would attenuate the protective anti-TLR4 effects of amniotic fluid and put newborns at risk for NEC.

Newborn mice with NEC had lower intestinal EGFR expression than healthy newborn mice. EGFR levels were restored with daily enteral delivery of amniotic fluid. Moreover, premature human infants with NEC showed lower intestinal EGFR expression than fetuses at a comparable gestational age and premature infants whose NEC had resolved.

These results suggest a lack of amniotic fluid-mediated EGFR signaling could predispose premature infants to NEC. Results were published in the *Proceedings of the National Academy of Sciences*.

## Baby steps

The team's next steps include clinical trials of the amniotic fluid delivery strategy to prevent NEC in premature infants. The group thinks amniotic fluid itself is a viable treatment option but also is interested in teasing out factors that could be purified to complement EGF to prevent NEC, either by inhibiting TLR4 signaling or modulating other pathways.

"We have not made much progress for NEC, a disease that strikes often with little forewarning in the second to fourth week of life or beyond," said Barbara Warner, professor of pediatrics at the **Washington University in St. Louis School of Medicine**. "The holy grail is really prevention. It is actually intriguing to ponder use or reuse of amniotic fluid for prevention of NEC rather than administration of exogenous substances."

"If further studies would indicate a possible therapeutic role of amniotic fluid for preterm infants, then the immediate challenge is to be able to collect enough amniotic fluid at elective caesarean sections to make this treatment feasible," said Per Torp Sangild, professor of human nutrition at the **University of Copenhagen**. "In addition, if we were to install a donor amniotic fluid bank, it would also be important to exclude any detrimental immunological or other negative side effects of providing amniotic fluid from different mothers."

"There is actually a large amount of amniotic fluid that is discarded with every delivery. It could be collected readily at the time of delivery by simple aspiration, providing enough volume for daily delivery to the preterm infant," noted David Hackam, team leader of the Pittsburgh researchers, associate dean for medical student research, professor of surgery and associate professor of cell biology and physiology at the University of Pittsburgh School of Medicine and co-director of the Fetal Diagnosis and Treatment Center at the **Children's Hospital of Pittsburgh of UPMC**. "A donor amniotic fluid bank could be a further possibility."

"Ideally, the next step would be to identify the specific components of amniotic fluid—presumably soluble proteins—that explain the Pittsburgh group's experimental findings," said Daniel DiGiulio, clinical instructor of infectious diseases at the **Stanford University School of Medicine**.

"A slurry made of amniotic fluid proteins and given enterally to infants born prematurely could be used as an attempt to mimic the protective effects of amniotic fluid," said Peter Giannone, associate professor of pediatrics and director of neonatal-prenatal medicine at **The Ohio State University Wexner Medical Center** and director of neonatology at **Nationwide Children's Hospital**.

Sangild said that "future studies in other animal models are a natural next step to further characterize the effects of amniotic fluid, now elegantly demonstrated by Hackam and co-workers in a mouse model of NEC. Preterm pigs spontaneously develop this devastating disease

**"Ideally, the next step would be to identify the specific components of amniotic fluid—presumably soluble proteins—that explain the Pittsburgh group's experimental findings."**

**— Daniel DiGiulio,  
Stanford University  
School of Medicine**

and appear to be another good model to test the protective effects of amniotic fluid.” Preterm pigs would be easier to handle than 10-day-old mice in order to establish the delicate feeding and enteral delivery protocols and compare the effects of amniotic fluid to mother’s milk, he said. “Maternal milk contains a significant amount of EGF-like activity.”

He also said “it would be important to acknowledge that effects may potentially differ among species—mice, pigs and humans. My group has observed that TLR expression or signaling did not significantly correlate with NEC sensitivity in pigs. Although the role of the TLR4 system and EGFR is convincing in the mouse model, I think it will be important to further differentiate between early initiating events of NEC and the later pathology effects in both the mouse and pig NEC model.”

The changes in the TLR4 system and EGFR might be a consequence of the disease rather than an initiating cause, said Sangild. “If TLR4 and EGFR are shown to be factors that lead to NEC, attempts could be made to influence these systems by means other than amniotic fluid.”

Hackam agreed. “My team already has used computer-assisted drug design to produce TLR4 antagonists to dampen intestinal inflammation. We have tested the lead compounds in the newborn mouse model of NEC and in human intestinal tissues *ex vivo*. Results will be published in the near future,” he said. Hackam also has ongoing projects to use the compounds to dampen inflammation in arthritis and sepsis.

TLR4 inhibitors in development include **Eisai Co. Ltd.**’s eritoran, which is in Phase III testing to treat sepsis; **Takeda Pharmaceutical Co.**

**Ltd.**’s TAK-242, also in Phase III trials for sepsis; and **VBL Therapeutics Ltd.**’s VB-201, which is in Phase I testing for rheumatoid arthritis (RA) and Phase II trials for psoriasis and inflammatory disease.

A patent application for the work has been filed by the University of Pittsburgh School of Medicine and is available for licensing.

**Baas, T.** *SciBX* 5(30); doi:10.1038/scibx.2012.776

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2. Afrazi, A. *et al. Pediatr. Res.* **69**, 183–188 (2011)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Children’s Hospital of Pittsburgh of UPMC**, Pittsburgh, Pa.

**Eisai Co. Ltd.** (Tokyo:4523; Osaka:4523), Tokyo, Japan

**Nationwide Children’s Hospital**, Columbus, Ohio

**The Ohio State University Wexner Medical Center**, Columbus, Ohio

**Stanford University School of Medicine**, Stanford, Calif.

**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

**University of Copenhagen**, Copenhagen, Denmark

**University of Pittsburgh School of Medicine**, Pittsburgh, Pa.

**VBL Therapeutics Ltd.**, Or Yehuda, Israel

**Washington University in St. Louis School of Medicine**, St. Louis, Mo.

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# Drug design on the fly

By Joanne Kotz, Senior Editor

Researchers at the **University of California, San Francisco** and **Mount Sinai School of Medicine** have used a *Drosophila* cancer model to identify small molecule kinase inhibitors that target a discrete spectrum of kinases.<sup>1</sup> The lead molecule blocked tumor growth in a mouse model of medullary thyroid carcinoma better than the marketed kinase inhibitor Caprelsa vandetanib. An undisclosed pharma is negotiating to license the IP.

Because multiple kinase signaling pathways are often dysregulated in the same cancer, targeting several kinases simultaneously may have greater efficacy than attacking a single kinase.

Although most kinase inhibitors in the clinic block more than one kinase, typically these molecules had been originally developed against single kinase targets; thus, any therapeutic benefits gained from hitting additional kinases is a result of chance rather than design.

Rationally designing an inhibitor that hits multiple kinases has been difficult because of the challenges in determining the optimal choice of targets and optimizing a single molecule to have the appropriate multitarget selectivity.

To address some of those challenges, UCSF's Kevan Shokat teamed up with Mount Sinai's Ross Cagan. They set out to develop a *Drosophila*-based screen for libraries of small molecule inhibitors that target variable combinations of kinases.

Shokat is chair of the cellular and molecular pharmacology department at UCSF. Cagan is a professor in the Department of Developmental and Regenerative Biology and associate dean of the graduate school of biological sciences at Mount Sinai and also a cofounder of *Drosophila*-based drug discovery company **Medros Inc.**

For their screen, they chose a *Drosophila* model of Ret proto-oncogene (RET)-driven medullary thyroid carcinoma (MTC). RET is mutated in the germline in the familial form of MTC, which accounts for 25% of cases, as well as somatically mutated in 25%–50% of the remaining patients with sporadic MTC.

First, the researchers screened a library of small molecules that inhibited RET and a variable spectrum of other kinases in a *Drosophila* model of a hereditary form of MTC.

The top hit from the screen, which resulted in 25% of the flies surviving to adulthood, had greater efficacy and lower toxicity than Caprelsa. In contrast, a closely related analog of the top hit inhibited RET with nearly identical potency but showed a different kinase-specificity profile and had significantly decreased efficacy.

Thus, efficacy did not correlate solely with RET inhibition.

Caprelsa is marketed by **AstraZeneca plc** to treat MTC. The drug was originally developed as an inhibitor of VEGF receptor (VEGFR), with weaker activity against epidermal growth factor receptor (EGFR), but later was found to inhibit RET.

The team next sought to determine which kinase targets outside of RET contributed to efficacy and toxicity.

Tests of a panel of kinase inhibitors with different levels of efficacy and toxicity based on the initial screen in genetically altered *Drosophila* suggested inhibiting the *Drosophila* homologs of RET, Src, S6 kinase (S6K), BRAF and CRAF (RAF1) contributed to efficacy, whereas blocking the homolog of mammalian target of rapamycin (mTOR; FRAP; RAFT1) led to toxicity.

Based on that information, the team designed AD80, an analog of the top hit of the original screen that had greater activity against Src, BRAF and CRAF and lower activity against mTOR.

The optimized molecule had better activity. In the MTC *Drosophila* model, about 80% of the flies receiving AD80 survived to adulthood.

Last, the authors tested AD80 in a mouse xenograft model of familial MTC. The molecule decreased tumor growth and weight loss, a measure of toxicity, compared with Caprelsa.

Results were published in *Nature*.

“Finally, we have found a screening approach that will tell us about the therapeutic index” of multitargeted kinase inhibitors, said Shokat. He noted that the key to identifying hits was starting with a small molecule library directed against RET kinase, which really “reduced the complexity.”

“AD80 could not have been discovered in a cell-based screen. It is hitting multiple targets that define several key pathways,” said Cagan. Identifying multitargeted molecules with “complex polypharmacology is not suited to cell-based or *in vitro* screens,” he added.

“Any approach that establishes hypotheses for rational combinations should be considered

interesting because determining effective combinations preclinically is very difficult. There is quite some potential in this approach. You can ask the basic biological question of what combinations work best in a biological context that is well defined—that is powerful,” said Christoph Lengauer, CSO of **Blueprint Medicines**, which is developing context-specific targeted cancer therapeutics.

The challenge now, says Lengauer, will be preclinical optimization of AD80. Lengauer said that optimizing a multitargeted kinase inhibitor may be difficult, and it might be better to use the *Drosophila* assay to identify a relevant set of targets that can then be inhibited therapeutically with a combination of selective inhibitors of individual kinases.

“Undesirable off-target effects can be avoided more easily when focusing medicinal chemistry efforts on tailoring compounds toward the selective inhibition of a single target rather than a desired group of proteins,” he said. Lengauer noted that combining highly selective individual kinase inhibitors is the approach Blueprint intends to pursue.

Shokat countered that a single inhibitor with polypharmacology may have advantages. “My hunch is that a single compound is better

**“Any approach that establishes hypotheses for rational combinations should be considered interesting because determining effective combinations preclinically is very difficult. There is quite some potential in this approach. You can ask the basic biological question of what combinations work best in a biological context that is well defined—that is powerful.”**

**—Christoph Lengauer,  
Blueprint Medicines**

because it will not give super-potent inhibition of any one target but will generally dampen the overall pathway,” he said.

### Increasing complexity

Shokat’s team is pursuing preclinical optimization of AD80, including conducting IND-enabling studies. The researchers also plan to use the screening approach in more genetically complex cancers.

Mutant RET was the only oncogene in the current model, said Shokat. “We’re really interested now in cancers that have multiple genetic alterations,” he said.

Meanwhile, Cagan’s laboratory is developing models of colorectal cancer. “We went into the human sequencing database and asked, what are the most common combinations of mutations reported in human colorectal cancers? The most common quadruple mutation involves Ras, PTEN [MMAC1; TEP1], APC [adenomatous polyposis coli] and p53,” he said.

Cagan’s group has engineered the quadruple mutation into *Drosophila* models, as well as all single, double and triple combinations of those four mutations. “We built all the models in four months flat,” he noted. “What we are seeing is that there is a fundamental difference between one hit

or two hits compared with four hits in terms of sensitivity to drugs.”

His team also is building *Drosophila* models of lung and breast cancer based on the genomics of patients with cancer. “We are trying to embrace the complexity, not simplify it,” said Cagan.

UCSF and Mount Sinai have filed a patent application that covers composition of matter on the inhibitors identified and method of use for the *Drosophila* model.

**Kotz, J. *SciBX* 5(30); doi:10.1038/scibx.2012.777**  
Published online Aug. 2, 2012

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### COMPANIES AND INSTITUTIONS MENTIONED

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Blueprint Medicines**, Cambridge, Mass.  
**Medros Inc.**, St. Louis, Mo.  
**Mount Sinai School of Medicine**, New York, N.Y.  
**University of California, San Francisco**, Calif.

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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 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
<b>Autoimmune disease</b>				
Arthritis; ankylosing spondylitis	IL-23; IL-23 receptor	<p>Mouse studies suggest inhibiting IL-23 signaling in a T cell subpopulation could help treat nonrheumatoid arthritis spondyloarthropathies, such as ankylosing spondylitis. In a mouse model of passive collagen-induced arthritis, IL-23 led to joint inflammation. In the same model, an antibody targeting the IL-23 p19 subunit decreased disease severity and inflammation at tendon-bone attachment sites compared with an isotype control. In those mice, the inflammatory effects of IL-23 were mediated by a subpopulation of IL-23 receptor-positive T cells at tendon-bone attachment sites. Next steps could include evaluating inhibition of IL-23 signaling in additional spondyloarthropathy models.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.778</b> Published online Aug. 2, 2012</p>	Patent application filed covering methods to modulate IL-23 activity; licensing status unavailable	<p>Sherlock, J.P. <i>et al. Nat. Med.</i>; published online July 1, 2012; doi:10.1038/nm.2817</p> <p><b>Contact:</b> Daniel J. Cua, Merck Research Laboratories, Palo Alto, Calif. e-mail: <a href="mailto:daniel.cua@merck.com">daniel.cua@merck.com</a></p>
<b>Cancer</b>				
B cell lymphoma	MicroRNA-155 (miR-155)	<p>Mouse studies suggest inhibiting miR-155 with locked nucleic acids (LNAs) could help treat low-grade B cell lymphomas, such as Waldenström's macroglobulinemia (WM). In a mouse xenograft model of WM, LNA-mediated inhibition of miR-155 decreased tumor growth compared with no miR-155 inhibition. In a coculture of a human WM cell line and primary WM bone marrow stromal cells, LNA-mediated inhibition of miR-155 decreased proliferation. Researchers did not disclose next steps, which could include evaluating the miR-155-targeting LNAs in additional B cell lymphoma subtypes.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.779</b> Published online Aug. 2, 2012</p>	Patent and licensing status undisclosed	<p>Zhang, Y. <i>et al. Blood</i>; published online July 13, 2012; doi:10.1182/blood-2012-02-410647</p> <p><b>Contact:</b> Irene M. Ghobrial, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:irene_ghobrial@dfci.harvard.edu">irene_ghobrial@dfci.harvard.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Brain cancer	Cyclin dependent kinase 1 (CDK1; CDC2); CDK2; phosphoinositide 3-kinase (PI3K)	<p>Mouse and cell culture studies suggest combined inhibition of CDK1 and CDK2 could help improve the efficacy of PI3K inhibitors in glioma. In a human glioma cell line, a PI3K inhibitor plus the CDK1 and CDK2 inhibitor seliciclib increased apoptosis compared with either compound alone. In a mouse xenograft model of human glioma, a PI3K inhibitor in combination with a CDK1 and CDK2 inhibitor resulted in smaller tumors than either inhibitor alone. Next steps could include evaluating the combination therapy of a PI3K inhibitor and CDK1 and CDK2 inhibitor in clinical trials. Cyclacel Pharmaceuticals Inc. has seliciclib in Phase II testing or earlier to treat multiple cancers.</p> <p>Merck &amp; Co. Inc. and Ligand Pharmaceuticals Inc. have dinaciclib, a CDK inhibitor that targets both CDK1 and CDK2, in Phase II testing to treat multiple cancers.</p> <p>At least five other companies have CDK inhibitors in Phase II trials or earlier to treat various cancers.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.780</b> Published online Aug. 2, 2012</p>	Patent and licensing status unavailable	<p>Cheng, C.K. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 16, 2012; doi:10.1073/pnas.1202492109 <b>Contact:</b> Qi-Wen Fan, University of California, San Francisco, Calif. e-mail: <a href="mailto:qiwen.fan@ucsf.edu">qiwen.fan@ucsf.edu</a> <b>Contact:</b> William A. Weiss, same affiliation as above e-mail: <a href="mailto:waweiss@gmail.com">waweiss@gmail.com</a></p>
Brain cancer	Transient receptor potential vanilloid 1 (TRPV1; VR1)	<p>Mouse studies suggest TRPV1 agonists could help treat high-grade astrocytomas. In a mouse model of brain cancer, neural progenitor cells migrated to high-grade astrocytomas and released endovanilloids that agonized Trpv1 and induced cell death. These effects were not found in <i>Trpv1</i> knockout mice or older mice with low levels of neural progenitor cells. In the mouse brain cancer model, systemic delivery of the TRPV1 agonist arvanil decreased the size of high-grade astrocytomas and increased survival compared with vehicle. Next steps include developing vanilloids that can be used in humans.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.781</b> Published online Aug. 2, 2012</p>	Findings unpatented; licensing status not applicable	<p>Stock, K. <i>et al. Nat. Med.</i>; published online July 22, 2012; doi:10.1038/nm.2827 <b>Contact:</b> Rainer Glass, Ludwig Maximilian University of Munich, Munich, Germany e-mail: <a href="mailto:rainer.glass@med.uni-muenchen.de">rainer.glass@med.uni-muenchen.de</a></p>
Cancer	Cerebral cavernous malformation 2 (CCM2); serine/threonine kinase 25 (STK25)	<p><i>In vitro</i> studies suggest increasing STK25 activity could help treat pediatric neural cancers. In human embryonic fibroblasts, STK25-targeting small hairpin RNA decreased CCM2-dependent cell death compared with control shRNA. In 478 patients with neuroblastoma, high STK25 levels were correlated with increased overall survival. Next steps include identifying small molecules that affect the expression or interactions of STK25 and CCM2.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.782</b> Published online Aug. 2, 2012</p>	Unpatented; licensing status not applicable	<p>Costa, B. <i>et al. J. Biol. Chem.</i>; published online July 10, 2012; doi:10.1074/jbc.C112.345397 <b>Contact:</b> Mike Fainzilber, Weizmann Institute of Science, Rehovot, Israel e-mail: <a href="mailto:mike.fainzilber@weizmann.ac.il">mike.fainzilber@weizmann.ac.il</a> <b>Contact:</b> Barbara Costa, same affiliation as above e-mail: <a href="mailto:barbara.costa@weizmann.ac.il">barbara.costa@weizmann.ac.il</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Unknown	<p>Mouse and retrospective patient studies suggest cardiac glycosides such as digoxin could complement certain chemotherapies to help treat cancer. In mice, the cardiac glycosides digoxin and digitoxin both stimulated cell death in tumor cells and elicited a protective antitumor immune response. In a retrospective analysis of patients with carcinoma receiving chemotherapy, digoxin was associated with increased survival compared with no digoxin. Next steps include screening additional chemical libraries for inducers of immunogenic cell death and designing a clinical trial to evaluate the cardiac glycosides in patients with head and neck cancers.</p> <p>Digoxin and digitoxin are generic cardiac glycosides used to treat atrial fibrillation and atrial flutter.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.783</b> Published online Aug. 2, 2012</p>	<p>Two patent applications filed; available for licensing from the Gustave Roussy Institute <b>Contact:</b> Isabelle Pelletier-Bressac, Gustave Roussy Institute, Villejuif, France e-mail: <a href="mailto:isabelle.pelletier-bressac@igr.fr">isabelle.pelletier-bressac@igr.fr</a> phone: +33 (0)1 42 11 60 86</p>	<p>Menger, L. <i>et al. Sci. Transl. Med.</i>; published online July 18, 2012; doi:10.1126/scitranslmed.3003807 <b>Contact:</b> Guido Kroemer, Georges Pompidou European Hospital, Paris, France e-mail: <a href="mailto:kroemer@orange.fr">kroemer@orange.fr</a> <b>Contact:</b> Oliver Kepp, University of South Paris XI, Bicêtre, France e-mail: <a href="mailto:oliver.kepp@igr.fr">oliver.kepp@igr.fr</a></p>
Lymphoma; leukemia	RNA polymerase I (Pol I)	<p>Cell culture and mouse studies suggest inhibitors of Pol I could help treat hematological cancers. In a panel of cancer cells derived from human hematological malignancies expressing wild-type p53, the small molecule Pol I inhibitor CX-5461 induced apoptotic cell death. In mice transplanted with lymphoma cells expressing wild-type p53, CX-5461 decreased tumor burden in lymph nodes compared with vehicle. Next steps include testing CX-5461 in an Australian Phase I trial to treat hematological cancers in 2H12.</p> <p>Cylene Pharmaceuticals Inc. is developing CX-5461 (<i>see Cylene takes pol position in cancer, page 1</i>).</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.784</b> Published online Aug. 2, 2012</p>	<p>Patented by Cylene Pharmaceuticals; available for licensing</p>	<p>Bywater, M.J. <i>et al. Cancer Cell</i>; published online July 10, 2012; doi:10.1016/j.ccr.2012.05.019 <b>Contact:</b> Ross D. Hannan, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia e-mail: <a href="mailto:ross.hannan@petermac.org">ross.hannan@petermac.org</a></p>
Ovarian cancer	Not applicable	<p>Mouse and cell culture studies suggest tumor-specific nanoparticles encapsulating the mRNA of an artificial transcription factor could help treat ovarian cancer. In a murine ovarian cancer cell line, nanoparticles loaded with artificial transcription factor mRNA decreased viability and invasiveness compared with nanoparticles loaded with control mRNA. In a mouse model of epithelial ovarian carcinoma, tail vein injection of nanoparticles loaded with the artificial transcription factor mRNA decreased tumor growth compared with injection of control nanoparticles. Next steps include evaluating toxicity of the nanoparticles and scaling up production.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.785</b> Published online Aug. 2, 2012</p>	<p>Nanoparticle technology patented; available for licensing from the University of Pittsburgh</p>	<p>Lara, H. <i>et al. J. Biol. Chem.</i>; published online July 10, 2012; doi:10.1074/jbc.M112.360768 <b>Contact:</b> Pilar Blancafort, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: <a href="mailto:pilar_blancafort@med.unc.edu">pilar_blancafort@med.unc.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cardiovascular disease</b>				
Heart failure	Apelin receptor (APLNR; APJ); apelin (APLN)	<i>In vitro</i> and mouse studies suggest selectively targeting one of two APJ functions could help prevent left ventricular hypertrophy (LVH) that leads to heart failure. In pressure overload mouse models of heart failure, <i>Apj</i> knockouts showed less LVH than <i>Apln</i> knockouts, suggesting Apj also can promote hypertrophy independent of Apln-Apj signaling. In <i>Apln</i> -deficient mouse cardiomyocytes, mechanical stretch that mimicked pressure overload induced lower levels of hypertrophic markers in <i>Apj</i> -deficient cells than in <i>Apj</i> -expressing cells. Ongoing work includes testing compounds that agonize APJ's antihypertrophic function to treat LVH.  <b>SciBX 5(30); doi:10.1038/scibx.2012.786</b> <b>Published online Aug. 2, 2012</b>	Unpatented; available for licensing or partnering	Scimia, M.C. <i>et al. Nature</i> ; published online July 18, 2012; doi:10.1038/nature11263 <b>Contact:</b> Pilar Ruiz-Lozano, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: <a href="mailto:prlozano@stanford.edu">prlozano@stanford.edu</a>
<b>Infectious disease</b>				
Norovirus; viral infection	Ubiquitin specific peptidase 14 tRNA-guanine transglycosylase (USP14; TGT)	Cell culture studies suggest inhibiting cellular deubiquitinases such as USP14 could help prevent RNA virus infection. In murine macrophage cell lines, pretreatment with a small molecule USP14 inhibitor led to lower norovirus titers than vehicle pretreatment. In cell lines derived from humans and nonhuman primates, USP14 inhibitor pretreatment led to lower viral titers than vehicle pretreatment following infection by three types of RNA viruses. Next steps include improving the drug-like properties of the inhibitor and evaluating its efficacy against other pathogens <i>in vivo</i> .  <b>SciBX 5(30); doi:10.1038/scibx.2012.787</b> <b>Published online Aug. 2, 2012</b>	Patent pending covering deubiquitinase inhibitors and their methods of use; available for licensing from the University of Michigan Office of Technology Transfer	Perry, J.W. <i>PLoS Pathog.</i> ; published online July 5, 2012; doi:10.1371/journal.ppat.1002783 <b>Contact:</b> Christiane E. Wobus, University of Michigan Medical School, Ann Arbor, Mich. e-mail: <a href="mailto:cwobus@umich.edu">cwobus@umich.edu</a>
Staphylococcus	Staphopain A	Cell culture studies suggest inhibiting the <i>Staphylococcus aureus</i> cysteine protease staphopain A could help treat staphylococcal infection. In human cell culture, staphopain A blocked activation, recruitment and migration of neutrophils, which play a key role in the host immune response. Next steps include developing an animal model to evaluate the effects of targeting the protease.  <b>SciBX 5(30); doi:10.1038/scibx.2012.788</b> <b>Published online Aug. 2, 2012</b>	Unpatented; licensing status not applicable	Laarman, A.J. <i>et al. EMBO J.</i> ; published online July 31, 2012; doi:10.1038/emboj.2012.212 <b>Contact:</b> S.H.M. Rooijackers, University Medical Center Utrecht, Utrecht, the Netherlands e-mail: <a href="mailto:s.h.m.rooijackers@umcutrecht.nl">s.h.m.rooijackers@umcutrecht.nl</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Depression	Adiponectin (ADIPOQ)	<p>Mouse studies suggest increasing ADIPOQ signaling in the brain could help treat stress-induced depression. In a mouse model of chronic social defeat, intracerebroventricular injection of an Adipoq-neutralizing antibody increased social aversion compared with IgG control injection. In mice, intracerebroventricular injection of Adipoq decreased depression-associated behaviors compared with vehicle injection. Next steps could include elucidating the signaling pathways and molecular targets responsible for the antidepressant-like effects of ADIPOQ.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.789</b> Published online Aug. 2, 2012</p>	Patent and licensing status unavailable	<p>Liu, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 9, 2012; doi:10.1073/pnas.1202835109  <b>Contact:</b> Xin-Yun Lu, The University of Texas Health Science Center at San Antonio, San Antonio, Texas            e-mail: <a href="mailto:lux3@uthscsa.edu">lux3@uthscsa.edu</a></p>
Huntington's disease (HD)	Huntingtin (HTT)	<p>Mouse and nonhuman primate studies suggest transient knockdown of <i>HTT</i> expression could help treat HD. In transgenic mouse models of HD, intracerebroventricular infusion of an antisense oligonucleotide against <i>HTT</i> mRNA decreased <i>HTT</i> expression and increased both motor function and survival compared with infusion of saline. The beneficial effects persisted for up to nine months after stopping treatment. In a nonhuman primate model of HD, the oligonucleotide decreased <i>HTT</i> expression throughout the brain compared with vehicle control. Next steps include clinical development of the anti-<i>HTT</i> oligonucleotide. Isis Pharmaceuticals Inc. collaborated in this study and has an unnamed anti-<i>HTT</i> oligonucleotide in preclinical development for HD.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.790</b> Published online Aug. 2, 2012</p>	Patented by Isis Pharmaceuticals; available for licensing	<p>Kordasiewicz, H.B. <i>et al. Neuron</i>; published online June 21, 2012; doi:10.1016/j.neuron.2012.05.009  <b>Contact:</b> Don W. Cleveland, University of California, San Diego, La Jolla, Calif.            e-mail: <a href="mailto:dcleveland@ucsd.edu">dcleveland@ucsd.edu</a></p>
Huntington's disease (HD)	Peroxisome proliferation-activated receptor- $\gamma$ coactivator 1 $\alpha$ (PPARGC1A; PGC-1 $\alpha$ )	<p>Human studies suggest mutations in a newly identified region of <i>PPARGC1A</i> could be a prognostic marker of HD. Genomics analysis of brain and other tissues from healthy individuals identified a new promoter region in <i>PPARGC1A</i> that was associated with several brain-specific RNA transcripts encoding previously unknown isoforms of <i>PPARGC1A</i>. Genomics analysis also identified associations between a SNP in the new <i>PPARGC1A</i> region and the age of disease onset in patients with HD. Planned work includes determining the function of the new mutant and wild-type forms of <i>PPARGC1A</i> in neurons from patients with HD and healthy controls, respectively.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.791</b> Published online Aug. 2, 2012</p>	Unpatented; available for partnering	<p>Soyal, S.M. <i>et al. Hum. Mol. Genet.</i>; published online May 15, 2012; doi:10.1093/hmg/dds177  <b>Contact:</b> Wolfgang Patsch, Paracelsus Medical University, Salzburg, Austria            e-mail: <a href="mailto:wolfgang.patsch@pmu.ac.at">wolfgang.patsch@pmu.ac.at</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pain	NADPH oxidase 4 (NOX4)	<p>Mouse studies suggest NOX4 inhibitors could help treat neuropathic pain. In mouse models of peripheral nerve injury-induced neuropathic pain, <i>Nox4</i> knockout decreased hypersensitivity to mechanical stimuli compared with wild-type <i>Nox4</i> expression. Postinjury sciatic nerve tissue from <i>Nox4</i> knockout models had higher levels of reactive oxygen species and showed greater demyelination than nerve tissue from wild-type controls. Planned work includes testing NOX4 inhibitors in animal models of neuropathic pain.</p> <p>Genkyotex S.A. has GKT137831, a dual NOX1 and NOX4 inhibitor, in Phase I testing to treat diabetic nephropathy and in preclinical testing to treat pulmonary fibrosis.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.792</b> Published online Aug. 2, 2012</p>	Patented by Goethe University Frankfurt; available for licensing or partnering	<p>Kallenborn-Gerhardt, W. <i>et al. J. Neurosci.</i>; published online July 25, 2012; doi:10.1523/JNEUROSCI.6227-11.2012</p> <p><b>Contact:</b> Achim Schmidtke, Goethe University Frankfurt, Frankfurt, Germany e-mail: <a href="mailto:schmidtke@em.uni-frankfurt.de">schmidtke@em.uni-frankfurt.de</a></p>
<b>Various</b>				
Cancer; ophthalmic disease	Ataxia telangiectasia mutated (ATM)	<p>Mouse studies suggest inhibiting ATM kinase activity could help treat diseases associated with pathological angiogenesis, including cancer and choroidal neovascularization (CNV). In mice, global or endothelial cell-specific <i>Atm</i> deficiency decreased pathological angiogenesis in the retina compared with normal <i>Atm</i> expression. In a mouse xenograft model of melanoma, <i>Atm</i> knockout decreased tumor growth compared with normal <i>Atm</i> expression and showed a synergistic effect with VEGF inhibition. Next steps include developing an <i>in vivo</i> ATM inhibitor.</p> <p><b>SciBX 5(30); doi:10.1038/scibx.2012.793</b> Published online Aug. 2, 2012</p>	Unpatented; licensing status not applicable	<p>Okuno, Y. <i>et al. Nat. Med.</i>; published online July 15, 2012; doi:10.1038/nm.2846</p> <p><b>Contact:</b> Yoshiaki Kubota, Keio University, Tokyo, Japan e-mail: <a href="mailto:ykubo33@a3.keio.jp">ykubo33@a3.keio.jp</a></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 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
<b>Computational models</b>			
Whole-cell computational model for predicting phenotype from genotype	A whole-cell computational model could guide development of <i>in silico</i> drug discovery technologies. A whole-cell computational model of <i>Mycoplasma genitalium</i> was generated by integrating 28 models of various bacterial processes. Model simulations were then used to make predictions about DNA-binding protein interactions, the effects of metabolism on cell cycle regulation and energy distribution within the cell. Simulations of single-gene disruptions predicted whether a gene was essential to cell growth and survival with 79% accuracy. Next steps include developing computational models of more complex organisms.  <b>SciBX 5(30); doi:10.1038/scibx.2012.794</b> <b>Published online Aug. 2, 2012</b>	Provisional patent application filed; licensing details available from the Stanford University Office of Technology Licensing	Karr, J.R. <i>et al. Cell</i> ; published online July 20, 2012; doi:10.1016/j.cell.2012.05.044 <b>Contact:</b> Markus W. Covert, Stanford University, Stanford, Calif. e-mail: <a href="mailto:mcovert@stanford.edu">mcovert@stanford.edu</a>
<b>Drug delivery</b>			
Shear-activated nanoparticles for targeting drugs to obstructed blood vessels	Shear-activated nanoparticles could be useful for targeted delivery of drugs to obstructed blood vessels. Microscale aggregates of poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles were designed to remain intact under normal blood flow but to disintegrate into nanoparticles under the high shear stress of obstructed vessels. As proof of concept, the PLGA nanoparticles were coated with the clot-lysing tissue plasminogen activator (tPA) and formed into microscale aggregates. In a mouse model of pulmonary embolism, tPA-coated aggregates accumulated at the injury site, broke up into nanoparticle components and dissolved emboli, whereas soluble tPA at a 10-fold higher dose failed to resolve the clot. Next steps could include optimizing the size and improving the biocompatibility of the particles, scaling up manufacturing and testing in large animal models.  Roche's Genentech Inc. unit and Boehringer Ingelheim GmbH market the tPA Activase alteplase to treat acute ischemic stroke, pulmonary embolism and myocardial infarction.  <b>SciBX 5(30); doi:10.1038/scibx.2012.795</b> <b>Published online Aug. 2, 2012</b>	Patented; available for licensing or startup formation from the Wyss Institute for Biologically Inspired Engineering at Harvard University	Korin, N. <i>et al. Science</i> ; published online July 5, 2012; doi:10.1126/science.1217815 <b>Contact:</b> Donald E. Ingber, Boston Children's Hospital, Boston, Mass. e-mail: <a href="mailto:don.ingber@wyss.harvard.edu">don.ingber@wyss.harvard.edu</a>
<b>Drug platforms</b>			
Chemically modified bispecific antibodies	Chemically modified bispecific antibodies could be more effective than monovalent antibodies for treating cancer. The 50 kDa bispecific antibodies bound T cells and cancer cells and were chemically modified with a selenocysteine amino acid residue to improve their cancer cell specificity. In human cancer cell lines and primary tumor cells from a patient with mantle cell lymphoma (MCL), the bispecific antibodies showed greater cytotoxicity than monovalent antibodies. Next steps could include testing the bispecific antibodies in models of other cancer types.  <b>SciBX 5(30); doi:10.1038/scibx.2012.796</b> <b>Published online Aug. 2, 2012</b>	Patent and licensing status unavailable	Cui, H. <i>et al. J. Biol. Chem.</i> ; published online July 3, 2012; doi:10.1074/jbc.M112.384594 <b>Contact:</b> Christoph Rader, Scripps Florida, Jupiter, Fla. e-mail: <a href="mailto:crader@scripps.edu">crader@scripps.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Mn <sup>2+</sup> -peptide complex for preserving immunogenicity of irradiated vaccine epitopes	A radioprotective Mn <sup>2+</sup> -peptide complex could help improve the efficacy of vaccines generated from lethally irradiated viruses and bacteria. Ionizing radiation that renders bacteria and viruses noninfective for vaccine use can also damage the protein epitopes that elicit a protective immune response. <i>In vitro</i> , a Mn <sup>2+</sup> -peptide complex recovered from the radiation-resistant bacterium <i>Deinococcus radiodurans</i> preserved the immunogenicity of both irradiated $\lambda$ bacteriophage and methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) proteins. In mice, immunization with an irradiated MRSA test vaccine prepared with the Mn <sup>2+</sup> -peptide complex protected against skin MRSA infection, whereas the same test vaccine prepared without the complex did not. Proof-of-concept animal studies are ongoing for a candidate vaccine against Venezuelan equine encephalitis virus, and vaccine candidates against other viruses are planned.  <b>SciBX 5(30); doi:10.1038/scibx.2012.797</b> <b>Published online Aug. 2, 2012</b>	Patent pending; available for licensing from the Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. Office of Technology Transfer <b>Contact:</b> Jonathan Gottlieb, Henry M. Jackson Foundation for the Advancement of Military Medicine Inc., Bethesda, Md. e-mail: <a href="mailto:jgottlieb@hjf.org">jgottlieb@hjf.org</a> phone: 240-694-2633	Gaidamakova, E.K. <i>et al. Cell Host Microbe</i> ; published online July 19, 2012; doi:10.1016/j.chom.2012.05.011 <b>Contact:</b> Michael J. Daly, Uniformed Services University of the Health Sciences, Bethesda, Md. e-mail: <a href="mailto:mdaly@usuhs.edu">mdaly@usuhs.edu</a> <b>Contact:</b> Sandip K. Datta, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:dattas@niaid.nih.gov">dattas@niaid.nih.gov</a>
Cord blood-derived induced neuronal cells (CB-iNCs)	<i>In vitro</i> and mouse studies suggest human CB-iNCs could be used to treat and study neuronal disorders. In isolated prominin 1 (PROM1; CD133)-expressing human cord blood cells, retrovirus-mediated expression of SOX2 and c-Myc (MYC) led to neuronal marker expression and differentiation into mature neuronal-like cells that could fire action potentials. In mice, fluorescently labeled CB-iNCs transplanted into the hippocampus integrated into host tissue and differentiated into functional neurons. Next steps include developing a protocol to create homogeneous neuronal populations.  <b>SciBX 5(30); doi:10.1038/scibx.2012.798</b> <b>Published online Aug. 2, 2012</b>	Patent application filed; available for licensing	Giorgetti, A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 18, 2012; doi:10.1073/pnas.1209523109 <b>Contact:</b> Juan Carlos Izpisua Belmonte, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: <a href="mailto:belmonte@salk.edu">belmonte@salk.edu</a> <b>Contact:</b> Fred H. Gage, same affiliation as above e-mail: <a href="mailto:gage@salk.edu">gage@salk.edu</a>
Crystal structure of the JH2 domain of Janus kinase-2 (JAK-2)	<i>In vitro</i> studies identified the crystal structure of the JH2 domain of JAK-2, which could guide the development of new drugs to treat myeloproliferative disorders. Activating mutations in the JH2 domain of JAK-2 are associated with myeloproliferative disorders, but most JAK-2 inhibitors target the protein's catalytic JH1 domain. Crystallography studies of JAK-2 showed that the JH2 mutant stabilizes an $\alpha$ -helix in the N-terminal lobe of JH2 to increase phosphorylation of JH1. Next steps include screening for compounds that can bind the V617F JH2 mutant and reduce JAK-2 kinase activity to basal levels.  At least 10 companies have JAK-2 inhibitors in development stages ranging from preclinical to marketed to treat myeloproliferative disorders and various cancers.  <b>SciBX 5(30); doi:10.1038/scibx.2012.799</b> <b>Published online Aug. 2, 2012</b>	Provisional patent application filed; unavailable for licensing	Bandaranayake, R.M. <i>et al. Nat. Struct. Mol. Biol.</i> ; published online July 22, 2012; doi:10.1038/nsmb.2348 <b>Contact:</b> Stevan R. Hubbard, New York University School of Medicine, New York, N.Y. e-mail: <a href="mailto:stevan.hubbard@med.nyu.edu">stevan.hubbard@med.nyu.edu</a> <b>Contact:</b> Olli Silvennoinen, University of Tampere and Tampere University Hospital, Tampere, Finland e-mail: <a href="mailto:olli.silvennoinen@uta.fi">olli.silvennoinen@uta.fi</a>
Genetic sequencing using nanochannel arrays	Sequencing studies suggest nanochannel arrays could be used for <i>de novo</i> genome sequencing. Sequencing using the nanochannel arrays involves electric field-driven movement of long, uncoiled, fluorescently labeled DNA molecules into a microfluidic chip in which they are held in individual nanochannels and automatically imaged to generate genome sequence maps. The approach generated sequence motif maps of 95 bacterial artificial chromosome clones covering the structurally diverse major histocompatibility complex and identified structural variants, haplotype differences and errors in assembly in the available reference sequences. Next steps could include using the technique to sequence structurally diverse diploid genomic regions.  <b>SciBX 5(30); doi:10.1038/scibx.2012.800</b> <b>Published online Aug. 2, 2012</b>	Patent and licensing status unavailable	Lam, E.T. <i>et al. Nat. Biotechnol.</i> ; published online July 15, 2012; doi:10.1038/nbt.2303 <b>Contact:</b> Pui-Yan Kwok, University of California, San Francisco, Calif. e-mail: <a href="mailto:pui.kwok@ucsf.edu">pui.kwok@ucsf.edu</a> <b>Contact:</b> Ming Xiao, Drexel University, Philadelphia, Pa. e-mail: <a href="mailto:ming.xiao@drexel.edu">ming.xiao@drexel.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Nanozymes for antiviral therapy	Nanoparticle-based, RNA-silencing complexes called nanozymes could be useful for antiviral therapy. The nanozymes consisted of gold nanoparticles linked to RNase A and loaded with DNA oligonucleotides targeting viral RNA. In cultured cells infected with HCV, nanozymes targeting HCV NS5A mRNA decreased NS5A protein levels by about 75% compared with control nanoparticles without RNase A. In a mouse model of HCV infection, the HCV NS5A-targeted nanozyme decreased HCV RNA levels compared with control nanoparticles. Next steps include evaluating the long-term efficacy of nanozyme-based treatments of HCV and other viral infections.  <b>SciBX 5(30); doi:10.1038/scibx.2012.801</b> <b>Published online Aug. 2, 2012</b>	Patent pending; available for licensing from the University of Florida <b>Contact:</b> Lenny Terry, University of Florida, Gainesville, Fla. e-mail: <a href="mailto:lterry@ufl.edu">lterry@ufl.edu</a> phone: 352-392-8929	Wang, Z. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 16, 2012; doi:10.1073/pnas.1207766109 <b>Contact:</b> Y. Charles Cao, University of Florida College of Medicine, Gainesville, Fla. e-mail: <a href="mailto:cao@chem.ufl.edu">cao@chem.ufl.edu</a> <b>Contact:</b> Chen Liu, same affiliation as above e-mail: <a href="mailto:liu@pathology.ufl.edu">liu@pathology.ufl.edu</a>
<b>Instrumentation</b>			
Combined photoacoustic and ultrasonic endoscopy system for <i>in vivo</i> imaging of soft tissues	An imaging system that combines photoacoustic and ultrasonic endoscopy could help improve <i>in vivo</i> imaging of soft tissues. In rabbits, the endoscopic system generated 3D visualization of a 14 cm-long and 18 mm-diameter volume that included the esophagus, its surrounding tissue and proximal organs. In rats, the system generated 3D visualizations of the lower gastrointestinal and lymphatic systems and enabled high-resolution visualization of vasculature, revealing optical and mechanical contrast differences not visible to ultrasonic endoscopy. Next steps include running clinical studies to test the system.  <b>SciBX 5(30); doi:10.1038/scibx.2012.802</b> <b>Published online Aug. 2, 2012</b>	Patent application filed; licensing status undisclosed	Yang, J.-M. <i>et al. Nat. Med.</i> ; published online July 15, 2012; doi:10.1038/nm.2823 <b>Contact:</b> Lihong V. Wang, Washington University in St. Louis, St. Louis, Mo. e-mail: <a href="mailto:lhwang@biomed.wustl.edu">lhwang@biomed.wustl.edu</a> <b>Contact:</b> Qifa Zhou, University of Southern California, Los Angeles, Calif. e-mail: <a href="mailto:qifazhou@usc.edu">qifazhou@usc.edu</a>
<b>Markers</b>			
Serum biomarker for Alzheimer's disease (AD)	A study in patients with AD suggests low plasma levels of apolipoprotein E (APOE) could help predict AD onset. In 396 patients with mild cognitive impairment, an early stage of AD, compared with healthy control subjects, the AD-associated <i>APOE4</i> allele was associated with lower plasma levels of APOE. After one year, patients from this cohort who advanced to full AD had lower plasma levels of APOE than patients whose disease did not progress. Next steps could include replicating the findings in a larger cohort and studying the relationship between APOE levels and other plasma markers.  <b>SciBX 5(30); doi:10.1038/scibx.2012.803</b> <b>Published online Aug. 2, 2012</b>	Patent and licensing status undisclosed	Soares, H.D. <i>et al. Arch. Neurol.</i> ; published online July 16, 2012; doi:10.1001/archneurol.2012.1070 <b>Contact:</b> Holly D. Soares, Bristol-Myers Squibb Co., Wallingford, Conn. e-mail: <a href="mailto:holly.soares@bms.com">holly.soares@bms.com</a>
Subtype-specific somatic mutations in medulloblastoma	Identification of new subtype-specific somatic mutations in medulloblastoma could aid the development of new treatments for the disease. Whole-exome hybrid capture and deep sequencing of 92 primary medulloblastoma samples identified 12 genes mutated at statistically significant frequencies, including new mutations in four genes: <i>DEAD box polypeptide 3 X-linked (DDX3X)</i> , <i>G protein pathway suppressor 2 (GPS2)</i> , <i>BCL6 co-repressor (BCOR)</i> and <i>LIM domain binding 1 (LDB1)</i> . The <i>DDX3X</i> mutations were associated with mutant <i><math>\beta</math>-catenin (CTNNB1)</i> in medulloblastoma. The <i>GPS2</i> , <i>BCOR</i> and <i>LDB1</i> mutations were associated with nuclear co-repressor signaling pathways in the disease. Next steps include determining whether targeting the genes and pathways results in a biological or therapeutic effect.  <b>SciBX 5(30); doi:10.1038/scibx.2012.804</b> <b>Published online Aug. 2, 2012</b>	Unpatented; licensing status not applicable	Pugh, T.J. <i>et al. Nature</i> ; published online July 22, 2012; doi:10.1038/nature11329 <b>Contact:</b> Yoon-Jae Cho, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:yjcho1@stanford.edu">yjcho1@stanford.edu</a> <b>Contact:</b> Scott L. Pomeroy, same affiliation as above e-mail: <a href="mailto:scott.pomeroy@childrens.harvard.edu">scott.pomeroy@childrens.harvard.edu</a> <b>Contact:</b> Matthew Meyerson, same affiliation as above e-mail: <a href="mailto:matthew_meyerson@dfci.harvard.edu">matthew_meyerson@dfci.harvard.edu</a>

