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SciBX: Science-Business eXchange will not be published on Dec. 22 and Dec. 29. It will resume its schedule the week of Jan. 5, 2012.

Splicing out BRAF's resistance

By Kai-Jye Lou, Staff Writer

U.S. researchers have uncovered a mechanism by which melanomas expressing mutant BRAF acquire resistance to targeted drugs.¹ The findings represent the first time a splice variant has been implicated in cancer drug resistance. The findings give companies a new resistance mechanism to screen against in the design of next-generation BRAF inhibitors and also further the case for combining Zelboraf with downstream kinase inhibitors.

BRAF is part of the Ras/Raf/MEK/MAPK signaling cascade, which is collectively known as the MAPK pathway. Activating mutations in BRAF—which result in tumor dependency on the MAPK signaling cascade—are found in about half of melanoma cases. The V600E mutation is by far the most predominant and occurs in about 90% of melanomas driven by mutant BRAF.²

In August, the FDA approved Zelboraf vemurafenib to treat unresectable or metastatic melanoma with the BRAF V600E mutation. The agency concurrently approved the cobas 4800 BRAF V600 Mutation Test from Roche for detecting the mutation. Zelboraf is marketed by Roche's Genentech Inc. unit and co-promoted with Daiichi Sankyo Co. Ltd. Daiichi gained the small molecule when it acquired Plexxikon Inc. for \$805 million in April.

Unsurprisingly, there have been documented cases of resistance to Zelboraf,²⁻⁶ but none was known to be mediated by alterations in BRAF.

"Vemurafenib is the most active agent identified in melanoma patients to date, but as with many other cancer therapies, resistance to this drug invariably develops over time," said David Solit, laboratory head in the human oncology and pathogenesis program at the Memorial Sloan-Kettering Cancer Center. "Thus, identifying the underlying mechanisms of resistance is critical in order to improve the care of these patients."

Now, a team led by Solit has identified an acquired resistance mechanism mediated by a structural change in BRAF itself.

The researchers first generated five Zelboraf-resistant clones from a human melanoma cell line carrying the V600E mutation. In 3 of the Zelboraf-resistant lines, cells expressed a truncated 61 kDa BRAF splice variant that lacked a domain responsible for binding Ras, an upstream GTPase in the MAPK signaling cascade. This domain prevents the dimerization of BRAF when Ras activation levels are low.⁷

Compared with full-length V600E, the truncated splice variant showed an increased ability to dimerize. Importantly, the researchers



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found that by introducing a mutation that prevented dimerization, the splice variant gained sensitivity to Zelboraf.

The group also looked at samples from 19 patients with V600E mutant melanomas that had acquired resistance to Zelboraf. Six of those samples expressed truncated BRAF transcripts lacking the exons encoding the Ras-binding domain. In contrast, truncated BRAF transcripts were not detected in melanomas that were vemurafenib-naïve or intrinsically resistant to BRAF inhibitors.

Results were published in *Nature*.

“Not only was the mechanism of resistance to vemurafenib identified by our group novel, but the generation of splice variants is in fact a novel paradigm of drug resistance in general and one that may be applicable in the setting of other kinase inhibitor-directed therapies,” said Solit, who is corresponding author on the paper.

Martin McMahon, the Efim Guzik distinguished professor of cancer biology at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, agreed.

“This is the first time in cancer where the mechanism of drug resistance is found to be due to a change in splicing,” he told SciBX. “The implication is that if this resistance mechanism is the case for BRAF in melanomas, it could also be the case for other genes in other forms of cancer.”

“This research further supports much of what we are already doing, as it suggests that combinations may be a potentially effective treatment strategy in the future.”

—Chris Bowden,
Genentech Inc.

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Combos and considerations

In addition to supporting the idea of combining Zelboraf with inhibitors of other members of the MAPK signaling cascade, drug developers can now consider the mechanism when designing new drugs.

“The role of Ras in mediating dimerization and the bypass of this need by alternative splice forms of oncogenic BRAF are important insights that are elegantly stressed in this manuscript,” said Gideon Bollag, SVP of research at Plexxikon. “The alternative splice forms can be identified by diagnostic tests,” and cells expressing the resistant splice form provide a model to identify combination or next-generation therapies, he added.

McMahon added that the results in the paper support going after multiple targets along the same signaling cascade.

Indeed, the Sloan-Kettering group showed that the Zelboraf-resistant cell lines were still sensitive to MEK inhibitors, which act downstream of BRAF.

Chris Bowden, VP of product development for clinical oncology at Genentech and the clinical lead on Zelboraf, noted that Genentech already is exploring combinations of Zelboraf with both biologics and other targeted therapies.

“This research further supports much of what we are already doing, as it suggests that combinations may be a potentially effective treatment strategy in the future,” said Bowden. “For example, we are researching this in a Phase I study of Zelboraf and GDC-0973, an investigational MEK inhibitor, in people with newly diagnosed V600E-positive melanoma and in those whose melanoma has progressed while on treatment with Zelboraf.”

Genentech received worldwide rights to GDC-0973 from **Exelixis Inc.** in 2008.

Bollag said Plexxikon is working on next-generation inhibitors that it hopes to advance into the clinic next year. He added that the

truncated BRAF splice variant and resistant cell lines described in the paper could be valuable reagents for screening and identifying such inhibitors.

Solit said his group is screening additional patients to get a better estimate of the prevalence of the truncated BRAF splice variant in melanoma.

“We are also looking to use the information to develop more effective BRAF inhibitors or combinations of inhibitors that work in patients who have developed this form of drug resistance,” he told *SciBX*.

Sloan-Kettering has a pending patent covering the work reported in *Nature*. The licensing status is undisclosed.

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COMPANIES AND INSTITUTIONS MENTIONED

Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568), Tokyo, Japan
Exelixis Inc. (NASDAQ:EXEL), South San Francisco, Calif.
Genentech Inc., South San Francisco, Calif.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Plexxikon Inc., Berkeley, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of California, San Francisco, Calif.

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TRND take two

By Chris Cain, Staff Writer

With 14 projects in place, the NIH's Therapeutics for Rare and Neglected Diseases program has a full plate. Now, the program will shift focus from finding projects to building infrastructure and advancing compounds into the clinic.

In May 2009, NIH spent \$24 million to launch Therapeutics for Rare and Neglected Diseases (TRND), with the goal of advancing the preclinical development of compounds.¹ Since its inception, TRND has started a total of 15 projects—5 pilot projects initially, followed by 4 projects in July² and 6 projects last month. Thus far, only one pilot project has been discontinued. Eight projects involve at least one biotech company.

Each of the 14 remaining projects targets a unique mechanism of action across 13 distinct rare or neglected disease areas (see Table 1, "TRND partnerships").

According to TRND director John McKew, the 14 projects represent "a full load with the current budget constraints" that TRND will maintain moving forward, using additional application rounds to replace completed projects or those that fail to meet program milestones. He expects to open a third round of applications next spring.

McKew, who also is chief of the Therapeutics Development Branch at the NIH Center for Translational Therapeutics, told *SciBX* the six projects started last month represent the end result of a year-long solicitation process in which TRND presented program details at road-show meetings across the U.S. The applications TRND received were roughly split between academic teams and biotechs and were evaluated by a panel of about 25 scientists from academia and industry with experience in drug development.

"The application evaluation was something we specifically put together for TRND. It has mid- to high-level folks in pharma or biotech and venture capitalists who have day jobs evaluating projects and portfolios. We filled it in with academics who have successfully developed therapeutics in a former life or within an academic setting," said McKew.

Table 1. TRND partnerships. List of NIH Therapeutics for Rare and Neglected Diseases (TRND) partnerships as of Dec. 12, 2011.

Source: NIH Center for Translational Therapeutics

Company/institution	Compound	Target/mechanism	Indication
Pilot projects			
AesRx LLC	Aes-103	Small molecule that binds sickle hemoglobin	Sickle cell disease
New Zealand Pharmaceuticals Ltd./National Human Genome Research Institute	N-Acetyl-D-mannosamine (ManNAc)	Correct sialic acid deficiency	Hereditary inclusion body myopathy (hIBM)
Leukemia & Lymphoma Society/The University of Kansas Medical Center/National Heart, Lung, and Blood Institute	Auranofin	Selectively kills chronic lymphocytic leukemia (CLL) cells	CLL
Niemann-Pick Type C disease foundations/Washington University in St. Louis/Albert Einstein College of Medicine of Yeshiva University	2-Hydroxypropyl-β-cyclodextrin (HPBCD)	Reduction of cholesterol and sphingolipid storage	Niemann-Pick disease type C1 (NPC1)
First round of solicited projects			
Afraxis Inc.	Not applicable	p21 protein (Cdc42 Rac)-activated kinase (PAK) inhibitor	Fragile X syndrome
ReveraGen Biopharma Inc.	VBP15	Modified glucocorticoid with fewer side effects	Duchenne muscular dystrophy (DMD)
Viamet Pharmaceuticals Inc.	VT-1129	Cytochrome P450 C-14 α-demethylase (CYP51) inhibitor	Cryptococcal meningitis
National Human Genome Research Institute	Not applicable	Inhibitor of core binding factor (CBF) protein interactions	CBF-driven acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL)
Second round of solicited projects			
Harvard Medical School	Dorsomorphin derivative (small molecule)	Bone morphogenetic protein type I receptor inhibitor	Fibrodysplasia ossificans progressiva
Lumos Pharma Inc.	CincY, an undisclosed repurposed molecule with an inactive IND	Blood brain barrier-penetrant creatine mimetic	X-linked creatine transporter defect (CTD)
The University of Alabama at Birmingham	CMX001, a lipophilic derivative of cidofovir	CNS-penetrant double-stranded DNA viral synthesis inhibitor	Neonatal herpes simplex virus infection
Concert Pharmaceuticals Inc.	Deuterium-modified praziquantel derivative	Small molecule antischistosome	Schistosomiasis
AVI BioPharma Inc.	AVI-5038, a phosphorodiamidate morpholino oligomer targeting <i>dystrophin</i> exon 50	Corrects <i>dystrophin</i> exon 50 splicing defect	Duchenne muscular dystrophy (DMD)
Cincinnati Children's Hospital Medical Center	Inhaled formulation of granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2)	Restore GM-CSF function	Pulmonary alveolar proteinosis

After the review period, TRND took the top-scoring applications, signed confidentiality agreements and performed due diligence.

McKew said the process became more efficient over time. “Round one was the first time our reviewers got together—we gave them directions without knowing exactly how it would work. Since then, we have refined the application, provided more detailed guidance to the reviewers and learned how to more efficiently conduct due diligence.”

For example, McKew said the program has become proficient at signing IP agreements. He said it can take as little as six to eight weeks for TRND and its partners to agree to a cooperative research and development agreement (CRADA) upon acceptance of a detailed project plan.

Seeking rare success

The second-round winners include a trio of biotechs. **AVI BioPharma Inc.** and **Concert Pharmaceuticals Inc.** are applying their antisense and deuteration technologies, respectively, to rare and neglected diseases. The third company, **Lumos Pharma Inc.**, is seeking to treat creatine transporter deficiency (CTD) with a small molecule creatine mimetic.

AVI is conducting preclinical safety studies of a phosphorodiamidate morpholino oligomer, AVI-5038, that corrects splicing defects in exon 50 of the *dystrophin* gene to treat Duchenne muscular dystrophy (DMD). The company’s lead product, Eteplirsen, which is in Phase II trials, uses the same technology to treat a distinct set of DMD patients with splicing defects in exon 51.

Concert is running preclinical studies of a deuterated form of praziquantel, a generic antischistosomiasis drug that requires repeated high dosing. The Concert compound has shown better stability *in vitro* than the parent molecule.

Lumos is developing a blood brain barrier–penetrant creatine mimetic to treat X-linked CTD. The disease is caused by mutation of a creatine transporter, limiting the availability of creatine in the brain and leading to mental disability.

“Prevalence studies have pretty consistently pegged CTD as the number-two cause of X-linked mental disability, with about 800–1,000 patients being born every year,” said Joseph Clark, professor of neurology at the **University of Cincinnati College of Medicine**. “This is a profoundly debilitating disease.”

There is no approved treatment for CTD.

Lumos spun out of the university based on Clark’s work in animal models of CTD. The company’s compound is a repurposed small molecule with an inactive IND for an undisclosed, acute indication. The TRND project seeks to complete IND-enabling chemistry,

manufacturing and controls, and toxicology studies, which are necessary because use in CTD patients would be chronic.

“We are building 40,000 square feet of space, with support for medicinal chemistry, scaled-up small molecule production and analytic space to do additional pharmacology studies. We’re also working to get an animal facility for pharmacokinetic studies.”

—*John McKew,*
National Institutes of Health

A growing TRND

McKew says a focus for TRND over the next year will be to complete development of additional infrastructure to improve internal preclinical development capabilities.

“We are building 40,000 square feet of space, with support for medicinal chemistry, scaled-up small molecule production and analytic space to do additional pharmacology studies. We’re also working to get an animal facility for pharmacokinetic studies.”

TRND has a staff of 25–30 individuals and an annual budget of \$24 million. TRND plans to hire more people to work in the lab space as it comes online.

McKew emphasized that a key goal for TRND in 2012 is bringing additional compounds into clinical testing.

He noted that two INDs have now been filed for two small molecules from TRND projects—Aes-103 from **AesRx LLC** to treat sickle cell disease and Auranofin developed in collaboration with the **Leukemia & Lymphoma Society**, **The University of Kansas Medical Center** and the **National Heart, Lung, and Blood Institute** for chronic lymphocytic leukemia (CLL). The first patient in the CLL project has been dosed in a Phase II trial at the University of Kansas Medical Center.

Aes-103 is a small molecule that increases the affinity of sickle cell hemoglobin for oxygen. Auranofin is a repurposed rheumatoid arthritis compound, marketed as Ridaura auranofin by **Prometheus Laboratories Inc.**

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COMPANIES AND INSTITUTIONS MENTIONED

AesRx LLC, Newton, Mass.
AVI BioPharma Inc. (NASDAQ:AVII), Bothell, Wash.
Concert Pharmaceuticals Inc., Lexington, Mass.
Leukemia & Lymphoma Society, White Plains, N.Y.
Lumos Pharma Inc., Austin, Texas
National Institutes of Health, Bethesda, Md.
National Heart, Lung, and Blood Institute, Bethesda, Md.
NIH Center for Translational Therapeutics, Bethesda, Md.
Prometheus Laboratories Inc., San Diego, Calif.
University of Cincinnati College of Medicine, Cincinnati, Ohio
The University of Kansas Medical Center, Kansas City, Kansas

Picturing pathology

By Tracey Baas, Senior Editor

A **Stanford University** team has developed a computational pathology system called C-Path that provides more accurate prognostic scores of breast cancer tissue than classical pathology.¹ The next steps are modifying the method to handle whole-tissue slide samples and seeing how it performs in a prospective, multicenter trial.

Traditionally, pathologists visually characterize the type and aggressiveness of breast cancer using only three cellular features—the percentage of tumor made up of tubular structures, the diversity of nuclei in cells and the frequency of cell division—and assign prognostic scores based on a scale first proposed in the 1920s. Identifying tissue types as skin, duct or organ lining (the epithelia) or connective tissue (the stroma) is an important part of the grading system.

A Stanford group led by Daphne Koller, professor of computer science, hypothesized that computer-aided analysis of digital images of tumor samples might identify new, clinically relevant cellular features and more accurately predict patient outcomes.

The first step was getting C-Path to differentiate stromal regions from epithelial regions of breast cancer samples. To do so, the group used digital images from breast cancer tissue microarrays obtained from patients with a known prognosis.

The team used image processing techniques to define a range of features that characterize the epithelial regions and stromal regions. The group also included many features that describe the more global, spatial structure of the tumor. Altogether, the researchers created a 6,642-feature set, the majority of which had not been previously used in analysis of pathology samples.

Next, the researchers used the known patient prognoses and the 6,642-feature set to construct C-Path such that it learned a scoring system predictive of patient outcome. As proof of concept, the group used C-Path to analyze digital images from a second cohort, obtained from a different hospital and a different patient population. The scores were significantly associated with overall survival ($p=0.001$).

C-Path evaluated data from breast cancer tissue microarrays containing sample cores that were 0.6 mm in diameter. Pathologists graded the same tissue microarray images as C-Path and found no significant association with survival ($p=0.4$). Pathologists typically use a microscope to study larger tissue samples fixed on a glass slide.

Further computational analysis showed only 11 of the 6,642 features—8 epithelial and 3 stromal—significantly contributed to the model's scoring system. In addition, the stromal features were a stronger predictor of patient outcomes than the epithelial features.

"A particularly interesting aspect of their study was that they found stromal features to be more predictive than epithelial features," said Gerardo Fernandez, medical director for digital pathology at **Roche's Ventana Medical Systems Inc.** unit. "Pathologists have been focusing on the same three microscopic epithelial features for almost a hundred years. Koller's study suggests that some of the stromal features might be equally informative."

Data were published in *Science Translational Medicine*. The work is currently unpatented and is available for licensing from Stanford

University. C-Path was built to work on **Definiens AG's** Developer XD image analysis platform.

Sample size

Despite C-Path's improved prognostic ability versus the naked eye, lead author Andrew Beck does not think pathologists are headed for extinction.

"I see the field of pathology thriving as more and more biological and computational tools are developed to extract larger and larger amounts of data from tissue samples," said Beck, who now is an assistant professor of pathology at **Harvard Medical School**. "I envision a future where pathologists have access to computational tools to assist with many tasks which are currently done manually. I think these technologies will enhance the practice of pathology."

Nevertheless, it's likely that more testing will be required before pathologists will revamp their standard procedures.

"Aside from the significant regulatory challenges in removing the physician from the diagnosis, the importance of clinical factors, tissue context and the inherent heterogeneity of cancer, and thus its diagnosis, will mean that computer assistance and imaging tools like these will remain an aid to pathologists for some time to come," said Steve Burnell, lifecycle leader for digital pathology and workflow at Roche Diagnostics.

One issue is that C-Path's calculations might have put pathologists at an unfair disadvantage. "The Stanford team had two separate groups of patient samples to work with but included a portion of one group to both train and test C-Path," said Ventana's Fernandez. "Ideally, one wants to use one group of samples to train and a separate group of samples to test" to avoid the potential of over-fitting the features.

Jared Schwartz, CMO at digital pathology company **Aperio Technologies Inc.**, said the small tumor sample size used by C-Path could increase the odds of errors. "Tumors have great heterogeneity, and thus sampling issues are a major hurdle. The smaller the biopsies, the greater the sampling errors. Most pathologists would want to collect more than one biopsy sample per patient to get a complete look at the tumor."

But with the right samples, Schwartz added, C-Path "demonstrates that increasingly powerful tools will be available to enhance pathologists' ability to provide more and hopefully more precise diagnostic information to improve patient outcomes."

Koller agreed. C-Path's "performance is considerably better when we have more than one sample from each tumor," she said.

Burnell wanted Koller's team to show that C-Path can handle the inherent variability and more complex processing that comes from looking at a larger surface area of tumor tissue.

Koller thinks looking at more tissue would actually improve C-Path's performance. "I would expect performance might get even better with whole-slide images, although we haven't really done that experiment," she said. "Moving from small tumor samples to whole-slide images is not a huge barrier."

Fernandez added that what he would like to see is more biological and pathological context extrapolated from the morphological features that C-Path uses to score samples. "They found clinically significant features based on outcome," he said. "Not all, however, had a sound pathological

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Priming chemo prediction

By Chris Cain, Staff Writer

Researchers at the **Dana-Farber Cancer Institute** have developed an *in vitro* assay that predicts patient response to chemotherapy by directly measuring how prone cells are to apoptosis.¹ **Eutropics Pharmaceuticals Inc.** has exclusively licensed the assay and is pursuing it as a prognostic indicator of chemotherapy effectiveness in multiple cancers.

Chemotherapy resistance is difficult to predict because many distinct pathways lead to resistance in different cancers. One common mechanism is overexpression of members of the B cell lymphoma 2 (BCL-2; BCL2) family, which causes resistance to chemotherapy-induced apoptosis. However this family consists of approximately 20 proteins with either pro- or antiapoptotic activity, and thus it can be difficult to accurately predict how prone cells are to apoptosis by measuring levels of BCL2 protein expression.

“Systems biologists are making it their career to figure out how levels of BCL2-family proteins relate to chemotherapy sensitivity. I chose a functional approach to asking the same question,” said Anthony Letai, associate professor of medicine at Dana-Farber and **Harvard Medical School**.

Letai’s goal was to develop an assay that could give a more direct readout of a tumor cell’s predisposition to apoptosis. He chose to focus on measuring mitochondrial membrane polarization, an indicator of a cell’s physiological health—the lower the polarization across the mitochondrial membrane, the more chemosensitive a cell is. Once a critical mitochondrial membrane depolarization threshold is reached, a cell becomes committed to apoptosis.

To probe tumor cell susceptibility to apoptosis, Letai’s team enlisted a peptide derived from proapoptotic members of the BCL2 family—

“It was very important that we develop an assay that did not require cell culture, as that has been a main stumbling block.”

—Anthony Letai,
Dana-Farber Cancer Institute

BCL2 homology domain 3 (BH3)—to elicit depolarization. The peptide interacts with and inhibits antiapoptotic members of the BCL2 family.

The lower the levels of BH3 needed to trigger depolarization, the more sensitive the tumor cell would be to chemotherapeutic treatment. Letai calls this relationship ‘mitochondrial priming’ because it describes how close the cell is to an apoptotic threshold even before treatment with chemotherapeutics.

“It was very important that we develop an assay that did not require cell culture, as that has been a main stumbling block,” said Letai. “We use bacterial cell culture all the time to determine bacterial sensitivity to antibiotics, but it doesn’t work well for chemotherapy because tumor cells don’t culture well *ex vivo* or they undergo phenotypic changes. It has certainly been tried but you don’t get a good correlation to *in vivo* chemo sensitivity.”

Letai had previously used a variation of the assay to determine the sensitivity of cancer cells to inhibitors of specific members of the BCL2 pathway.² The unanswered question was whether it could be adapted as a general method to measure cellular response to chemotherapeutics.

In samples from patients with multiple myeloma (MM), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) or ovarian cancer, increased mitochondrial depolarization in the assay correlated with improved response. This suggests the therapeutic index of cytotoxic chemotherapeutics may depend on increased mitochondrial priming in cancer cells.

For example, AML patients with greater mitochondrial depolarization were more likely to achieve complete remission than patients with low levels of depolarization ($p=0.0027$). Similarly, ALL patients with high depolarization were more likely to be relapse free ($p=0.0012$), and ovarian cancer patients with high depolarization had increased progression-free survival ($p=0.0003$).

In total, 85 patient samples were assessed by the technique before the start of chemotherapy, of which 51 had available clinical follow-up data. Patients were treated with a range of cytotoxic chemotherapies, including DNA-damaging agents and antimetabolic agents. Proteasome

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(Continued from “Picturing pathology” p. 6)

explanation. How do these features help explain pathologic grade and outcome in patients? What are the biological underpinnings?”

Michael Becich, chair of biomedical informatics at the **University of Pittsburgh**, was less interested in the biology and more focused on the “details about the machine learning used with C-Path. Perhaps as the IP is established, the team will provide more bioinformatics details.”

The Stanford team is working on extending the method on whole-tissue slide samples and hopes to set up a prospective, multicenter trial.

Ultimately, Koller would like C-Path to be able to use breast cancer sample data and predict which drugs would produce the best response in a given patient.

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COMPANIES AND INSTITUTIONS MENTIONED

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Definiens AG, Munich, Germany
Harvard Medical School, Boston, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Stanford University, Stanford, Calif.
University of Pittsburgh, Pittsburgh, Pa.
Ventana Medical Systems Inc. (NASDAQ:VMSI), Tucson, Ariz.

inhibitors including Velcade bortezomib were used in the MM patients.

Velcade induces apoptosis of MM cells, and resistance to the proteasome inhibitor has been linked to the expression of BCL2 family members. Velcade is marketed in the U.S. by **Takeda Pharmaceutical Co. Ltd.'s Millennium Pharmaceuticals Inc.** subsidiary to treat MM and mantle cell lymphoma.

Finally, treatment of chemoresistant tumors with a small molecule BCL2-family inhibitor increased membrane depolarization and restored sensitivity to a panel of cytotoxic cancer drugs compared with treatment using vehicle.

Taken together, the data suggest apoptotic sensitivity plays a role in determining chemotherapy efficacy.

Results were published in *Science*.

Clinical utility

Letai has exclusively licensed the assay to Eutropics, a company he cofounded in 2007 to develop the assay and small molecule inhibitors of a BCL2 family member called myeloid cell leukemia sequence 1 (MCL1).

Michael Cardone, cofounder, president and CEO of Eutropics, said the company is developing the assay both as a prognostic test for chemotherapy sensitivity and as a companion diagnostic for its preclinical MCL1 inhibitors. He said the company recently completed a contract with the **National Cancer Institute** to develop the test as a companion diagnostic for treatment of MM with Velcade.

He added, "We will demonstrate the clinical and commercial utility of the assay for use with MM and AML therapies that are currently in use or in clinical development. As we do this we will be well prepared to use the test with our MCL1 inhibitor when it enters the clinic in the next two to three years."

Ingrid Wertz, research scientist at **Roche's Genentech Inc.** unit, said the assay presents a good alternative to expression-based analysis of the BCL2 pathway. She said that, in fact, expression analysis can miss both activating and inactivating modifications to BCL2 family members.

Abbott Laboratories and Genentech are co-developing Navitoclax (ABT-263; RG7433) for solid tumors and hematological malignancies.

Navitoclax is a small molecule inhibitor of BCL2, BCL-X_L and BCL2-like 2 (BCL2L2; BCLW).

Andreas Strasser, professor of the molecular genetics of cancer at **The Walter and Eliza Hall Institute of Medical Research**, said the advantage of Eutropics' assay is that it looks "more at the overall functionality of the machinery rather than the individual components, compared with western blotting of BCL2, MCL1 or other members. Unless you were to test all of them, you are only looking at some aspects of apoptosis."

Wertz added that BCL2-family proteins "are not the whole picture—proteins and pathways other than the BCL2 family also regulate cell death." She said that one next step would be to identify tumor types in which mitochondrial priming does not correlate with chemosensitivity and then try to understand why.

Eutropics said its assay is available for licensing.

Cain, C. *SciBX* 4(48); doi:10.1038/scibx.2011.1343
Published online Dec. 15, 2011

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1. Ni Chonghaile, T. *et al. Science*; published online Oct. 27, 2011; doi:10.1126/science.1206727
Contact: Anthony Letai, Dana-Farber Cancer Institute, Boston, Mass.
e-mail: anthony_letai@dfci.harvard.edu
2. Certo, M. *et al. Cancer Cell* 9, 351–365 (2006)

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
Dana-Farber Cancer Institute, Boston, Mass.
Eutropics Pharmaceuticals Inc., Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
Harvard Medical School, Boston, Mass.
Millennium Pharmaceuticals Inc. (NASDAQ:MLNM), Cambridge, Mass.
National Cancer Institute, Bethesda, Md.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Multiple sclerosis (MS)	Smoothered (SMO)	<i>In vitro</i> and mouse studies suggest increasing hedgehog signaling could help treat MS. In a mouse model of experimental autoimmune encephalomyelitis (EAE), antagonizing the hedgehog pathway receptor Smo increased disease severity compared with that seen using vehicle. In human blood brain barrier endothelial cells, activation of hedgehog signaling decreased expression of inflammatory mediators and leukocyte signaling compared with those seen using vehicle control. Next steps could include testing the strategy in additional animal models.	Unpatented; unavailable for licensing	Alvarez, J.I. <i>et al. Science</i> ; published online Dec. 1, 2011; doi:10.1126/science.1206936 Contact: Alexandre Prat, University of Montreal, Montreal, Quebec, Canada e-mail: a.prat@umontreal.ca
SciBX 4(48); doi:10.1038/scibx.2011.1344 Published online Dec. 15, 2011				
Cancer				
Acute myelogenous leukemia (AML)	NF-κB	Mouse and cell culture studies suggest pyrithione zinc and ouabain could be useful for treating AML. In a human AML cell line, the two compounds inhibited NF-κB-mediated prosurvival signaling and increased apoptosis compared with no treatment. In a mouse xenograft model of AML, the compounds significantly inhibited tumor growth compared with no treatment. Next steps include determining the therapeutic window and safety profiles of the molecules. Ouabain is a generic approved to treat heart failure. Pyrithione zinc is used in over-the-counter antidandruff and antiseborrhea products.	Unpatented; unavailable for licensing	Tailler, M. <i>et al. Oncogene</i> ; published online Nov. 21, 2011; doi:10.1038/onc.2011.521 Contact: O. Kepp, Gustave Roussy Institute, Villejuif, France e-mail: oliver.kepp@igr.fr Contact: G. Kroemer, same affiliation as above e-mail: kroemer@orange.fr
SciBX 4(48); doi:10.1038/scibx.2011.1345 Published online Dec. 15, 2011				
B cell lymphoma	F-box protein 11 (FBXO11); B cell CLL lymphoma 6 (BCL6)	<i>In vitro</i> and mouse studies suggest increasing FBXO11 levels could help treat BCL6-overexpressing diffuse large B cell lymphoma (DLBCL). FBXO11 is a component of the ubiquitin complex that degrades the pro-oncogenic BCL6. The <i>FBXO11</i> gene was deleted or mutated in 14.8% and 14.3% of human DLBCL cell lines, respectively. In <i>FBXO11</i> -deleted DLBCL cell lines, vector-mediated reconstitution of FBXO11 led to BCL6 degradation and cell death. In mice bearing <i>FBXO11</i> -deleted DLBCL cells, vector-mediated reconstitution of <i>FBXO11</i> suppressed tumor growth compared with that seen using empty vector control. Next steps could include identifying a strategy to upregulate FBXO11.	Patent and licensing status unavailable	Duan, S. <i>et al. Nature</i> ; published online Nov. 23, 2011; doi:10.1038/nature10688 Contact: Michele Pagano, New York University School of Medicine, New York, N.Y. e-mail: michele.pagano@nyumc.org Contact: Roberto Chiarle, University of Turin, Turin, Italy e-mail: roberto.chiarle@unito.it
SciBX 4(48); doi:10.1038/scibx.2011.1346 Published online Dec. 15, 2011				
Cancer	Dopamine D2 receptor	<i>In vitro</i> and mouse studies suggest dopamine or dopamine D2 receptor agonists could help treat cancer. In mice with human prostate and colon tumors, exogenous dopamine stabilized blood vessels and lowered hypoxia compared with no treatment. Unstable tumor vasculature could limit chemotherapy delivery to tumors. In mice, dopamine increased 5-fluorouracil (5-FU) accumulation at the tumor and decreased tumor growth compared with dopamine or 5-FU alone. Next steps include testing dopamine and existing D2 receptor agonists in cancer patients.	Findings unpatented; unavailable for licensing	Chakroborty, D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 5, 2011; doi:10.1073/pnas.1108696108 Contact: Sujit Basu, The Ohio State University, Columbus, Ohio e-mail: sujit.basu@osumc.edu Contact: Partha Sarathi Dasgupta, Chittaranjan National Cancer Institute, Kolkata, India e-mail: partha42002@yahoo.com
SciBX 4(48); doi:10.1038/scibx.2011.1347 Published online Dec. 15, 2011				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Epidermal growth factor receptor 1 (EGFR1; HER1; ERBB1); EGFR4 (HER4; ERBB4)	<p>Mouse studies suggest an EGF decoy receptor could help treat cancer. In mice with pancreatic, lung and prostate cancer xenografts, TRAP-Fc, a recombinant protein generated from extracellular domains of EGFR1 and EGFR4, inhibited tumor growth compared with vehicle. In a xenograft mouse model of breast cancer, TRAP-Fc-secreting breast cancer cells had lower growth and lung metastasis than parent cells. Next steps include large-scale production and testing of TRAP-Fc in humans.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1348 Published online Dec. 15, 2011</p>	Patented; available for licensing	<p>Lindzen, M. <i>et al. Oncogene</i>; published online Nov. 21, 2011; doi:10.1038/onc.2011.518</p> <p>Contact: Y. Yarden, Weizmann Institute of Science, Rehovot, Israel e-mail: yosef.yarden@weizmann.ac.il</p>
Cancer; colorectal cancer; melanoma; non-small cell lung cancer (NSCLC)	StAR-related lipid transfer domain containing 9 (STARD9)	<p><i>In vitro</i> studies suggest inhibiting STARD9 could help treat cancer. In human cervical cancer, colorectal cancer, NSCLC and melanoma cell lines, <i>STARD9</i> small interfering RNA increased mitotic arrest and apoptosis compared with scrambled control siRNA. Also in the cervical cancer cell line, <i>STARD9</i> siRNA plus the generic chemotherapeutic paclitaxel had a synergistic effect on apoptosis compared with either agent alone. Planned studies include examining the effects of <i>Stard9</i> knockout in mouse models of cancer.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1349 Published online Dec. 15, 2011</p>	Patent and licensing status undisclosed	<p>Torres, J.Z. <i>et al. Cell</i>; published online Dec. 9, 2011; doi:10.1016/j.cell.2011.11.020</p> <p>Contact: Jorge Z. Torres, University of California, Los Angeles, Calif. e-mail: torres@chem.ucla.edu</p>
Colorectal cancer	Checkpoint kinase 1 (Chk1)	<p>Mouse studies identified an isoquinoline-based Chk1 inhibitor called SAR-020106 that could help treat colorectal cancer. In a mouse xenograft model of human colorectal cancer, the lead Chk1 inhibitor plus irinotecan resulted in greater tumor growth inhibition than either compound alone. Next steps could include evaluating SAR-020106 in additional animal models of cancer. Sareum Holdings plc has oral Chk1 inhibitors in preclinical development for various cancers including colorectal cancer. At least six other companies have Chk1 inhibitors in Phase I/II testing or earlier to treat cancer.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1350 Published online Dec. 15, 2011</p>	Patent and licensing status unavailable	<p>Reader, J.C. <i>et al. J. Med. Chem.</i>; published online Nov. 23, 2011; doi:10.1021/jm2007326</p> <p>Contact: Ian Collins, The Institute of Cancer Research, Surrey, U.K. e-mail: ian.collins@icr.ac.uk</p> <p>Contact: John C. Reader, Sareum Holdings plc, Cambridge, U.K. e-mail: john.reader@sareum.co.uk</p>
Leukemia	c-Myc (MYC)	<p><i>In vitro</i> studies suggest genomic c-Myc quadruplex DNA could be used to treat leukemia. In human leukemic cell lines, an oligonucleotide encoding the quadruplex-forming c-Myc promoter sequence decreased c-Myc mRNA, protein expression and cellular proliferation and increased cell death compared with a mutated c-Myc promoter sequence that could not form a quadruplex structure. Ongoing work includes IND-enabling toxicity and efficacy studies.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1351 Published online Dec. 15, 2011</p>	Patented; licensed to Advanced Cancer Therapeutics LLC	<p>Sedoris, K.C. <i>et al. Mol. Cancer Ther.</i>; published online Nov. 14, 2011; doi:10.1158/1535-7163.MCT-11-0515</p> <p>Contact: Donald M. Miller, University of Louisville, Louisville, Ky. e-mail: donaldmi@ulh.org</p>
Liver cancer	Hepatocyte nuclear factor 4 α (HNF4A; TCF); microRNA-124 (miR-124)	<p>Mouse and patient sample studies suggest increasing signaling in the HNF4A-miR-124 pathway could help treat hepatocellular carcinoma (HCC). In humans, HCC tissue had lower levels of HNF4A and its downstream effector miR-124 than normal liver tissue. In a mouse model of HCC, systemic treatment with miR-124 prevented tumor growth compared with control miRNA treatment. Next steps include evaluating miR-124 delivery in additional mouse liver cancer models.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1352 Published online Dec. 15, 2011</p>	Unpatented; unavailable for licensing	<p>Hatzia Apostolou, M. <i>et al. Cell</i>; published online Dec. 9, 2011; doi:10.1016/j.cell.2011.10.043</p> <p>Contact: Dimitrios Iliopoulos, Dana-Farber Cancer Institute, Boston, Mass. e-mail: dimitrios_iliopoulos@dfci.harvard.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Melanoma	BRAF; Ras	<p>Patient and cell culture studies suggest targeting truncated BRAF variants could help treat BRAF V600E mutant melanomas that have acquired resistance to BRAF kinase inhibitors. In 6 of 19 patients, BRAF V600E mutant melanomas that have acquired resistance to RAF inhibitors expressed truncated BRAF transcripts lacking the Ras-binding domain, whereas Zelboraf-naïve mutant melanomas did not. Next steps include screening additional patients to better estimate the prevalence of this resistance mechanism and using the results to develop more effective BRAF inhibitors or combinations of inhibitors.</p> <p>Zelboraf, an oral small molecule inhibitor of the oncogenic BRAF V600E from Daiichi Sankyo Co. Ltd. and Roche, is marketed to treat melanoma.</p> <p>Roche also has RG7256, a BRAF inhibitor, in Phase I testing for melanoma.</p> <p>GSK2118436, a BRAF inhibitor from GlaxoSmithKline plc, is in Phase III testing for melanoma (<i>see Splicing out BRAF's resistance, page 1</i>).</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1353 Published online Dec. 15, 2011</p>	Patent pending; licensing status undisclosed	<p>Poulidakos, P.I. <i>et al. Nature</i>; published online Nov. 23, 2011; doi:10.1038/nature10662</p> <p>Contact: David B. Solit, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: solitd@mskcc.org</p>
Infectious disease				
Infectious disease	Bacterial cystathionine β -synthase; bacterial cystathionine γ -lyase	<p><i>In vitro</i> studies suggest inhibiting hydrogen sulfide (H_2S) production could help treat bacterial infections. <i>Staphylococcus aureus</i>, <i>Bacillus anthracis</i> and <i>Pseudomonas aeruginosa</i> strains with genetic or chemical inactivation of the H_2S-producing enzymes cystathionine β-synthase or cystathionine γ-lyase had greater sensitivity to gentamicin than strains expressing functional versions of either enzyme. Next steps include high throughput screening for small molecule inhibitors of bacterial H_2S-producing enzymes.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1354 Published online Dec. 15, 2011</p>	Patent application filed; available for licensing	<p>Shatalin, K. <i>et al. Science</i>; published online Nov. 18, 2011; doi:10.1126/science.1209855</p> <p>Contact: Evgeny Nudler, New York University School of Medicine, New York, N.Y. e-mail: evgeny.nudler@nyumc.org</p>
Viral infection	Prostaglandin D_2 (PGD_2); PGD_2 receptor subtype DP1	<p>Mouse studies suggest inhibiting PGD_2 could help treat viral infections in aged populations. In aged mice, compared with in young mice, influenza A virus or SARS virus stimulated a weaker $CD8^+$ T cell immune response, and the strength of the response was inversely correlated with PGD_2 levels. In aged mice infected with SARS virus, an inhibitor of the PGD_2 receptor DP1 improved survival compared with vehicle control. Next steps include measuring PGD_2 levels in infected and uninfected human lung samples.</p> <p>TS-022, a small molecule DP1 inhibitor from Taisho Pharmaceutical Co. Ltd., is in Phase II testing to treat dermatitis.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1355 Published online Dec. 15, 2011</p>	Patent application about to be filed; available for licensing	<p>Zhao, J. <i>et al. J. Clin. Invest.</i>; published online Nov. 21, 2011; doi:10.1172/JCI59777</p> <p>Contact: Stanley Perlman, The University of Iowa, Iowa City, Iowa e-mail: stanley-perlman@uiowa.edu</p>
Inflammation				
Allergy; asthma	Translationally controlled tumor protein (TCTP; HRF)	<p>Mouse studies suggest inhibiting HRF could help treat allergy and asthma. In mice, a tagged peptide HRF inhibitor decreased allergen-induced skin inflammation compared with tag alone. In a model of allergen-induced asthma, the inhibitor lowered mast cell-dependent airway inflammation and airway hyper-responsiveness compared with tag alone. Next steps include developing lead HRF inhibitors and evaluating them in animal models of allergies.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1356 Published online Dec. 15, 2011</p>	Patent application filed; licensing status undisclosed	<p>Kashiwakura, J.-i. <i>et al. J. Clin. Invest.</i>; published online Dec. 1, 2011; doi:10.1172/JCI59072</p> <p>Contact: Toshiaki Kawakami, La Jolla Institute for Allergy & Immunology, La Jolla, Calif. e-mail: toshi@liai.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Musculoskeletal disease				
Musculoskeletal disease	Bone morphogenetic protein 2 (BMP2); BMP7 (OP-1); CREB binding protein (CREBBP); CBP	Mouse studies suggest BMP2 and BMP7 could help prevent skeletal dysplasias caused by <i>CBP</i> mutations. In a mouse model of Rubinstein-Taybi syndrome induced by <i>Cbp</i> deficiency, <i>in utero</i> delivery of recombinant human BMP2 and BMP7 partially corrected embryonic skeletal dysplasias compared with delivery of saline control. Next steps include assessing the effects of BMP-based therapy on the development of other organs and on fetal viability. SciBX 4(48); doi:10.1038/scibx.2011.1357 Published online Dec. 15, 2011	Unpatented; available for licensing	Shim, J.-H. <i>et al. J. Clin. Invest.</i> ; published online Dec. 1, 2011; doi:10.1172/JCI59466 Contact: Laurie H. Glimcher, Harvard School of Public Health, Boston, Mass. e-mail: lglimche@hsph.harvard.edu Contact: Jae-Hyuck Shim, same affiliation as above e-mail: jshim@hsph.harvard.edu
Neurology				
Addiction	4-Aminobutyrate aminotransferase (ABAT; GABA-AT)	Rat studies identified a GABA-AT inactivator that could help treat cocaine addiction. In rats, oral treatment with the GABA-AT inactivator (1S,3S)-3-amino-4-difluoromethylenyl-1-cyclopentanoic acid (CPP-115) inhibited cocaine-induced dopamine increases and reward learning at lower doses than the marketed GABA-AT inactivator vigabatrin. In the rats, CPP-115 showed less retinal toxicity than vigabatrin. Next steps include clinical testing of the compound. Catalyst Pharmaceutical Partners Inc. has vigabatrin in Phase II/III testing to treat addiction. SciBX 4(48); doi:10.1038/scibx.2011.1358 Published online Dec. 15, 2011	Composition of matter and use of CPP-115 has been patented; exclusively licensed to Catalyst Pharmaceutical Partners; available for partnerships	Pan, Y. <i>et al. J. Med. Chem.</i> ; published online Nov. 30, 2011; doi:10.1021/jm201231w Contact: Richard B. Silverman, Northwestern University, Evanston, Ill. e-mail: Agman@chem.northwestern.edu
Alzheimer's disease (AD)	Mitogen-activated protein kinase kinase 4 (MAP2K4; MKK4); MAP2K7 (MKK7)	Cell culture and mouse studies suggest antagonizing MKK4 and MKK7 could help treat AD. In cultured neurons, combined <i>Mkk4</i> and <i>Mkk7</i> deletion decreased β -amyloid ($A\beta$) toxicity compared with that in wild-type controls. In a mouse model of AD, brains lacking both <i>Mkk4</i> and <i>Mkk7</i> had lower amyloid plaque and dystrophic neurite levels than brains with intact <i>Mkk4</i> and <i>Mkk7</i> . Next steps include testing the effects of <i>Mkk4</i> and <i>Mkk7</i> deletion in additional mouse models of AD and identifying inhibitors of the targets. SciBX 4(48); doi:10.1038/scibx.2011.1359 Published online Dec. 15, 2011	Unpatented; licensing status not applicable	Mazzitelli, S. <i>et al. J. Neurosci.</i> ; published online Nov. 23, 2011; doi:10.1523/JNEUROSCI.4491-11.2011 Contact: Cathy Tournier, The University of Manchester, Manchester, U.K. e-mail: cathy.tournier@manchester.ac.uk
Spinal cord injury (SCI)	Not applicable	Rat studies suggest dental-derived stem cells could help treat SCI. In a rat model of acute SCI, transplantation of human stem cells derived from teeth improved hind limb locomotor function compared with transplantation of human bone marrow stromal cells or skin-derived fibroblasts or injection of vehicle. Ongoing work includes testing dental-derived stem cells in a rat model of chronic SCI and a nonhuman primate model of acute SCI. SciBX 4(48); doi:10.1038/scibx.2011.1360 Published online Dec. 15, 2011	Patent application filed by Nagoya University; available for licensing or partnering	Sakai, K. <i>et al. J. Clin. Invest.</i> ; published online Dec. 1, 2011; doi:10.1172/JCI59251 Contact: Akihito Yamamoto, Nagoya University Graduate School of Medicine, Nagoya, Japan e-mail: akihito@med.nagoya-u.ac.jp
Other				
Poisoning	Bactericidal/permeability-increasing protein (BPI)	Mouse and human studies suggest a recombinant BPI fragment could help decrease radiation toxicity. Patients receiving radiation conditioning for hematopoietic stem cell transplant showed endotoxemia and had lower BPI levels than before treatment. In irradiated mice, the recombinant BPI fragment plus a fluoroquinolone accelerated hematopoietic recovery, promoted stem and progenitor cell expansion and resulted in a 65%–80% survival rate compared with 0%–25% for vehicle plus fluoroquinolone. Next steps include studies in additional animals. SciBX 4(48); doi:10.1038/scibx.2011.1361 Published online Dec. 15, 2011	Covered by issued and filed patents; licensed to an undisclosed company	Guinan, E.C. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 23, 2011; doi:10.1126/scitranslmed.3003126 Contact: Eva C. Guinan, Children's Hospital Boston, Boston, Mass. e-mail: eva_guinan@dfci.harvard.edu

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
Chemistry			
High throughput identification of chiral oligomers of pentenoic amides (COPAs) as protein ligands	<p>Screening libraries of COPAs could help identify new lead compounds. A library of 160,000 COPA compounds was synthesized on beads, and the resulting chemical structures could be determined by mass spectrometry. Screening the library against the DNA-binding domain of p53 identified a compound that bound the domain noncovalently at low micromolar concentrations. Next steps include identifying industrial partnerships to advance the compound class.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1362 Published online Dec. 15, 2011</p>	Provisional patent application filed; available for licensing or partnering	<p>Aquino, C. <i>et al. Nat. Chem.</i>; published online Nov. 20, 2011; doi:10.1038/nchem.1200 Contact: Glenn C. Micalizio, Scripps Florida, Jupiter, Fla. e-mail: micalizio@scripps.edu Contact: Thomas Kodadek, same affiliation as above e-mail: kodadek@scripps.edu</p>
Photocatalytic redox method for incorporating trifluoromethyl (CF ₃) groups into drug compounds	<p>A method of chemical synthesis could incorporate CF₃ groups into drug compounds to help improve their <i>in vivo</i> stability. CF₃ groups increase the metabolic stability of many drugs compared with their non-CF₃-containing analogs. The method used a photosensitive redox catalyst at room temperature to add CF₃ to aryl carbon structures in Lipitor atorvastatin, ibuprofen, lidocaine, a precursor of Aricept donepezil and other biologically active molecules at ≥78% yields. Ongoing work includes scaling up and optimizing the method and developing other nonphotocatalyzed methods for CF₃ incorporation.</p> <p>Pfizer Inc. markets the HMG-CoA reductase inhibitor Lipitor to treat hypercholesterolemia, stroke, coronary artery disease (CAD), myocardial infarction (MI) and other cardiovascular indications. Pfizer and Eisai Co. Ltd. market Aricept, a reversible acetylcholinesterase (AChE) inhibitor, to treat Alzheimer's disease (AD).</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1363 Published online Dec. 15, 2011</p>	Unpatented; unlicensed	<p>Nagib, D.A. & MacMillan, D.W.C. <i>Nature</i>; published online Dec. 8, 2011; doi:10.1038/nature10647 Contact: David W.C. MacMillan, Princeton University, Princeton, N.J. e-mail: dmacmill@princeton.edu</p>
Drug platforms			
Chemical-genetic interaction networks for target discovery against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	<p>Chemical-genetic interaction networks could help identify therapeutic targets that sensitize MRSA to antibiotics. Antisense knockdown of a panel of 245 <i>S. aureus</i> genes in combination with an antibiotics screen led to a chemical-genetic interaction network. The network was used to identify genes that sensitized MRSA to β-lactam antibiotics. In a MRSA strain and β-lactam-resistant <i>S. epidermidis</i> strain, inhibition of one of the identified genes, <i>glucosamine-fructose-6-phosphate aminotransferase (GlmS)</i>, increased sensitivity to a β-lactam antibiotic compared with <i>GlmS</i> expression. Next steps include identifying additional small molecules that disrupt members of the interaction network for β-lactam antibiotics.</p> <p>SciBX 4(48); doi:10.1038/scibx.2011.1364 Published online Dec. 15, 2011</p>	Patent application filed; licensing status undisclosed	<p>Lee, S.H. <i>et al. Chem. Biol.</i>; published online Nov. 23, 2011; doi:10.1016/j.chembiol.2011.08.015 Contact: Terry Roemer, Merck & Co. Inc., Kenilworth, N.J. e-mail: terry_roemer@merck.com</p>

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Mammalian cell-based discovery of high-affinity human antibodies from IgG libraries	A human cell line-based platform could be used to generate high-affinity human antibodies from immunologically diverse IgG libraries. The platform used multiple rounds of selection, somatic hypermutation and affinity maturation to identify a lead antibody against nerve growth factor (NGF). In human cell lines, the antibody caused dose-dependent inhibition of NGF binding to its receptor and to the NGF antibody tanezumab. AnaptysBio Inc. has already used the platform to identify ANB004, a human mAb against IL-17. AnaptysBio has ANB004 and the anti-NGF mAb in preclinical development to treat autoimmune indications and pain, respectively. Tanezumab (PF-4383119), a humanized mAb against NGF from Pfizer Inc., is in Phase III testing to treat pain.	Patented by MRC Laboratory of Molecular Biology and Albert Einstein College of Medicine of Yeshiva University; licensed to AnaptysBio	Bowers, P.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 7, 2011; doi:10.1073/pnas.1114010108 Contact: Peter M. Bowers, AnaptysBio Inc., San Diego, Calif. e-mail: pbowers@anaptysbio.com
	SciBX 4(48); doi:10.1038/scibx.2011.1365 Published online Dec. 15, 2011		
Rational design of glycoconjugate vaccines	Glycoconjugate vaccines that maximize the presentation of carbohydrate-specific T cell epitopes to the immune system could lead to the development of more effective vaccines. In mice, a glycoconjugate vaccine against the type III polysaccharide of group B <i>Streptococcus</i> induced higher antigen-specific IgG titers than a control glycoconjugate vaccine based on an existing platform technology. In mouse pups, the new vaccine protected 100% of animals against lethal challenge with group B <i>Streptococcus</i> , whereas control vaccine protected only 65%. Next steps could include using the approach to develop glycoconjugate vaccines against additional types of microbial infections.	Patent application filed; licensing information available from Research Ventures and Licensing at Partners HealthCare	Avci, F.Y. <i>et al. Nat. Med.</i> ; published online Nov. 20, 2011; doi:10.1038/nm.2535 Contact: Dennis L. Kasper, Harvard Medical School, Boston, Mass. e-mail: dennis_kasper@hms.harvard.edu
	SciBX 4(48); doi:10.1038/scibx.2011.1366 Published online Dec. 15, 2011		
Imaging			
Topically applied, tumor-activated fluorescence probe for ovarian cancer biopsy and resection	A topically applied, tumor-activated fluorescence probe may help improve biopsy and resection of ovarian tumors. The imaging probe g-glutamyl hydroxymethyl rhodamine green (gGlu-HMRG) becomes fluorescent when activated by γ -glutamyltransferase, which is overexpressed on the cell surface of ovarian and other cancers. In xenograft mouse models of disseminated human ovarian cancer, gGlu-HMRG sprayed onto the peritoneal surface permitted visualization of tumors as small as 1 mm in diameter within minutes. Next steps include evaluating the probe using fresh surgical ovarian cancer specimens.	Patent applications filed; available for licensing through The University of Tokyo	Urano, Y. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 23, 2011; doi:10.1126/scitranslmed.3002823 Contact: Hisataka Kobayashi, National Institutes of Health, Bethesda, Md. e-mail: kobayash@mail.nih.gov Contact: Yasuteru Urano, The University of Tokyo, Tokyo, Japan e-mail: uranokun@m.u-tokyo.ac.jp
	SciBX 4(48); doi:10.1038/scibx.2011.1367 Published online Dec. 15, 2011		
Markers			
Metabolomic signature for metastatic colon cancer prognosis	A patient study identified an NMR signature that could help determine metastatic colon cancer prognosis. In 45 patients with metastatic colon cancer and 96 healthy controls, proton NMR identified a metabolomic signature that classified patients based on overall survival. In a validation study in 108 patients with metastatic colon cancer, the signature predicted overall survival more accurately than <i>K-Ras</i> mutational status. Next steps include using proton NMR to identify prognostic signatures in additional diseases. The researchers have founded Giotto Biotech s.r.l., which provides proton NMR metabolomic analysis on a fee-for-service basis.	Unpatented; licensing status not applicable	Bertini, I. <i>et al. Cancer Res.</i> ; published online Nov. 11, 2011; doi:10.1158/0008-5472.CAN-11-1543 Contact: Ivano Bertini, University of Florence, Florence, Italy e-mail: ivanobertini@cerm.unifi.it
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