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By *Benjamin Boettner, Associate Editor*

Three separate teams have directly converted human fibroblasts to proliferative liver cells and thus eliminated a key drawback of using induced pluripotent stem cells to treat damaged livers—the inability of the resulting differentiated cells to repopulate damaged liver.<sup>1-3</sup>

Each team had a different twist on getting the cells to divide, but the common thread was that fibroblasts were directly programmed to cell states that are part of the hepatocyte differentiation pathway. Next steps could include taking the protocols' lentiviral manipulations out of the equation and further improving the maturation of the resulting hepatocytes.

Patients with chronic liver disease live for an average of 12 years with compensated cirrhosis before they enter a state of rapid decline marked by ascites, encephalopathy and other complications.<sup>4</sup> Because the demand for livers for transplantation exceeds the supply, a logical alternative is to use induced pluripotent stem (iPS) cell technology.

The idea is straightforward: take a patient's own cells, usually fibroblasts, revert them to an iPS cell state and then differentiate them *in vitro* into an autologous supply of hepatocytes. The problem comes at the last step, with different research groups reporting that iPS cell differentiation to mature hepatocytes is impeded and the resulting hepatocytes have dramatically diminished ability to proliferate.

Three teams have now developed independent protocols that overcome these limitations.

A team led by Sheng Ding and Holger Willenbring developed a method involving the retroviral introduction of three pluripotency genes—*OCT4*, *SOX2* and *KLF4*—into human newborn fibroblasts and brief exposure of the cells to medium containing endoderm-promoting factors together with the small molecule CHIR99021, which stimulates wingless-type MMTV integration site (WNT) pathway signaling.

Ding is a senior investigator at the **Gladstone Institute of Cardiovascular Disease** and a professor of pharmaceutical chemistry at the **University of California, San Francisco**. Willenbring is an associate professor in the **UCSF School of Medicine's** division of transplant surgery.

Lijian Hui at the **Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences** took a different approach, converting human fetal fibroblasts directly into hepatocytes by transducing them with lentiviruses carrying three genes: *HNF1 homeobox A* (*HNF1A*), *hepatocyte nuclear factor 4α* (*HNF4A*; *TCF*) and *forkhead box A3* (*FOXA3*). Together, those genes promote hepatocyte lineage commitment and maturation.

The team removed the proliferation barrier by overexpressing the

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viral SV40 large T antigen in the resulting hepatocytes. SV40 is an inhibitor of cell cycle-regulating proteins including p53.

Hui is a professor at the Shanghai Institutes' Institute of Biochemistry and Cell Biology.

Finally, Hongkui Deng, Yan Shi and Shichun Lu introduced lentiviruses expressing a set of three hepatocyte fate conversion factors—*HNF1A*, *HNF4* and *one cut homeobox 1* (*ONECUT1*; *HNF6*)—into primary human fetal limb fibroblasts. The group then used a second set of maturation factors including *activating transcription factor 6* (*ATF6*), *prospero-related homeobox 1* (*PROX1*) and *CCAAT enhancer binding protein-a* (*CEBPA*) and siRNAs to inhibit p53 and *c-Myc* (*MYC*), thus releasing the cells from cell cycle inhibition.

Deng is a professor at **Peking University's** college of life sciences and a principal investigator at the Key Laboratory of Chemical Genomics. Shi is an associate professor at the **Peking University Shenzhen Graduate School** and an investigator at the **Key Laboratory of Chemical Genomics**. Lu is a chief physician at the **Chinese PLA General Hospital**.

**Hepatocyte differences**

The UCSF team's procedure converted fibroblasts into what the group calls induced multipotent progenitor cell-derived endodermal progenitor cells (iMPC-EPCs). By growing the fibroblasts in medium that favors endoderm differentiation, the group prevented the cells from reverting to a pluripotent iPS cell-like state and instead directly converted them to the endoderm lineage from which hepatocytes normally emerge.

In culture, iMPC-EPCs spontaneously gave rise to hepatocyte-like cells, dubbed iMPC-Heps, that kept dividing. The results thus provided proof of principle that direct lineage conversion of fibroblasts to hepatocytes via iMPC-EPCs maintained proliferation.

The team then screened and identified a set of small molecules that increased iMPC-EPCs' conversion and an additional set of small molecules that, together with hepatocyte-promoting factors, improved differentiation into iMPC-Heps.

The resulting cells closely resembled proliferative fetal primary hepatocytes as judged by their expression of hepatocyte markers *HNF4A*, *albumin* genes,  $\alpha_1$ -*antitrypsin* (*AAT*; *A<sub>1</sub>AT*; *SERPINA1*) and *cytokeratin 8* (*CK8*; *KRT8*).

In an immune-deficient mouse model of liver failure, transplanted iMPC-Heps kept proliferating for at least 6 months and repopulated 2% of liver parenchyma. Animals receiving transplants survived significantly longer than nontransplanted controls.

Previous iPS cell-based studies only achieved about 0.05% liver repopulation.

iMPC-Heps continued to mature and produced functional, drug-metabolizing cytochrome P450 (p450) enzymes and albumin levels that were tenfold higher than those in controls.

Data were published in *Nature*.

Gladstone has filed for a patent covering the reprogramming conditions to generate hepatocytes from fibroblasts, and the IP is available for licensing.

"The authors cut short the amount of time that fibroblasts were exposed to regulatory proteins that induce pluripotency so that the

cells did not revert to a pluripotent state but rather only reverted to a multipotent state. By starting from the multipotent state, they could generate liver-like cells that appear better than if they had started from the pluripotent state,” said Kenneth Zaret.

Zaret is a professor of cell and developmental biology at the **Perelman School of Medicine at the University of Pennsylvania** and associate director of the **University of Pennsylvania’s** Institute for Regenerative Medicine.

The two Chinese teams did not include passage through a multipotent iMPC-EPC-like state in their protocols and generated cells that were already further downstream in the hepatocyte lineage. To tackle the proliferation problem, the teams interfered with the expression of central cell cycle regulators.

Both teams termed the resulting cells HiHeps (human induced hepatocytes) and reported that the cells had some of the hallmarks of adult hepatocytes. The HiHeps also had higher hepatocyte activity than the iMPC-Heps produced by the UCSF team.

HiHeps expressed the genes relevant for hepatocyte identity, metabolic activity and detoxification mediated through p450 enzyme systems. Indeed, both groups showed that the HiHeps were able to metabolize model drugs.

Transplanted HiHeps also colonized liver parenchyma in mouse models of liver injury with repopulation efficiencies of 0.3%–4.2% (Shanghai Institutes for Biological Sciences) and up to 30% (Peking University), producing substantial quantities of albumin and improving survival.

The two approaches were published in *Cell Stem Cell*.

The Shanghai Institutes for Biological Sciences has filed for a patent covering HiHep derivation from human fibroblasts. The IP is not available for licensing. The researchers at Peking University did not disclose the IP status of their method.

### Growing up hepatocytes

It is early days for all three approaches, making head-to-head comparisons for potential in human regenerative approaches difficult. Regardless, each approach needs to do away with viral integration and improve final hepatocyte maturation before it can be further translated.

Salman Khetani, an assistant professor of mechanical and biomedical engineering at **Colorado State University** and cofounder and member of the scientific board of **Hepregen Corp.**, said that there were some notable differences between the UCSF findings and those from the Chinese teams.

The former, he said, showed “unsurpassed longevity of transplanted cells that lasted for more than six months.” The two groups from China, however, had “more impressive *in vitro* functional characterization data relative to freshly isolated primary human hepatocytes.”

Wolfram Goessling, an assistant professor in the Department of

Medicine at **Harvard Medical School** and the **Harvard Stem Cell Institute**, said, “A crucial difference between the protocols is the pervasive use of chemicals in the study by the Gladstone Institute and UCSF, which circumvented direct inhibition of cell cycle regulators like the tumor suppressor p53 and present an advantage.”

In all cases, Zaret said, viral delivery of the reprogramming factors needs to be replaced.

“For clinical applications, it seems highly likely that a nonviral method of delivery of the regulatory proteins will be key. The viral method could disrupt genes in the cell, with long-term, unanticipated consequences,” he said.

Both Zaret and Khetani wanted to see more long-term data on the efficacy of transdifferentiated hepatocytes.

“Protocols to better mature the iMPC-Heps/HiHeps into functional hepatocytes *in vitro* so they can demonstrate better functions after transplantation *in vivo* should be a prime goal,” Khetani said.

He added that various microscale and 3D engineering techniques that simulate a tissue environment *in vitro* have been previously applied to primary hepatocytes and could potentially be used with the induced hepatocyte-like cells to achieve better maturation.

Ruslan Semechkin said that the analysis of the final hepatocyte products needs to be more comprehensive before they are deemed a histocompatible source for modeling and treating liver diseases. Semechkin is CSO at **International Stem Cell Corp.**

“Most inherited liver disease phenotypes are observed only in fully differentiated cells,” he said. Thus, “the degree to which human

fibroblasts can be differentiated into hepatocytes will affect the extent to which the disease can be modeled *in vitro* and in follow-up studies *in vivo*.”

“More activities and markers that closely resemble those of primary hepatocytes should be assessed,” Semechkin continued. “Hepatic characteristics should be demonstrated using drug metabolism experiments on the gene expression and functional level. In-depth analysis of a number of parameters including hepatic transport proteins, mature hepatic transcription factors, albumin secretion, production of bile acids and bilirubin as well as mitochondrial functions would be informative.”

He said that International Stem Cell “would be interested in rapid testing of the protocol presented in the *Nature* paper.” He also wanted to see a head-to-head comparison of the transdifferentiated hepatocytes versus pluripotent stem cell–derived hepatocytes.

Better characterization and *in vitro* maturation will also provide a basis for the cells to be used in disease modeling and drug testing.

Ding told *SciBX*, “We are planning to further optimize the process, especially focusing on hepatocyte *in vitro* maturation, before developing clinical-stage GMP conditions.”

Ding’s group also has identified small molecules to differentiate several other lineages including cardiomyocytes and pancreatic cells.

**“For clinical applications, it seems highly likely that a nonviral method of delivery of the regulatory proteins will be key. The viral method could disrupt genes in the cell, with long-term, unanticipated consequences.”**

**—Kenneth Zaret,  
Perelman School of Medicine at the  
University of Pennsylvania**

**“Protocols to better mature the iMPC-Heps/HiHeps into functional hepatocytes *in vitro* so they can demonstrate better functions after transplantation *in vivo* should be a prime goal.”**

**—Salman Khetani,  
Colorado State University**

The team from the Shanghai Institutes for Biological Sciences is planning to test techniques that could eliminate viral integration events from the procedure, including the use of mRNAs and small molecules.

The Peking University group did not comment on its future plans.

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# Easy Access IP: ahead of the game or easy way out?

By C. Simone Fishburn, Senior Editor

As university technology transfer offices grapple with how best to commercialize their discoveries, about 25 international universities are turning to Easy Access IP, a strategy to give patented inventions away for free. Supporters argue that giving away IP attracts potential investors, while some non-adopter technology transfer office heads think companies will only be attracted by well-fleshed-out legal agreements.

At the heart of the debate is an issue technology transfer offices (TTOs) and other stakeholders in translational research have talked about for years—the inefficiency and expense associated with licensing university patents.

Earlier this year, the **Brookings Institution** released a report that helped quantify the problem. The report looked at numbers from 155 TTOs that are members of the **Association of University Technology Managers** and found that less than 13% of universities generate enough revenue from licensing deals to cover their operating costs.<sup>1</sup>

The goal of Easy Access IP is to drive down those expenses. Kevin Cullen pioneered the strategy in 2010 when he was at the **University of Glasgow** and found that the cost of supporting all the activities involved in licensing inventions was rarely matched by the revenues received.

Cullen is now CEO of **NewSouth Innovations**, the tech transfer arm of **The University of New South Wales**.

Easy Access IP differs from the standard TTO model of patenting and licensing for profit as many inventions as possible. Instead, a university still patents the invention, but it gives away the majority—often up to about 95%—of its IP licenses for free, thus bypassing the high costs and lengthy negotiations that often prevent academic discoveries from being commercialized.

Deals require a one-page contract in which the licensor commits to perform some activity related to the invention within three years, agrees to acknowledge the university if the IP is successfully exploited and guarantees not to take action against the university for pursuing research in that area.

Other TTO heads, including Tom Hockaday, think investing time and resources in more conventional licensing activities brings the most value to universities. Hockaday is managing director of **Isis Innovation Ltd.**, the tech transfer unit of the **University of Oxford**.

“Doing proper commercial deals is the best way to attract financial investment because that way companies have the security that they are developing a product based on a strong legal agreement and solid IP,” he said.

Cullen countered that traditional licensing deals only work about 5% of the time. “The problem is that this model has been shown not to work for the majority of IP, and we need to find new ways of getting more of that

95% put to use to increase the relevance and usefulness of the research base,” he said.

He said that the experience at the University of New South Wales was that the financial cost of moving IP out of the university was less than the intangible benefits created by getting IP in the hands of industry once cumbersome and expensive contracts were out of the picture.

Such intangible advantages, he said, include the potential economic effects of companies creating products based on university IP, benefits to patients and other end users and enhancements to the university’s reputation.

“The proportion of technologies with potential for a financial return to the university is very low. Easy Access IP is a logical model for unlocking the nonfinancial value of the majority of university-developed technologies,” said Cullen.

Hockaday said that he prefers a system such as the Isis Smart IP Scheme, which was set up to give small and medium enterprises (SMEs) greater flexibility and reduced risk by using a phased program to access university IP projects.

“We launched the Oxford Isis Smart IP Scheme a while ago to encourage IP uptake for SMEs. For many years we have offered simple evaluation agreements so a company can have a quick look at a technology to see if it wants to invest further,” he said. “With Easy Access IP, universities invest in TTOs with a view to giving their research fruits away. We are investing in TTOs with a view to commercializing the research [and] transferring the technology to industry so that ideas from Oxford receive investment and may be converted into better products and services.”

Cullen responded that his university “invests in the TTO to maximize the benefits deriving from our research; sometimes it is financial return, sometimes social or economic development benefits, sometimes reputational benefits. We are tasked with finding innovative ways of maximizing this mix of benefits.”

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## COMPANIES AND INSTITUTIONS MENTIONED

**Association of University Technology Managers**, Deerfield, Ill.

**Brookings Institution**, Washington, D.C.

**Isis Innovation Ltd.**, Oxford, U.K.

**NewSouth Innovations**, Sydney, New South Wales, Australia

**University of Glasgow**, Glasgow, U.K.

**The University of New South Wales**, Sydney, New South Wales, Australia

**University of Oxford**, Oxford, U.K.

“Doing proper commercial deals is the best way to attract financial investment because that way companies have the security that they are developing a product based on a strong legal agreement and solid IP.”

—Tom Hockaday, Isis Innovation Ltd.

“The proportion of technologies with potential for a financial return to the university is very low. Easy Access IP is a logical model for unlocking the nonfinancial value of the majority of university-developed technologies.”

—Kevin Cullen,  
NewSouth Innovations

# Translational tidbits

By Kai-Jye Lou, Senior Writer

At least \$440 million in new support for public-private partnerships was allocated last month globally. Almost \$230 million of that amount is earmarked for the NIH's Accelerating Medicines Partnership<sup>1</sup> (see Table 1, "Selected public-private partnerships for February 2014").

Accelerating Medicines Partnership members will collaborate on projects to identify and validate disease targets in Alzheimer's disease (AD), type 2 diabetes, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Over the public-private partnership's 5-year run, the NIH will provide \$118.9 million in funding, and industry partners will provide the remaining \$110.6 million in the form of funding and in-kind contributions.

The second-largest public-private partnership announced in February was the European Gram-Negative Antibacterial Engine (ENABLE) project, which is getting \$116 million over 6 years and is focused on developing antibacterial compounds. In third place was the ARTERIA project, which has received C\$49.2 million (\$44.6 million) and is focused on cardiovascular disease.

## Antibacterial engine

Last month, the **Innovative Medicines Initiative** (IMI) launched the third project under its New Drugs 4 Bad Bugs (ND4BB) initiative. The ENABLE project aims to build and manage a discovery platform for testing and optimizing early discovery-stage molecules for drug-resistant, Gram-negative bacterial infections.

The seven candidates already in the project's portfolio will be reviewed by ENABLE's Portfolio Management Committee before entering the development pipeline. One candidate each was sourced from **Redx Pharma Ltd.**, **Northern Antibiotics Ltd.** and **biomol-**

**informatics S.L.**; the other four came from the not-for-profit research organization **Medina Foundation** and from a trio of European universities.

"In theory, a maximum of four candidates can be developed at any one time, and more candidates will be sought to feed in as candidate programs are stopped and capacity becomes available," said ENABLE spokesperson Claire Skentelbery, who is secretary general at biotech trade organization **European Biotechnology Network**. "We will launch an open call at the start of March to begin the process of identifying new candidates external to the current consortium that can feed into the pipeline as space becomes free."

The IMI will provide ENABLE with €59 million (\$80.5 million) in funding, and project members will provide another €26 million (\$35.5 million) in in-kind contributions. **GlaxoSmithKline plc** and **Uppsala University** are leading the project.

The project's goal is to complete Phase I trials for at least one candidate by 2019. ENABLE currently has 32 members, including 3 pharmas and 11 small and medium enterprises.

The other two ongoing projects launched under IMI's ND4BB initiative are COMBACTE and TRANSLOCATION. COMBACTE is focused on developing innovative trial designs for antibacterial agents, whereas TRANSLOCATION is researching the cell permeability of Gram-negative bacteria.

## A hearty investment

The **Montreal Heart Institute** launched its ARTERIA project to aid the development of new treatments and diagnostics for cardiovascular disease.

The project's goal is to use genetic profiles to improve treatment outcomes in patients who have or are at risk for cardiovascular diseases such as atherosclerosis.

ARTERIA has five focus areas. These include validating diagnostics for statin-induced muscle toxicity and incorporating them into care

**"We will launch an open call at the start of March to begin the process of identifying new candidates external to the current consortium that can feed into the pipeline as space becomes free."**

—Claire Skentelbery,  
European Biotechnology Network

**Table 1. Selected public-private partnerships for February 2014.** Over \$440 million in new funding commitments and in-kind contributions was earmarked for public-private partnerships in February. This was primarily driven by the NIH's Accelerating Medicines Partnership, the Innovative Medicines Initiative (IMI)'s European Gram-Negative Antibacterial Engine (ENABLE) project and the Montreal Heart Institute's ARTERIA project.

Source: *BioCentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
AbbVie Inc. (NYSE:ABBV); Biogen Idec Inc. (NASDAQ:BIIB); Bristol-Myers Squibb Co. (NYSE:BMJ); Eli Lilly and Co. (NYSE:LLY); GlaxoSmithKline plc (LSE:GSK; NYSE:GSK); Johnson & Johnson (NYSE:JNJ); Merck & Co. Inc. (NYSE:MRK); Pfizer Inc. (NYSE:PFE); Sanofi (Euronext:SAN; NYSE:SNY); Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)	NIH	Autoimmune disease; endocrine/metabolic disease; neurology	\$229.5 million	Accelerating Medicines Partnership to identify and validate disease targets, with an initial focus on Alzheimer's disease (AD), type 2 diabetes, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)
GlaxoSmithKline	IMI; Uppsala University	Infectious disease	€85 million (\$116 million)	ENABLE project to progress antibacterial research programs through discovery and Phase I testing
Roche (SIX:ROG; OTCQX:RHHBY); Servier; AstraZeneca plc (LSE:AZN; NYSE:AZN); Valeant Pharmaceuticals International Inc. (TSX:VRX; NYSE:VRX)	Montreal Heart Institute	Cardiovascular disease; diagnostics; genomics	C\$49.2 million (\$44.6 million)	ARTERIA project to develop treatments and diagnostics for cardiovascular disease

(Continues on p. 7)

Table 1. Selected public-private partnerships for February 2014. (Continued)

Companies	Institutions	Business area	Disclosed value	Purpose
European Federation of Pharmaceutical Industries and Associations	Pfizer–University of Granada–Junta de Andalucía Centre for Genomics and Oncological Research (GENYO); IMI	Autoimmune disease	€22.7 million (\$31.1 million)	Five-year PRECISESADS research project to provide a molecular map to guide therapy in systemic autoimmune diseases
ImaginAb Inc.	Duke–NUS Graduate Medical School; National Research Foundation	Cardiovascular disease; cancer; endocrine/metabolic disease	\$15 million	Partnership to establish Imaging Biomarker Development Lab to develop <i>in vivo</i> molecular imaging agents for cardiovascular and metabolic disease and cancer
California Stem Cell Inc.	California Institute for Regenerative Medicine; University of California, Irvine	Ophthalmic disease	\$4.5 million	Partnership to develop human stem cell–derived, transplantable, 3D retinal tissue to treat incurable retinal diseases, such as retinitis pigmentosa and age-related macular degeneration (AMD)
Fluidda N.V.; Materialise N.V.	University of Antwerp; Columbia University; University of Pennsylvania	Pulmonary disease; transplantation	€1 million (\$1.4 million)	Consortium to detect signs of rejection after lung transplantation using Fluidda's functional respiratory imaging
Abivax S.A.S.	Cuban Center for Genetic Engineering and Biotechnology	Infectious disease	Undisclosed	Partnership to co-develop a therapeutic vaccine in Phase IIB testing to treat chronic HBV infection
Audentes Therapeutics Inc.	Genethon	Gene/cell therapy; musculoskeletal disease	Undisclosed	Partnership to develop Audentes' AT001 to treat X-linked myotubular myopathy
AstraZeneca	University of California, San Francisco	Pharmaceuticals	Undisclosed	Three-year partnership to discover and develop small molecules and biologics to treat a range of indications
DBV Technologies (Euronext:DBV)	Icahn School of Medicine at Mount Sinai	Autoimmune disease	Undisclosed	Partnership to conduct preclinical testing of epicutaneous antigens via DBV's Viaskin skin patch technology to treat Crohn's disease
GlaxoSmithKline	The University of Edinburgh	Hepatic disease	Undisclosed	Partnership under GSK's Discovery Partnerships with Academia to discover and develop treatments for liver fibrosis or cirrhosis
RaQualia Pharma Inc. (JASDAQ:4579)	Nagoya University	Neurology; gastrointestinal disease	Unavailable	Partnership to identify a drug candidate, with a focus on pain and GI indications
Pfizer	Massachusetts Institute of Technology	Pharmaceuticals	Undisclosed	Three-year partnership to translate discoveries in synthetic biology to advance drug discovery and development technologies, including cellular genome engineering

regimens; running studies to validate genetic markers and other biomarkers to identify patients who respond well to high-density lipoprotein–targeting therapies; running studies to validate a plasma biomarker to help predict a favorable response to vascular anti-inflammatory agents; determining whether various anti-inflammatory agents produce measurable vascular effects and clinical benefits in vascular disease patients; and identifying genetic factors that could help

determine the benefits of drugs designed to lower heart rates.

The government of Quebec has provided ARTERIA with C\$18.2 million (\$16.5 million) in funding, and industry partners have contributed another C\$31 million (\$28.1 million) in the form of private investments. The Montreal Heart Institute is leading the project.

ARTERIA's industry partners include **Roche**, the Servier Canada Inc. subsidiary of **Servier**, the **MedImmune LLC** unit of **AstraZeneca plc**

and the Valeant Canada Inc. subsidiary of **Valeant Pharmaceuticals International Inc.**

### Grant news is good news

February saw the **Cancer Prevention & Research Institute of Texas** (CPRIT) announce its first round of grants since December 2012.

CPRIT distributes taxpayer money to Texas-based academic and industry cancer researchers. The institute ran into problems in mid-2012 when then-CSO Alfred Gilman accused the institute's executive leadership of tampering with the scientific peer review of grant proposals.<sup>2</sup>

Texas Gov. Rick Perry and state legislators froze CPRIT's grant-giving authority in December 2012 and asked the agency to create a new plan for vetting grant proposals. The state lifted the moratorium last October, and the agency issued a new call for proposals two months later.<sup>3</sup>

In its new round of funding, CPRIT awarded 3-year grants totaling \$63.2 million to 6 cancer companies that are based in or planning to relocate to Texas. The agency also awarded 4 research and 7 training grants totaling \$22.9 million to academic and medical centers across the state.

Among companies relocating to the state, Maryland's **Beta Cat Pharmaceuticals Inc.** will receive up to \$15.9 million to develop inhibitors against an undisclosed cancer target in the  $\beta$ -catenin (CTNNB1) pathway.

Michigan's **ProNAi Therapeutics Inc.** will receive up to \$14 million for Phase II testing of PNT2258, a cancer therapeutic targeting a DNA sequence upstream of B cell lymphoma 2 (BCL-2; BCL2) promoters.

Canada's **Essa Pharma Inc.** will receive up to \$12 million for a program to develop a blocker of the N-terminal domain of the androgen receptor for prostate cancer.

The three in-state companies getting CPRIT grants are **DNatrix Inc.**, **CerRx Inc.** and **ProPep Surgical LLC**.

DNatrix will get up to \$10.8 million to develop a genetically modified adenovirus to treat glioblastoma. The company's DNX-2401 is in Phase I testing for recurrent glioblastoma multiforme (GBM). CerRx is getting up to \$6 million to develop ceramide-modulating therapeutics to treat cancer. The company's lead compound is an i.v. formulation of the synthetic retinoid derivative fenretinide that has completed Phase I trials.

Fenretinide is known to decrease ceramide synthesis.

ProPep will get up to \$4.4 million to do real-time nerve identification during robotic prostatectomy, which could help decrease post-surgery rates of sexual dysfunction and urinary incontinence.

Recipients of CPRIT research grants are the **Baylor College of Medicine**, **Rice University**, **The University of Texas Medical Branch** and **The University of Texas Southwestern Medical Center**.

Rice will get up to \$3.9 million for a project to identify new biomarker signatures of cancer and its progression and to develop new diagnostic and screening tests for such cancers. UT Medical Branch will get up to \$3.2 million to perform comparative effectiveness research on the care and treatments provided to patients with cancer in Texas. Baylor will get up to \$2.2 million to study genetic events that lead to metastasis of osteosarcoma and to develop targeted therapies for the disease. UT Southwestern will get up to \$1.8 million to develop new techniques to image the size and metabolic state of a tumor.

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Published online March 20, 2014

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3. Oshrovich, L. *SciBX* 5(43); doi:10.1038/scibx.2012.1128

### COMPANIES AND INSTITUTIONS MENTIONED

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Baylor College of Medicine**, Houston, Texas  
**Beta Cat Pharmaceuticals Inc.**, Gaithersburg, Md.  
**biomol-informatics S.L.**, Madrid, Spain  
**Cancer Prevention & Research Institute of Texas**, Austin, Texas  
**CerRx Inc.**, Lubbock, Texas  
**DNatrix Inc.**, Houston, Texas  
**Essa Pharma Inc.**, Vancouver, British Columbia, Canada  
**European Biotechnology Network**, Brussels, Belgium  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Innovative Medicines Initiative**, Brussels, Belgium  
**MedImmune LLC**, Gaithersburg, Md.  
**Medina Foundation**, Granada, Spain  
**Montreal Heart Institute**, Montreal, Quebec, Canada  
**National Institutes of Health**, Bethesda, Md.  
**Northern Antibiotics Ltd.**, Helsinki, Finland  
**ProNAi Therapeutics Inc.**, Kalamazoo, Mich.  
**ProPep Surgical LLC**, Austin, Texas  
**Redx Pharma Ltd.**, Liverpool, U.K.  
**Rice University**, Houston, Texas  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Servier**, Neuilly-sur-Seine, France  
**The University of Texas Medical Branch**, Galveston, Texas  
**The University of Texas Southwestern Medical Center**, Dallas, Texas  
**Uppsala University**, Uppsala, Sweden  
**Valeant Pharmaceuticals International Inc.** (TSX:VRX; NYSE:VRX), Montreal, Quebec, Canada

# Plasma lipids: harbingers of AD?

By Michael J. Haas, Senior Writer

A panel of plasma lipids could represent a new diagnostic tool for identifying patients likely to develop Alzheimer's disease before symptoms appear, according to new clinical findings from a team of U.S. researchers.<sup>1</sup> Although the lipid panel could help enrich clinical trials of AD therapeutics for likely responders, validation studies will need to confirm its specificity for AD over other forms of dementia.

Diagnosis of AD and its precursor, mild cognitive impairment (MCI), currently involves detecting changes in biomarkers that often occur together with or after the onset of neurocognitive symptoms. In addition, measuring levels of the key biomarkers— $\beta$ -amyloid (A $\beta$ ) and its peptides, and microtubule-associated protein- $\tau$  (MAPT; tau; FTDP-17)—requires invasive procedures such as lumbar puncture or costly and time-consuming methods such as PET imaging or functional MRI scans.

Simple blood tests to detect AD noninvasively before the onset of symptoms have become the Holy Grail for diagnosing the disease. Several studies have tried to correlate the progression of MCI to AD with blood levels of small molecules, A $\beta$  peptides, tau or other proteins.<sup>2-4</sup> However, none has identified blood markers that could predict which cognitively normal individuals are at risk of developing AD.

To bridge this diagnostic gap, a team headed by Mark Mapstone and Howard Federoff conducted a 5-year clinical study to look for plasma markers in individuals age 70 or older with no cognitive impairment that could predict which of them would develop AD or amnesic MCI (aMCI)—the memory-related form of MCI that most often progresses to AD.

Mapstone is an associate professor of neurology and neurogeriatrics at the **University of Rochester Medical Center School of Medicine and Dentistry**. He co-led the team with Howard Federoff, EVP of health sciences at **Georgetown University** and executive dean of the **Georgetown University School of Medicine**.

The team included researchers from the **Unity Health System, Rochester General Hospital** and the **University of California, Irvine School of Medicine**.

## Panel power

The team enrolled 525 participants with no history of major neurological, psychiatric or blood disorders. Blood samples were withdrawn and cognitive tests performed at the start of the study and every year thereafter.

Of the 74 patients who were identified with symptoms of AD or aMCI during the study, 46 already had symptoms at the start of the study but had never been diagnosed with aMCI or AD. The other 28 became

symptomatic during the study's course. The average time for the latter group—labeled 'converters'—to show symptoms was 2.1 years.

From the original 525 participants, another 73 age-matched individuals with no cognitive impairment were selected as normal controls.

The team performed lipidomic and metabolomic analyses of the plasma samples and found a panel of 10 lipids whose levels were significantly lower in the normal-functioning converters before they developed symptoms than in the control group. The lipid levels remained low after the converters showed signs of cognitive impairment and were comparable to levels in the 46 patients with AD or aMCI.

The lipid panel included eight phosphatidylcholines and two acylcarnitines, all of which are components of cell membranes in multiple cell types. The team proposed that the observed changes in plasma lipids might reflect a breakdown of neuronal cell membranes that precedes the onset of subtle cognitive changes. Their hypothesis was based on multiple studies that identified associations between AD and low phospholipid levels in plasma and the CNS.<sup>5-10</sup>

Finally, the team developed a mathematical model that used the 10 lipid markers to predict which initially unaffected individuals would develop aMCI or AD with 90% sensitivity and 90% specificity.

According to the paper's authors, the findings suggest that the panel of lipid markers could be used to identify cognitively normal individuals who would convert to a diagnosis of aMCI or AD within two or three years.

The study was published in *Nature Medicine*.

## Lipid AD-vances

"The study potentially opens a new door in biomarker development for Alzheimer's disease," said Stephen Salloway. "Having a plasma profile that is associated with the disease and that can predict its progression would be a major advance."

Salloway is director of neurology and the Memory and Aging Program at **Butler Hospital** and a professor of neurology and psychiatry at **The Warren Alpert Medical School of Brown University**.

According to Norman Foster, director of the Center for Alzheimer's Care, Imaging and Research, senior investigator at The Brain Institute and a professor of neurology at **The University of Utah**, "The ability to predict the onset of clinical symptoms in two to three years would definitely advance the field by allowing the benefits of treatments to be identified over a very short time."

Xiaoming Guan added that the markers should be tested in a younger population to see whether the changes in these lipids can be detected even earlier. Guan is senior director of the Neurodegeneration Discovery Performance Unit at **GlaxoSmithKline plc's** R&D center in Shanghai.

GSK has three compounds in the clinic to treat AD: rilapladib (SB 659032), a small molecule inhibitor of lipoprotein-associated phospholipase A<sub>2</sub> (PLA<sub>2</sub>G7; PAFAH; Lp-PLA<sub>2</sub>), is in Phase IIa testing; SB-742457 (742457), a serotonin (5-HT<sub>6</sub>) receptor

**"Having a plasma profile that is associated with the disease and that can predict its progression would be a major advance."**

—Stephen Salloway, *Butler Hospital*

**"The ability to predict the onset of clinical symptoms in two to three years would definitely advance the field by allowing the benefits of treatments to be identified over a very short time."**

—Norman Foster,  
*The University of Utah*

antagonist, is in Phase II trials; and 2647544, an Lp-PLA<sub>2</sub> inhibitor, is in Phase I testing. In addition, GSK and **Affiris AG** have three vaccines against A $\beta$  in Phase I to Phase II testing to treat AD.

According to Richard Pither, CEO of **Cytox Ltd.**, the ability to detect which presymptomatic patients are likely to develop AD could be particularly beneficial for companies developing disease-modifying therapies.

“This panel of markers could help get those compounds into the right patients,” he said.

Cytox develops diagnostic tests for identifying patients at risk of AD or other forms of dementia.

However, Howard Fillit said that in addition to validating the findings in a larger patient population, the team needs to establish that the markers are specific for AD.

Fillit is executive director and CSO of the **Alzheimer’s Drug Discovery Foundation** and a clinical professor of geriatrics, medicine and neuroscience at **Mount Sinai Hospital**.

Because the team did not use cerebrospinal fluid (CSF) markers or PET imaging scans to diagnose MCI and AD in the converters, it is not certain that they actually had the diseases, he said.

Indeed, Salloway and Foster said that it would be useful to examine whether the changes in plasma lipid levels coincide with changes in CSF or PET imaging markers for AD.

Foster added that the findings should be replicated in other populations, using A $\beta$  and/or tau markers to show whether the lipids in the panel are altered when there is evidence of AD pathology.

Determining whether the lipid markers correlate with CSF and imaging markers for AD would also help rule out—or rule in—Lewy body dementia and other forms of non-AD-related dementia in the converters, Pither said. “Looking at these lipids in patients who have other forms of dementia could also help determine whether the markers are AD specific or not.”

Fillit added that because most people aged 70 and older have comorbidities such as atherosclerosis, vascular abnormalities in the brain or other cardiovascular conditions, “the altered lipid levels might just be markers for cognitive impairment due to vascular inflammation, not Alzheimer’s disease.”

Mapstone agreed that the lipid markers need to be validated in a larger and more demographically diverse population than was used in the study. But he countered Fillit’s concerns about comorbidities by pointing out that the same risk factors for MCI unrelated to AD were probably present in the controls as well as the converters.

“We haven’t looked at those comorbidities in our cohort, but I think that if we did, we wouldn’t see major differences in them between the converters and controls—just as we saw no differences in the frequency of apolipoprotein E  $\epsilon$ 4 between the two groups,” he said. “But we did see differences in the lipid levels.”

Last week, the **Alzheimer’s Association** issued a statement noting that the findings were preliminary and required replication and validation in larger, more diverse populations. The organization declined *SciBX*’s request for further comment.

### Road map for markers

The team’s immediate next step is to validate the lipid markers in a larger, retrospective study using banked plasma samples—such as those from

the Alzheimer’s Disease Neuroimaging Initiative (ADNI), Mapstone told *SciBX*. Once the samples are in hand, he expects to be able to complete the validation within a few months.

ADNI is a public-private partnership launched in 2004 that includes the Alzheimer’s Association and the **Foundation for the National Institutes of Health**.

In the meantime, the researchers are continuing to follow the 21 converters who developed aMCI to see whether they go on to develop full AD.

In addition, Mapstone told *SciBX* that although the lipid panel is not ready for use as a routine AD screening test, it could be used to assist patient selection in clinical trials in AD.

“Our approach could enrich the trial population with a larger fraction of potential converters than other markers such as apolipoprotein E  $\epsilon$ 4, which carries a 30% risk of AD,” he said.

“Potential converters would be randomized between the placebo and treatment arms. We would expect the converters in the placebo group to progress to MCI or AD, thus providing validation of the markers. We would also monitor the individuals identified as nonconverters to confirm that they did not develop MCI or AD, which would further validate the markers,” he said.

To monitor treatment responses and track disease progression, the trial would use CSF and PET imaging markers because they are considered the gold standards, he added.

Mapstone said that a forthcoming paper by the team will report data from transcriptome analysis of plasma from its study cohort and integrate those findings with the lipid data reported in *Nature Medicine*.

Ultimately, the team aims to use a systems biology approach—incorporating lipidomic, transcriptomic and genomic data from the study cohort—to identify cognitively normal individuals who will develop MCI and AD.

Other efforts to identify markers for early detection of AD and for monitoring disease progression include the ADNI. The study has enrolled more than 1,000 participants, including patients with AD or MCI, individuals at risk of developing AD and controls who have no memory problems.<sup>11</sup>

Mapstone said that Georgetown and the **University of Rochester** have filed a patent application covering the *Nature Medicine* findings. The technology will be available for licensing once the validation study on banked samples has been completed.

**Haas, M.J. *SciBX* 7(11); doi:10.1038/scibx.2014.305  
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**Affiris AG**, Vienna, Austria  
**Alzheimer's Association**, Chicago, Ill.  
**Alzheimer's Drug Discovery Foundation**, New York, N.Y.  
**Butler Hospital**, Providence, R.I.  
**Cytos Ltd.**, Birmingham, U.K.  
**Foundation for the National Institutes of Health**, Bethesda, Md.  
**Georgetown University**, Washington, D.C.

**Georgetown University School of Medicine**, Washington, D.C.  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
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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>				
Autoimmune disease	Chemokine CXC motif ligand 10 (CXCL10; IP-10); CXC chemokine receptor 3 (CXCR3)	<p>Human sample and mouse studies suggest inhibiting CXCL10 could help treat vitiligo. Depigmentation in the skin of patients with vitiligo is caused by CD8<sup>+</sup> T cell-induced melanocyte death. In lesion biopsies from patients with vitiligo, compared with skin biopsies from healthy individuals, CXCL10 expression was increased. In blood samples from patients, but not in samples from healthy controls, CXCR3—the CXCL10 receptor—was expressed on CD8<sup>+</sup> T cells. In a mouse model of vitiligo, an anti-CXCL10 antibody decreased depigmentation compared with an anti-CXCL9 (MIG) antibody or saline, and in animals with established disease the antibody increased repigmentation. Next steps include investigating chemical and antibody-mediated inhibition of CXCL10, CXCR3 or both in mouse models of vitiligo.</p> <p>Bristol-Myers Squibb Co.'s MDX-1100, a human mAb against CXCL10, is in Phase II testing to treat inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Novimmune S.A.'s CXCL10-binding mAb, NI-0801, is in Phase II trials to treat cirrhosis and liver disease.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.306</b>  <b>Published online March 20, 2014</b></p>	Unpatented; licensing status not applicable	<p>Rashighi, M. <i>et al. Sci. Transl. Med.</i>; published online Feb. 12, 2014; doi:10.1126/scitranslmed.3007811</p> <p><b>Contact:</b> John E. Harris, University of Massachusetts Medical School, Worcester, Mass.  e-mail:  <a href="mailto:john.harris@umassmed.edu">john.harris@umassmed.edu</a></p>
Psoriasis	IL-22; pim-1 (PIM1)	<p>Mouse studies suggest inhibiting IL-22 or PIM1 could help treat psoriasis. In a xenotransplant mouse model of severe human psoriasis, injection of an anti-IL-22 mAb reduced psoriasis symptoms as effectively as an anti-tumor necrosis factor (TNF) mAb. Gene expression network analysis of IL-22-injected skin, anti-IL-22 mAb-injected skin and the xenotransplant mouse model identified a core set of 32 differentially expressed genes, including <i>PIM1</i>. In a chemically induced mouse model of psoriasis, knockout or topical pharmacological inhibition of Pim1 blocked skin inflammation. Next steps could include testing the topical application of small molecule PIM1 inhibitors in patients with psoriasis.</p> <p>Generon (Shanghai) Corp. Ltd. has a recombinant protein containing a human IL-22 dimer, F-652, in Phase I trials to treat inflammation.</p> <p>Selvita S.A. has SEL24, a PIM1 kinase inhibitor, in preclinical development for cancer.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.307</b>  <b>Published online March 20, 2014</b></p>	Patent and licensing status unavailable	<p>Perera, G.K. <i>et al. Sci. Transl. Med.</i>; published online Feb. 12, 2014; doi:10.1126/scitranslmed.3007217</p> <p><b>Contact:</b> Frank O. Nestle, King's College London, London, U.K.  e-mail:  <a href="mailto:frank.nestle@kcl.ac.uk">frank.nestle@kcl.ac.uk</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cancer</b>				
Acute myeloid leukemia (AML)	Spleen tyrosine kinase (SYK); FMS-like tyrosine kinase 3 (FLT3; CD135)	<p>Cell-based and mouse studies suggest combined inhibition of SYK and FLT3 could help treat AML. Internal tandem duplication (ITD) mutations in <i>FLT3</i> have been associated with AML. In <i>FLT3-ITD</i> AML cell lines and patient-derived primary cells, pharmacological and shRNA inhibition of SYK decreased cell growth compared with no inhibition. In a mouse model of <i>FLT3-ITD</i>-dependent myeloproliferative disease, shRNA against Syk prolonged survival and decreased granulocyte proliferation and lymphocyte maturation compared with control shRNA. In mice, combined SYK and FLT3 inhibitors increased survival and decreased leukocytosis compared with either agent alone. Next steps could include testing combinations of FLT3 and SYK inhibitors in additional animal models of AML. The FLT3 inhibitor used in the study, quizartinib, is from Ambit Biosciences Corp. and is in Phase II testing for AML. The SYK inhibitor, PRT062607, is from Portola Pharmaceuticals Inc. and Biogen Idec Inc. and is in preclinical studies for asthma and other inflammatory disorders.</p> <p>At least eight additional companies have FLT3 inhibitors in clinical and preclinical testing to treat cancers, and at least five additional companies have SYK inhibitors in clinical and preclinical testing for various indications including cancer.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.308</b> Published online March 20, 2014</p>	Patent and licensing status unavailable	<p>Puissant, A. <i>et al. Cancer Cell</i>; published online Feb. 10, 2014; doi:10.1016/j.ccr.2014.01.022</p> <p><b>Contact:</b> Kimberly Stegmaier, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:kimberly_stegmaier@dfci.harvard.edu">kimberly_stegmaier@dfci.harvard.edu</a></p>
Brain cancer	CpG island methylation; polycomb repressive complex 2 (PRC2); enhancer of zeste homolog 2 (EZH2)	<p>Patient sample, cell culture and mouse studies suggest EZH2 inhibitors could help treat certain forms of ependymomas. In tumor samples from patients with posterior fossa ependymoma, DNA methylation pattern analysis showed that a subgroup of samples isolated from patients with poor prognosis had a greater amount of CpG island methylation than other samples. In two mouse models of ependymoma from this subgroup, a compound that targets the EZH2-containing complex PRC2 decreased tumor volume and increased survival compared with vehicle. In cell cultures derived from this subgroup, the EZH2 inhibitor GSK343 decreased H3K27 methylation compared with an inactive compound and derepressed PRC2-regulated genes. Next steps could include Phase I trials to treat patients with poor prognosis.</p> <p>GSK343 is available as a chemical probe through the Structural Genomics Consortium.</p> <p>Epizyme Inc.'s selective EZH2 inhibitor, E7438, is in Phase I/II testing to treat lymphomas.</p> <p>Constellation Pharmaceuticals Inc., GlaxoSmithKline plc and Novartis AG also have EZH2 discovery programs.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.309</b> Published online March 20, 2014</p>	Patent and licensing status unavailable	<p>Mack, S.C. <i>et al. Nature</i>; published online Feb. 19, 2014; doi:10.1038/nature13108</p> <p><b>Contact:</b> M.D. Taylor, The Hospital for Sick Children, Toronto, Ontario, Canada e-mail: <a href="mailto:mdtaylor@sickkids.ca">mdtaylor@sickkids.ca</a></p> <p><b>Contact:</b> Andrey Korshunov, German Consortium for Translational Cancer Research, Heidelberg, Germany e-mail: <a href="mailto:andrey.korshunov@med.uni-heidelberg.de">andrey.korshunov@med.uni-heidelberg.de</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer	TANK-binding kinase 1 (TBK1); inhibitor of $\kappa$ -light polypeptide gene enhanced in B cells kinase- $\epsilon$ (IKBKE; IKK-i); HER2 (EGFR2; ErbB2; neu)	<i>In vitro</i> and mouse studies suggest inhibiting TBK1 could help treat HER2 <sup>+</sup> breast cancers. In cultured HER2 <sup>+</sup> human breast cancer cells, an inhibitor of TBK1 and IKBKE plus the HER2 inhibitor Tykerb lapatinib prevented sphere formation, a surrogate for cancer stem cell potential, better than either treatment alone. The TBK1 and IKBKE inhibitor also increased Tykerb-induced apoptosis compared with Tykerb alone. In xenograft HER2 <sup>+</sup> tumor-bearing mice, inhibition of TBK1 and IKBKE plus treatment with Tykerb suppressed tumor growth more effectively than either treatment alone. Next steps include developing an inhibitor of TBK1 and IKBKE with a longer half-life <i>in vivo</i> . GlaxoSmithKline plc markets Tykerb to treat breast cancer.  <b>SciBX 7(11); doi:10.1038/scibx.2014.310</b> <b>Published online March 20, 2014</b>	Findings unpatented; licensing status not applicable	Deng, T. <i>et al. Cancer Res.</i> ; published online Jan. 31, 2014; doi:10.1158/0008-5472.CAN-13-2138 <b>Contact:</b> Eldad Zacksenhaus, Toronto General Research Institute, University Health Network, Toronto, Ontario, Canada e-mail: <a href="mailto:eldad.zacksenhaus@utoronto.ca">eldad.zacksenhaus@utoronto.ca</a>
Cancer	IL-33 (NF-HEV)	Mouse studies suggest IL-33 could be used as an adjuvant for cancer immunotherapy. In mice, intramuscular injection of an E6 transforming protein (human papillomavirus-16; HpV16gp1) and E7 transforming protein (human papillomavirus-16; HpV16gp2) DNA vaccine with plasmids encoding full-length or truncated IL-33 increased the number of antigen-specific interferon- $\gamma$ (IFN $\gamma$ )-producing T cells compared with injection of the DNA vaccine alone. Both IL-33 adjuvants stimulated CD4 <sup>+</sup> and CD8 <sup>+</sup> antigen-specific T cells, and the full-length IL-33 stimulated an antigen-specific IgG response. In mice with tumors expressing the HPV antigens, vaccine plus either adjuvant rapidly induced complete tumor regression, whereas vaccine alone rarely led to complete regression. Next steps could include testing the adjuvant potential of IL-33 with additional DNA vaccines. Inovio Pharmaceuticals Inc., a collaborator on the study, has IL-33-encoding DNA in preclinical testing as a cancer vaccine adjuvant.  <b>SciBX 7(11); doi:10.1038/scibx.2014.311</b> <b>Published online March 20, 2014</b>	Patent and licensing status unavailable	Villarreal, D.O. <i>et al. Cancer Res.</i> ; published online Jan. 21, 2014; doi:10.1158/0008-5472.CAN-13-2729 <b>Contact:</b> David B. Weiner, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:dbweiner@mail.med.upenn.edu">dbweiner@mail.med.upenn.edu</a>
Colon cancer	Notch 3 (NOTCH3); Musashi RNA binding protein 1 (MSI1)	<i>In vitro</i> and mouse studies suggest inhibiting NOTCH3 could help treat colon cancer. In colon cancer cell lines and metastatic colorectal cancer samples, NOTCH3 stimulation induced expression of MSI1 to reinforce intracellular Notch signaling, whereas the anti-NOTCH2 and NOTCH3 antibody OMP-59R5 prevented the MSI1 increase. In mice with NOTCH3-expressing colon cancer xenografts, the anti-NOTCH antibody decreased MSI1 levels and tumor burden compared with a control antibody. Next steps include clinical testing of a NOTCH3 antibody to treat colon cancer. OncoMed Pharmaceuticals Inc.'s OMP-59R5 is in Phase I/II testing for pancreatic cancer and small cell lung cancer.  <b>SciBX 7(11); doi:10.1038/scibx.2014.312</b> <b>Published online March 20, 2014</b>	Unpatented; unavailable for licensing	Pasto, A. <i>et al. Cancer Res.</i> ; published online Feb. 13, 2014; doi:10.1158/0008-5472.CAN-13-2022 <b>Contact:</b> Stefano Indraccolo, Veneto Institute of Oncology, Padova, Italy e-mail: <a href="mailto:stefano.indraccolo@unipd.it">stefano.indraccolo@unipd.it</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Lung cancer	TANK-binding kinase 1 (TBK1); inhibitor of $\kappa$ -light polypeptide gene enhancer in B cells kinase- $\epsilon$ (IKBKE; IKK-i); Janus kinase-1 (JAK-1); JAK-2; K-Ras (KRAS)	Cell culture and mouse studies suggest inhibiting TBK1 could help treat lung cancers driven by <i>KRAS</i> mutations. In cultured cells, the JAK-1 and JAK-2 inhibitor momelotinib also inhibited TBK1 and IKBKE, two kinases required for <i>KRAS</i> -mediated oncogenic cytokine expression. In a mouse model of <i>KRAS</i> -driven lung cancer, momelotinib decreased tumor volume more than docetaxel after four weeks of treatment. In the mouse model, momelotinib plus a MEK inhibitor increased cancer cell death compared with either treatment alone. Next steps could include clinical testing of momelotinib with or without a MEK inhibitor in <i>KRAS</i> -mutant lung cancers. Gilead Sciences Inc.'s momelotinib (CYT387) is in Phase III testing to treat myeloproliferative disorder.  <b>SciBX 7(11); doi:10.1038/scibx.2014.313</b> Published online March 20, 2014	Findings unpatented; licensing status not applicable	Zhu, Z. <i>et al. Cancer Discov.</i> ; published online Jan. 20, 2014; doi:10.1158/2159-8290.CD-13-0646 <b>Contact:</b> William C. Hahn, Dana-Farber Cancer Institute, Boston, Mass. e-mail: <a href="mailto:william_hahn@dfci.harvard.edu">william_hahn@dfci.harvard.edu</a>
<b>Cardiovascular disease</b>				
Atherosclerosis	Squalene synthase (SQS; FDFT1); cyclooxygenase (COX)	<i>In vitro</i> and mouse studies suggest a new class of trifunctional, cholesterol-limiting, anti-inflammatory, antioxidant compounds could help treat atherosclerosis. Chemical synthesis and <i>in vitro</i> testing of phenothiazine-morpholine and phenothiazine-benzothiazine analogs identified four lead compounds that inhibited SQS, COX and lipid peroxidation at high nanomolar to micromolar $IC_{50}$ values and that decreased oxidation of human low-density lipoprotein (LDL) compared with vehicle. In mice fed a high-fat diet, lead compounds decreased serum levels of LDL and total cholesterol and increased serum levels of high-density lipoprotein (HDL) compared with vehicle. Ongoing work includes optimizing the lead compounds to treat atherosclerosis and other disorders involving dyslipidemia.  <b>SciBX 7(11); doi:10.1038/scibx.2014.314</b> Published online March 20, 2014	Unpatented; unlicensed	Matralis, A.N. & Kourounakis, A.P. <i>J. Med. Chem.</i> ; published online Feb. 25, 2014; doi:10.1021/jm401842e <b>Contact:</b> Angeliki P. Kourounakis, University of Athens, Athens, Greece e-mail: <a href="mailto:angeliki@pharm.uoa.gr">angeliki@pharm.uoa.gr</a>
<b>Infectious disease</b>				
<i>Candida</i> ; fungal infection	Not applicable	<i>In vitro</i> studies suggest a new class of synthetic polymers could help treat <i>Candida albicans</i> and other fungal infections. Chemical synthesis, SAR studies and <i>in vitro</i> testing of a series of nylon-3 polymers identified several lead compounds with low micromolar minimum inhibitory concentration (MIC) values against <i>C. albicans</i> , including strains resistant to the generic antifungals fluconazole and amphotericin B, and against <i>Cryptococcus neoformans</i> . In human red blood cells, the compounds did not induce significant hemolysis at the MICs tested. Ongoing work includes optimization of the lead compounds.  <b>SciBX 7(11); doi:10.1038/scibx.2014.315</b> Published online March 20, 2014	Patent application filed by the Wisconsin Alumni Research Foundation; available for licensing or partnering	Liu, R. <i>et al. J. Am. Chem. Soc.</i> ; published online March 7, 2014; doi:10.1021/ja500036r <b>Contact:</b> Samuel H. Gellman, University of Wisconsin-Madison, Madison, Wisc. e-mail: <a href="mailto:gellman@chem.wisc.edu">gellman@chem.wisc.edu</a> <b>Contact:</b> Kristyn S. Masters, same affiliation as above e-mail: <a href="mailto:kmasters@wisc.edu">kmasters@wisc.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Inflammation</b>				
Chronic granulomatous disease (CGD)	IL-1 receptor	<p>Mouse and human studies suggest IL-1 receptor antagonists could help prevent infections and treat colitis in patients with CGD. Patients with CGD have a mutated NADPH complex, which results in reactive oxygen species deficiency and leads to defective autophagy. In CGD mice with <i>Aspergillus fumigatus</i> infection or chemically induced colitis, the IL-1 receptor inhibitor Kineret anakinra increased survival and decreased colitis symptoms compared with no treatment. In monocytes from patients with CGD exposed to <i>Aspergillus</i>, Kineret restored autophagy and phagocytic responses to normal levels. In two patients with CGD and colitis, three months of Kineret led to progressive improvement of colitis symptoms with no infections. Next steps could include testing anakinra in larger patient cohorts.</p> <p>Swedish Orphan Biovitrum AB markets Kineret, an IL-1 receptor antagonist, to treat rheumatoid arthritis (RA) and cryopyrin-associated periodic syndrome (CAPS).</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.316</b> Published online March 20, 2014</p>	Patent and licensing status unavailable	<p>de Luca, A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 18, 2014; doi:10.1073/pnas.1322831111</p> <p><b>Contact:</b> Charles A. Dinarello, University of Colorado Denver, Aurora, Colo. e-mail: <a href="mailto:cdinarello@mac.com">cdinarello@mac.com</a></p>
<b>Musculoskeletal disease</b>				
Musculoskeletal disease	p38 mitogen-activated protein kinase (p38 MAPK; MAPK14)	<p><i>In vitro</i> and mouse studies suggest partial inhibition of p38 MAPK signaling could help regenerate muscle in aged patients. In skeletal muscle stem cells from aged mice, self-renewal capacity was decreased and signaling through the p38 MAPK <math>\alpha</math>-isoform and <math>\beta</math>-isoform was increased compared with what was seen in muscle stem cells from young mice. Muscle stem cells from aged mice cultured on soft hydrogels with a p38 MAPK <math>\alpha</math>-isoform and <math>\beta</math>-isoform inhibitor had greater self-renewal capacity than cells cultured on hydrogels alone. In aged mice with muscle injury, transplantation of aged muscle stem cells treated with the p38 MAPK inhibitor and expanded with the culture system restored muscle strength to normal levels. Next steps include applying the approach to human muscle regeneration.</p> <p>At least seven companies have p38 MAPK inhibitors in Phase II testing or earlier for various indications including cancer and pain.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.317</b> Published online March 20, 2014</p>	<p>For findings in first study, patent application filed; available for licensing</p> <p>For findings in second study, patent and licensing status unavailable</p>	<p>Cosgrove, B.D. <i>et al. Nat. Med.</i>; published online Feb. 16, 2014; doi:10.1038/nm.3464</p> <p><b>Contact:</b> Helen M. Blau, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:hblau@stanford.edu">hblau@stanford.edu</a></p> <p><b>Contact:</b> Penney M. Gilbert, University of Toronto, Toronto, Ontario, Canada e-mail: <a href="mailto:penney.gilbert@utoronto.ca">penney.gilbert@utoronto.ca</a></p> <p>Bernet, J.D. <i>et al. Nat. Med.</i>; published online Feb. 16, 2014; doi:10.1038/nm.3465</p> <p><b>Contact:</b> Bradley B. Olwin, University of Colorado at Boulder, Boulder, Colo. e-mail: <a href="mailto:bradley.olwin@colorado.edu">bradley.olwin@colorado.edu</a></p>
<b>Neurology</b>				
Amyotrophic lateral sclerosis (ALS); epilepsy	Solute carrier family 1 glial high affinity glutamate transporter member 2 (SLC1A2; EAAT2; GLT-1)	<p><i>In vitro</i> and mouse studies suggest EAAT2 translational activators could help treat neurological disorders including ALS and epilepsy. In mixed cultures of astrocytes and neurons, a small molecule transcriptional activator of EAAT2 protected neurons from excitotoxic cell death. In a transgenic mouse model of ALS, i.p. administration of the EAAT2 activator after disease onset delayed motor impairments and extended survival. In a mouse model of epilepsy, the activator decreased mortality and spontaneous recurrent seizures compared with vehicle. Next steps could include testing the activators in other disease models driven by neuronal excitotoxicity.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.318</b> Published online March 20, 2014</p>	Patent and licensing status unavailable	<p>Kong, Q. <i>et al. J. Clin. Invest.</i>; published online Feb. 24, 2014; doi:10.1172/JCI66163</p> <p><b>Contact:</b> Chien-Liang Glenn Lin, The Ohio State University, Columbus, Ohio e-mail: <a href="mailto:lin.492@osu.edu">lin.492@osu.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Anxiety	Transient receptor potential cation channel subfamily C member 4 (TRPC4)	<p>Mouse studies suggest inhibiting TRPC4 could help treat anxiety. In multiple behavioral assays that assess innate fear, <i>Trpc4</i>-deficient mice had less anxiety than wild-type mice. In the mice, deletion of <i>Trpc4</i> had no effect on learned fear responses, motor coordination or balance. Next steps could include determining how activation of TRPC4 and related channels contribute to anxiety and determining which TRP channel is the most suitable target for clinical intervention.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.319</b> Published online March 20, 2014</p>	Patent and licensing status unavailable	<p>Riccio, A. <i>et al. J. Neurosci.</i>; published online March 5, 2014; doi:10.1523/JNEUROSCI.2274-13.2014 <b>Contact:</b> David E. Clapham, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:dclapham@enders.tch.harvard.edu">dclapham@enders.tch.harvard.edu</a></p>
<b>Renal disease</b>				
Renal disease	Phosphodiesterase-4 (PDE-4)	<p>Rat and <i>in silico</i> studies suggest blocking PDE-4 inhibition could help treat kidney disease by sustaining podocyte differentiation. In glomeruli isolated from a rat model of kidney disease, proteomics and <i>in silico</i> kinase and network analyses identified a reduction of signaling through cAMP responsive element binding protein 1 (Creb1; Creb) that regulated podocyte differentiation markers. In the rat model, blocking cAMP hydrolysis with a PDE-4 inhibitor decreased proteinuria compared with no treatment and restored normal podocyte morphology. Next steps include testing a series of PDE-4 inhibitors in the rat model and investigating how components of the cAMP network affect different disease stages.</p> <p>Kyorin Pharmaceutical Co. Ltd. markets the small molecule PDE-4 and PDE-10 inhibitor Ketas ibudilast to treat asthma. Takeda Pharmaceutical Co. Ltd., Forest Laboratories Inc., Merck &amp; Co. Inc. and Mitsubishi Tanabe Pharma Corp. market Daliresp roflumilast for chronic obstructive pulmonary disease (COPD). At least four other companies have PDE-4 inhibitors in Phase III or earlier trials to treat respiratory disease.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.320</b> Published online March 20, 2014</p>	Unpatented; licensing status not applicable	<p>Azeloglu, E.U. <i>et al. Sci. Signal.</i>; published online Feb. 4, 2014; doi:10.1126/scisignal.2004621 <b>Contact:</b> Ravi Iyengar, Mount Sinai School of Medicine, New York, N.Y. e-mail: <a href="mailto:ravi.iyengar@mssm.edu">ravi.iyengar@mssm.edu</a> <b>Contact:</b> John Cijiang He, same affiliation as above e-mail: <a href="mailto:cijiang.he@mssm.edu">cijiang.he@mssm.edu</a></p>
<b>Transplantation</b>				
Graft rejection	CD28; CD244 natural killer cell receptor 2B4 (CD244; 2B4)	<p>Mouse studies suggest selective CD28 blockade could help prevent transplant rejection. In mice with alloreactive skin grafts, a CD28-selective domain antibody (dAb), which lacked an Fc domain and only blocked the CD28<sup>+</sup> T cell co-stimulatory pathway, extended graft survival better than Orenzia abatacept. Orenzia is a T cell co-stimulation blocker that inhibits both CD28 co-stimulatory and CTLA-4 (CD152) co-inhibitory signals. In the mice, the CD28-selective dAb decreased donor-reactive CD4<sup>+</sup> and CD8<sup>+</sup> T cell accumulation at the graft site compared with a control dAb and induced expression of the T cell co-inhibitory receptor 2B4 on CD8<sup>+</sup> T cells. Next steps could include testing the antibody in additional transplant models and enhancing the co-inhibitory properties of 2B4.</p> <p>Bristol-Myers Squibb Co. and Ono Pharmaceutical Co. Ltd. market Orenzia to treat rheumatoid arthritis (RA).</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.321</b> Published online March 20, 2014</p>	Patent and licensing status unavailable	<p>Liu, D. <i>et al. J. Exp. Med.</i>; published online Feb. 3, 2014; doi:10.1084/jem.20130902 <b>Contact:</b> Mandy L. Ford, Emory University, Atlanta, Ga. e-mail: <a href="mailto:mandy.ford@emory.edu">mandy.ford@emory.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Various</b>				
Autoimmune disease; cancer	Proteasome	<p><i>In vitro</i> studies identified belactosin A proteasome inhibitors with peptide boronate warheads that could help treat cancer or autoimmune diseases. <i>In vitro</i>, the compounds inhibited the 20S proteasome's chymotrypsin-like activity better than the marketed proteasome inhibitor Velcade bortezomib and decreased growth of a human colon cancer cell line compared with compounds lacking the modified warhead. The most potent compound specifically inhibited proteasome activity, whereas Velcade also inhibited cathepsin A and cathepsin G. Next steps could include testing the inhibitors in disease models.</p> <p>Takeda Pharmaceutical Co. Ltd. and Johnson &amp; Johnson market Velcade to treat multiple myeloma (MM) and mantle cell lymphoma (MCL).</p> <p>Amgen Inc. and Ono Pharmaceutical Co. Ltd. market the selective proteasome inhibitor Kyprolis carfilzomib to treat MM.</p> <p>At least 10 companies have proteasome inhibitors in Phase III or earlier testing to treat various cancers.</p> <p><b>SciBX 7(11); doi:10.1038/scibx.2014.322</b>  <b>Published online March 20, 2014</b></p>	Patent and licensing status unavailable	<p>Kawamura, S. <i>et al. J. Med. Chem.</i>; published online Feb. 13, 2014; doi:10.1021/jm500045x</p> <p><b>Contact:</b> Satoshi Shuto, Hokkaido University, Sapporo, Japan  e-mail: <a href="mailto:shu@pharm.hokudai.ac.jp">shu@pharm.hokudai.ac.jp</a></p>

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## 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>Assays &amp; screens</b>			
Plasma lipid signature to identify presymptomatic individuals that may progress to Alzheimer's disease (AD)	Clinical data suggest plasma lipids could help identify presymptomatic individuals who will develop AD or mild cognitive impairment (MCI). The 5-year study included 46 patients who already had AD or MCI, 28 initially unaffected individuals who were diagnosed with AD or MCI during the study and 73 unaffected age-matched controls. In plasma samples from the participants, lipidomics analysis identified a panel of 8 phosphatidylcholines and 2 acylcarnitines that predicted the conversion of unaffected patients to diagnosis with AD or MCI with 90% sensitivity and 90% specificity. A forthcoming manuscript will report the results of transcriptomic and genomic analyses of plasma samples from the same cohort ( <i>see Plasma lipids: harbingers of AD?</i> , page 9).	Patented by the University of Rochester and Georgetown University; unlicensed	Mapstone, M. <i>et al. Nat. Med.</i> ; published online March 9, 2014; doi:10.1038/nm.3466 <b>Contact:</b> Howard J. Federoff, Georgetown University, Washington, D.C. e-mail: <a href="mailto:hjf8@georgetown.edu">hjf8@georgetown.edu</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.323</b> <b>Published online March 20, 2014</b>		
Telomerase promoter activity-based assay to detect circulating tumor cells (CTCs)	An adenovirus that expresses GFP from the telomerase promoter could be used to detect CTCs in patients with brain cancer. Telomerase activity is elevated in nearly all types of tumor cells but not normal cells. In blood samples from patients with glioma undergoing radiation therapy, the reporter-based assay detected CTCs in 8 of 11 patients pre-radiation therapy, 1 of 8 patients post-radiation therapy and 0 of 10 healthy controls. In sequential blood samples from two patients, the reporter assay distinguished progressive disease and tumor recurrence in one patient from pseudoprogression in the second patient. Next steps could include using the assay in larger cohorts of patients with glioma.	Patent filed; licensing status undisclosed	MacArthur, K.M. <i>et al. Cancer Res.</i> ; published online Feb. 13, 2014; doi:10.1158/0008-5472.CAN-13-0813 <b>Contact:</b> Jay F. Dorsey, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:jayd@uphs.upenn.edu">jayd@uphs.upenn.edu</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.324</b> <b>Published online March 20, 2014</b>		
<b>Disease models</b>			
A hepatoma-based cell culture model that supports the entire cycle of HBV and HCV	Cell culture studies suggest a hepatoma-based cell culture model could aid the study of HBV and HCV infection and replication. The hepatocellular carcinoma (HCC)-derived cell line called HLCZ01 originated from tumor tissue obtained from a male patient with HCV infection. <i>In vitro</i> , the cell line supported infection of clinically isolated HBV and HCV, producing infectious viral particles. In the cells, agents that block infection in other models and in humans decreased infection compared with no treatment. Next steps include using the cell line to explore mechanisms of viral entry and host-virus interactions.	HLCZ01 patented; unavailable for licensing	Yang, D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 10, 2014; doi:10.1073/pnas.1320071111 <b>Contact:</b> Haizhen Zhu, Hunan University, Hunan, China e-mail: <a href="mailto:zhuhaizhen69@yahoo.com">zhuhaizhen69@yahoo.com</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.325</b> <b>Published online March 20, 2014</b>		
<b>Drug platforms</b>			
Bispecific, diagnostic antibodies for enhanced detection of dimerized or phosphorylated oncoproteins	Cell culture studies suggest bispecific antibodies specific for dimerized or phosphorylated proteins could be used in cancer diagnostics. In cultured, ligand-stimulated human breast cancer cells, antibodies targeting HER2 (EGFR2; ErbB2; neu) and epidermal growth factor receptor 3 (EGFR3; HER3; ErbB3) that were fused by peptide or DNA linkers led to staining of HER2-HER3 dimers, whereas unlinked, monovalent antibodies did not. In formalin-fixed, paraffin-embedded breast cancer cells, an antibody recognizing both a phosphorylated and an unphosphorylated epitope of HER3 increased detection sensitivity and decreased cross-reactivity compared with monovalent antibodies. Next steps include further optimizing assay sensitivity and applicability to human tissue samples and extending the assay to additional cancer targets.	Patent applications filed; available for licensing	van Dieck, J. <i>et al. Chem. Biol.</i> ; published online Feb. 13, 2014; doi:10.1016/j.chembiol.2013.12.018 <b>Contact:</b> Michael Tacke, Roche Diagnostics GmbH, Penzberg, Germany e-mail: <a href="mailto:michael.tacke@roche.com">michael.tacke@roche.com</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.326</b> <b>Published online March 20, 2014</b>		

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Induced multipotent progenitor cell–derived human hepatocytes (iMPC-Heps) with proliferative and functional potential <i>in vivo</i>	Cell culture and mouse studies suggest human iMPC-Heps could be used for disease modeling and could enable autologous liver therapy. Human hepatocytes derived from induced pluripotent stem (iPS) cells have previously been shown to have broad metabolic activity but lack the proliferative potential required for efficient liver regeneration. In cell culture, human fibroblasts engineered to express <i>OCT4</i> , <i>SOX2</i> and <i>KLF4</i> and also treated with small molecule combinations transdifferentiated into iMPC-derived endoderm progenitors that could be further converted to iMPC-Heps by additional chemicals and growth factors. In a mouse model of liver injury, transplanted iMPC-Heps proliferated for at least 9 months, matured <i>in vivo</i> and repopulated up to 2% of the liver, and they led to 10% higher serum albumin levels than no transplant. Next steps include further optimizing <i>in vitro</i> maturation of iMPC-Heps (see <b>A liver divided</b> , page 1).	Patent filed covering reprogramming conditions to generate hepatocytes from fibroblasts; available for licensing	Zhu, S. <i>et al. Nature</i> ; published online Feb. 23, 2014; doi:10.1038/nature13020 <b>Contact:</b> Holger Willenbring, University of California, San Francisco, Calif. e-mail: <a href="mailto:willenbring@stemcell.ucsf.edu">willenbring@stemcell.ucsf.edu</a> <b>Contact:</b> Sheng Ding, Gladstone Institute of Cardiovascular Disease, San Francisco, Calif. e-mail: <a href="mailto:sheng.ding@gladstone.ucsf.edu">sheng.ding@gladstone.ucsf.edu</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.327</b> <b>Published online March 20, 2014</b>		
Müller glia cells as a source for regenerative retinal neuronal cell types	<i>In vitro</i> and mouse studies suggest Müller glia cells can be used to generate transplantable retinal progenitor cells for treating damaged or degenerating retinas. In specific cell culture conditions, <i>p53</i> <sup>-/-</sup> Müller glia could be induced to proliferate, convert into Müller glia–derived progenitor-like cells (MRPs) expressing retinal progenitor markers and further differentiate into cone and rod photoreceptors. In mice, <i>p53</i> <sup>-/-</sup> MRPs injected into retinal tissue engrafted and differentiated into photoreceptors and retinal ganglion cells, which are important for transmission of visual information from photoreceptors to different brain regions. Next steps include developing retinal differentiation protocols for wild-type mouse Müller glia cells.	Patent and licensing status undisclosed	Zhao, J.J. <i>et al. J. Biol. Chem.</i> ; published online Feb. 12, 2014; doi:10.1074/jbc.M113.532671 <b>Contact:</b> Kang Zhang, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:kang.zhang@gmail.com">kang.zhang@gmail.com</a> <b>Contact:</b> Jack Jiagang Zhao, same affiliation as above e-mail: <a href="mailto:j3zhao@ucsd.edu">j3zhao@ucsd.edu</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.328</b> <b>Published online March 20, 2014</b>		
<b>Markers</b>			
Cerebrospinal fluid (CSF) levels of soluble CD19 to detect CNS disease in patients with lymphoma	Human sample studies suggest measuring soluble CD19 in CSF could be used to detect CNS disease in lymphoma patients and to aid prognosis and guide treatment. In CSF samples from 91 patients with diffuse large B cell lymphoma (DLBCL) and 22 with Burkitt lymphoma, high levels of soluble CD19 were found in patients with overt CNS disease that was either detectable by the presence of lymphoma cells in flow cytometry analysis or by suspicious neurological symptoms. In the samples, high soluble CD19 levels were associated with shorter event-free and overall survival. Next steps include improving the accessibility of the method.	Patent application filed; available for licensing	Muñiz, C. <i>et al. Blood</i> ; published online Feb. 5, 2014; doi:10.1182/blood-2013-11-537993 <b>Contact:</b> Alberto Orfao, Institute of Biomedical Investigation of Salamanca and University of Salamanca, Salamanca, Spain e-mail: <a href="mailto:orfao@usal.es">orfao@usal.es</a>
	<b>SciBX 7(11); doi:10.1038/scibx.2014.329</b> <b>Published online March 20, 2014</b>		
Circulating giant macrophages as diagnostic markers for metastasizing tumors	Human sample studies suggest detection of circulating giant macrophages could be used to predict solid tumor metastasis. In blood samples from a cohort of 79 patients with breast, prostate or pancreatic cancer, a low-pressure filtration system with precision microfilters isolated cancer-associated, macrophage-like cells (CAMLs) with giant cellular morphology and large, atypical nuclei in 83%–97% of the samples. CAMLs were positive for markers from engulfed cancer cells and markers from angiogenic endothelial cells, and in 10% of the cases the cells were associated with circulating tumor cells. Next steps include identifying clinical applications for CAML measurements such as assessing tumor responses to specific therapy. Creatv MicroTech Inc. markets the CellSieve microfiltration assay to isolate CAMLs.	Patent application filed; available for licensing	Adams, D.L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 18, 2014; doi:10.1073/pnas.1320198111 <b>Contact:</b> Daniel L. Adams, Creatv MicroTech Inc., Rockville, Md. e-mail: <a href="mailto:dan@creatvmicrotech.com">dan@creatvmicrotech.com</a>
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