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AMPlifying targets

By C. Simone Fishburn, Senior Editor

Although small- and medium-sized biotechs are absent from the NIH's new Accelerated Medicines Partnership with industry and not-for-profit organizations, consortium leaders expect that making results publicly available on their search for new targets and biomarkers in four diseases will benefit all players. However, it is unclear whether the $230 million, 5-year fund is adequately financed to meet the partnership's goal of accelerating target discovery.

The public-private partnership (PPP) includes 10 companies, 5 disease-oriented not-for-profit organizations and the **Pharmaceutical Research and Manufacturers of America** (PhRMA) (*see* **Table 1, "Participants in the NIH AMP consortium"**). The operations and governance of the PPP will be managed by the **Foundation for the National Institutes of Health** (FNIH), a not-for-profit entity set up in the early 1990s to support the NIH by forming and facilitating PPPs for biomedical research and training.

The NIH and industry partners are contributing equally to the total fund for the Accelerated Medicines Partnership (AMP). In addition, some not-for-profit organizations are giving financial support, and all parties are making in-kind contributions such as scientists, expertise, technology and access to patient samples.

The NIH's share of the AMP budget is coming from the NIH institutes responsible for the therapeutic areas being investigated—Alzheimer's disease (AD), type 2 diabetes, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (*see* **Table 1, "Participants in the NIH AMP consortium"**).

About $130 million will go to AD projects, $58 million to type 2 diabetes and $42 million to the autoimmune diseases RA and SLE.

AMP will fund research that uses DNA sequencing, proteomics, single-cell analysis, bioengineered cells and imaging, and it will use big data tools to integrate information from human tissue and blood samples, clinical trials and demographic studies.

NIH director Francis Collins hopes AMP will help reduce the more than 50% failure rate of Phase II and Phase III trials. According to Collins, the failure rate results largely from poor target selection and preclinical experiments in cell-based or animal models that do not properly represent human disease.

"We want to learn about how to place the right bets on targets, to give you a higher likelihood of success," said Collins in an interview with *BioCentury This Week* television.

Elias Zerhouni noted that although there is considerable industry activity in some of the selected disease areas, AMP is focused on elucidating underlying mechanisms of those diseases. Zerhouni is

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president of global R&D at **Sanofi** and was director of the NIH from 2002 to 2008.

"We're hitting a wall in terms of the understanding of biology of many diseases," he told *SciBX*. "In diabetes, we know the consequences of the disease but not the causes. The same is true with Alzheimer's disease. There is no clear-cut understanding at the mechanistic level. The methodologies in the lab don't represent the human situation. We need solutions for precision medicine to generate targets that relate to human diseases."

According to David Wholley, the science-driven approach and focus on disease distinguish AMP from Europe's **Innovative Medicines Initiative** (IMI), a PPP involving government and academic organizations. In contrast to AMP, he said, IMI is aimed at spurring the development of new companies and providing a regional economic stimulus.

Wholley is director of the Biomarkers Consortium at FNIH.

Bill Chin, EVP of science and regulatory affairs at PhRMA, agreed that the scope and focus of AMP set it apart from the many other PPPs in the translational space.

"There is much basic science and science in the clinical realm, but not much in the area of target development. This is a rare combination of academics, NIH, nonprofits and industry," he told *SciBX*. "AMP seeks to look at the critical bottleneck in the industry, which is to find out what we need to target."

Coalition of the willing

According to Zerhouni, the idea for AMP was seeded many years ago when the NIH concluded that something needed to be done to speed the development of new drugs.

In the past two years, NIH leaders held numerous one-on-one meetings with pharma R&D heads as well as workshops to define the goals, structure and scope of AMP. The concept of a precompetitive alliance focused on target validation was the idea from the outset,[1] but reaching agreement on disease areas and research strategies took many discussions.

"We brought industry in from the beginning to increase the chance we'll ask the right questions and bring the right answers," Chin told *SciBX*.

"What took time in building this alliance was reaching consensus on the research approach. Getting agreement on the numbers and the plan before the companies would commit was difficult—people had to agree on the costs and the timelines before signing up," said George Vradenburg, who is cofounder and chairman of the not-for-profit **USAgainstAlzheimer's** and a member of the AD steering committee of AMP.

"There's a real evolution from the industry perspective in what's competitive and what's not," Wholley said on *BioCentury This Week*. "It used to be that products of the genome were considered competitive. The line has now moved to be around the therapy and the compound."

One sticking point for AMP was whether or not to include schizophrenia.

Roche had been interested in collaborating on schizophrenia but did not join AMP when that disease was dropped. A company spokesperson said that Roche is open to joining if another opportunity arises.

"I would like to get schizophrenia back in," said Collins. "We did have a whole design together—about how we'd go after it—but ultimately there was not a critical mass of companies that felt it was a high enough priority for them. Without that we couldn't include it in AMP. I hope we'll be able to add schizophrenia in another year as we see some success for the model."

Something for everyone

Chin said that it was important to have multiple companies in AMP engaged in each disease area. "Once you have five to six companies, you get a diversity of opinions that adds texture and wisdom," he said.

Douglas Williams, EVP of R&D at **Biogen Idec Inc.**, said that the AD project was the impetus for joining. Biogen Idec is the lone biotech member of AMP.

"We think it's a very effective way of partnering with academia to move forward the process of target validation and disease biology," he told *SciBX*. "We needed the catalyst of the NIH stepping forward with increased financial commitment—that's what sets this apart and gives this the critical mass of resources and expertise to the problem."

> **"We needed the catalyst of the NIH stepping forward with increased financial commitment—that's what sets this apart and gives this the critical mass of resources and expertise to the problem."**
>
> ***—Douglas Williams, Biogen Idec Inc.***

According to Wholley, the open access to AMP results should level the playing field—even for companies that do not participate.

"Biotechs wouldn't put their money into this—nor should they. They need to preserve their resources," Zerhouni told *SciBX*.

Chin wants to see more companies join the consortium. He said that he is talking with other members of PhRMA and will provide them with updates as the AMP programs move forward.

UPPPing the ante

The precise contribution of each organization has not been disclosed, but on average each company will give $1–2 million per year. The average annual R&D budget of the participating companies is about $5 billion.

Magali Haas said that the consortium is a step in the right direction but likely needs a bigger budget.

"We have to ask: what's the appropriate level of investment?" she said. "It's the right approach, has all the right players and the right focus—on biomarkers and mechanisms—but this is woefully underfunded for the magnitude of what's needed for Alzheimer's disease. It will be difficult to accelerate the pace with that amount of funding. They'll have to make trade-offs—for example, by limiting the number of markers they can assess. I'd rather they make the appropriate investment now as this is the first step in a long process."

Haas is founder and CEO of **Orion Bionetworks**, a not-for-profit alliance of public and private partners developing predictive computerized models for CNS diseases. Orion is not a member of AMP.

Like Haas, Sandra Raymond, president and CEO of the **Lupus Foundation of America Inc.**, supports the AMP model and is concerned about funding.

"$20 million buys a lot of basic science, but it doesn't buy the huge cohorts and databanking or biobanking that you'd like to see," she told *SciBX*.

Collins and Wholley both said that AMP is a pilot program that they hope to grow in the future. They would like to add new therapeutic areas and recruit new participants once they have data to show the current plan is working.

Targets and biomarkers

According to Wholley, there are three tracks for distributing AMP funds.

The NIH will disburse its 50% contribution via the normal NIH grant process. The FNIH holds the remaining money from industry and the not-for-profit entities. A portion will go to supplement the NIH grants, and the rest will be disbursed directly by the FNIH. The grants will all go to extramural scientists, Wholley told *SciBX*.

A portion of the AD funds will go to embedding biomarker screening into several existing disease-prevention studies sponsored by the NIH, companies and not-for-profit organizations. In addition, three ongoing NIH-funded studies to identify and validate new targets will receive further money to support screening of RNA and proteomics panels. This funding will create network models using systems biology to validate targets involved in disease progression.

Williams hopes that the AMP funding will lead to the development of new biomarkers to track AD patient progression that are better than the currently used β-amyloid (Aβ). If the project proves successful, the studies could identify new pathways that drive pathogenesis in all or a subset of patients with AD, he told *SciBX*.

According to Meryl Comer, the emphasis on biomarkers reflects a paradigm shift toward understanding the need for early diagnosis of AD, especially in presymptomatic populations.

Table 1. Participants in the NIH AMP consortium. The NIH has formed a public-private partnership, called the Accelerated Medicines Partnership (AMP), with industry and not-for-profit organizations to accelerate discovery of targets and biomarkers in Alzheimer's disease (AD), type 2 diabetes, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The not-for-profit Foundation for the National Institutes of Health will manage the funds and operations.

Government	Industry	Not-for-profit organizations
FDA	**AbbVie Inc.** (NYSE:ABBV)	**Alzheimer's Association**
NIH Office of the Director	**Biogen Idec Inc.** (NASDAQ:BIIB)	**American Diabetes Association**
National Institute on Aging	**Bristol-Myers Squibb Co.** (NYSE:BMY)	**Foundation for the National Institutes of Health**
National Institute of Diabetes and Digestive and Kidney Diseases	**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK)	**Geoffrey Beene Foundation Alzheimer's Initiative**
National Institute of Arthritis and Musculoskeletal and Skin Diseases	**Johnson & Johnson** (NYSE:JNJ)	**Lupus Foundation of America Inc.**
National Institute of Allergy and Infectious Diseases	**Eli Lilly and Co.** (NYSE:LLY)	**Pharmaceutical Research and Manufacturers of America**
	Merck & Co. Inc. (NYSE:MRK)	**Rheumatology Research Foundation**
	Pfizer Inc. (NYSE:PFE)	**USAgainstAlzheimer's**
	Sanofi (Euronext:SAN; NYSE:SNY)	
	Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)	

"If we can get better at characterizing the early signs and getting treatments, we could change the current mindset of physicians, which is to shy away from diagnosing Alzheimer's," she told *SciBX*. Comer is president of the **Geoffrey Beene Foundation Alzheimer's Initiative**, which is a member of AMP.

Comer said that her organization is providing in-kind assistance, for example, by launching registries and helping recruit subjects for clinical trials.

The type 2 diabetes program also aims to capitalize on data from previous or ongoing NIH studies.

Wholley told *SciBX* that the goal is to have a disease portal within two years that will integrate genomewide association studies, sequencing and other data from NIH studies in type 2 diabetes. Following that, he said, AMP will sponsor deep sequencing or further analysis of genes that show significant correlation with disease.

Robert Ratner said that the project holds the potential to find diabetes biomarkers that can predict toxic outcomes such as cardiovascular side effects in addition to finding new targets for treating the disease.

He added that **FDA** requirements for cardiovascular outcomes trials for diabetes compounds have created a need to look for rare adverse effects and find predictors of positive and negative responses to medication.

Ratner is CSO and CMO of the **American Diabetes Association**.

For SLE and RA, Collins and Chin said that the goal is to understand the molecular players that go awry in the immune system. In SLE, patients have widely varying symptoms, and the disease can affect different organs in different individuals.

According to Raymond, AMP will fund genomewide association studies and will support studies on single cells, tissues and blood subsets from patients.

"We will throw -omics at this disease: genomics, proteomics, metabolomics. This technology is not available to everyone, so it will be done in an integrated fashion between the partners," she told *SciBX*.

Wholley said that when the AMP projects do yield new targets, "companies will then have to take on an awful lot of work to take things forward from there. We are not a drug company; we're not producing treatments. There's an area in the middle [of basic research and therapeutic development] to make the whole ecosystem more efficient, and that's what AMP is," he said.

A more in-depth discussion can be viewed at the full *BioCentury This Week* interview with Collins, Wholley, Chin and Raymond.

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REFERENCES

1. Cain, C. *BioCentury* **20**(45), A8–A10; Nov. 5, 2012

COMPANIES AND INSTITUTIONS MENTIONED

American Diabetes Association, Alexandria, Va.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Food and Drug Administration, Silver Spring, Md.
Foundation for the National Institutes of Health, Bethesda, Md.
Geoffrey Beene Foundation Alzheimer's Initiative, Washington, D.C.
Innovative Medicines Initiative, Brussels, Belgium
Lupus Foundation of America Inc., Washington, D.C.
National Institutes of Health, Bethesda, Md.
Orion Bionetworks, Cambridge, Mass.
Pharmaceutical Research and Manufacturers of America, Washington, D.C.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
USAgainstAlzheimer's, Washington, D.C.

Herding catalysts at UCSF

By Lev Osherovich, Senior Writer

AstraZeneca plc has a burgeoning network of public-private partnerships, but until now the pharma has lacked a presence in the San Francisco Bay Area, one of the U.S.'s major hubs of life sciences innovation. AstraZeneca now has remedied that, as its **MedImmune LLC** biologics unit is piggybacking onto an **NIH**-sponsored initiative to support translational research at the **University of California, San Francisco**.

MedImmune will become the first industry sponsor of UCSF's Catalyst Awards, a grant program for researchers interested in translational applications of their work. The Catalyst Awards first launched in 2010 and previously were funded entirely by the NIH's Clinical and Translational Science Awards (CTSA) program.

"Our goal has been to leverage the variety of expertise in the Bay Area. Our consultants and advisors create a virtual incubator for UCSF researchers interested in commercialization of their basic research."

—June Lee, University of California, San Francisco

MedImmune will work with UCSF's CTSA administrator, the Clinical and Translational Science Institute (CTSI), to identify and fund translational research and build a portfolio of collaborations at UCSF.

"This is a three-year collaboration with the CTSI at UCSF," said Bing Yao, SVP of respiratory, inflammation and autoimmunity R&D at MedImmune. "This collaboration is different than our other collaborations in that it is focused exclusively on translational science. This also gives us access to research in the Bay Area."

June Lee, a professor of medicine at UCSF, said that the Catalyst program aims to provide UCSF researchers with funds to explore the commercial or translational applications of their basic research. Lee is director of Early Translational Research at CTSI.

"We have two calls for proposals annually and four tracks for each cycle—therapeutics, diagnostics, devices and digital health," said Lee. MedImmune will sponsor the therapeutics track.

Financial terms of the partnership were not disclosed, but Yao and Lee said that the company will have the option to in-license or independently finance Catalyst Award projects.

Yao said that MedImmune will have representatives on the Catalyst Award selection committee and will provide access to company resources and expertise to grant recipients.

Translational turf

Over the last three years, AstraZeneca has built an extensive network of academic collaborations geared toward filling the pharma's early pipeline. In 2013, AstraZeneca led the industry in forming public-private partnerships (PPPs), entering at least 14 disclosed PPPs with a variety of academic institutions worldwide.[1]

Among MedImmune's academic partnerships were a 5-year, $6.5 million collaboration with **The Johns Hopkins University** and a $7 million deal with the **University of Maryland, Baltimore**. Both of those partnerships focus on discovery and evaluation of new biologics across a broad range of disease areas.

Although MedImmune will be the first company to provide money to the Catalyst Awards, CTSI itself does have other ties to industry.

In January, CTSI partnered with **Quest Diagnostics Inc.** to research, develop and validate laboratory-created tests for oncology, neurology and women's health.

Quest will provide up to $0.5 million each for 2 projects by UCSF researchers. One project involves using Quest's microarray-based genetic profiling platform to discover and validate biomarkers for autism spectrum disorder (ASD). The other project focuses on identifying biomarkers of favorable drug response in brain cancer.

UCSF is eligible for royalties and services developed by Quest based on the joint projects. Lee said that the details of a third project partnered with Quest will be disclosed shortly.

Lee said that in addition to handing out Catalyst Award money, CTSI has built a network of about 140 biopharma consultants in the San Francisco Bay Area. These consultants work with Catalyst Award recipients and other UCSF researchers to plan discovery and pre-IND studies for translational projects.

"Our goal has been to leverage the variety of expertise in the Bay Area," said Lee. "Our consultants and advisors create a virtual incubator for UCSF researchers interested in commercialization of their basic research."

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REFERENCES

1. Edelson, S. & Lou, K.-J. *SciBX* **7**(7); doi:10.1038/scibx.2014.188

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
The Johns Hopkins University, Baltimore, Md.
MedImmune LLC, Gaithersburg, Md.
National Institutes of Health, Bethesda, Md.
Quest Diagnostics Inc. (NYSE:DGX), Madison, N.J.
University of California, San Francisco, Calif.
University of Maryland, Baltimore, Md.

The XII factor

By Amy Donner, Senior Editor

Factor XII sits atop one branch of the clotting cascade but has not been pursued for treating and preventing thrombosis because it was seen as a minor player in blood coagulation. Now, a group from the **Karolinska Institute** and **CSL Ltd.** has shown that inhibiting the factor can prevent clotting without increasing the risk of bleeding,[1] making it one of the only anticoagulants able to accomplish such a feat.

A group from **Isis Pharmaceuticals Inc.** and **McMaster University** obtained similar results with factor XII,[2] but the biotech maintains that blocking a downstream target, factor XI, is a better approach.

Whether blocking factor XII or factor XI will be a better strategy will probably be determined in the clinic (*see* **Table 1, "Targeting the intrinsic pathway of coagulation and the kallikrein-kinin system"**).

Passing over factors

The main reason factor XII was passed over as an anticoagulant stemmed from observational studies of patients who had a deficiency of the enzyme. Those patients had normal hemostatic capacity—the formation of fibrin-based clots—and did not have an increased risk of bleeding from either an injury or a spontaneous event.[3]

As a result, said Thomas Renné, almost everyone assumed that factor XII was not important for forming clots. Renné, a professor of clinical chemistry and coagulation research at the Karolinska Institute and **Karolinska University Hospital** as well as a professor of clinical chemistry at the **University Medical Center Hamburg-Eppendorf**, suspected otherwise.

When Renné was a scientist at the **University of Wuerzburg** in 2005, he and his colleagues showed that *factor XII*–deficient mice were protected from thrombosis, which hinted that the enzyme could be a target for antithrombotic therapy.[4]

That work caught the interest of CSL, which set about exploring whether the outcomes in knockout mice could be replicated by pharmacological inhibition of factor XII.

Con Panousis, director of antibody technologies at CSL, said that the company spent several years testing small protein inhibitors of factor XII, but the compounds had off-target effects or were immunogenic.

Now, CSL and Karolinska have developed an antibody against factor XII and have provided the clearest picture to date of what happens when the target is blocked in animals.

The team screened a human Fab–based phage antibody library for compounds that could specifically inhibit the proteolytic activity of factor XIIa, which is the active form of factor XII. The group isolated an antibody, 3F7, which dose-dependently inhibited factor XIIa activity *in vitro* with an IC_{50} of 13 nM.[1]

"We believe that in addition to central venous catheters, other blood-contacting medical devices, such as vascular grafts, mechanical heart valves and left ventricular assist devices, also trigger clotting. Therefore, the ASOs could be used for long-term prevention of clotting for a wide variety of medical devices."

—Jeffrey Weitz, McMaster University

In a mouse model of thrombosis, 3F7 dose-dependently decreased occlusion rates and decreased time to occlusion compared with control antibody or saline. In the same mice, 3F7 neither increased blood loss nor prolonged bleeding.

In a rabbit model of cardiopulmonary bypass, 3F7 provided thromboprotection comparable to that of heparin. However, the antibody did not prolong incision-provoked bleeding.

That finding suggests that 3F7 might prevent thrombosis in acute indications like bypass surgery without increasing the risk of bleeding.

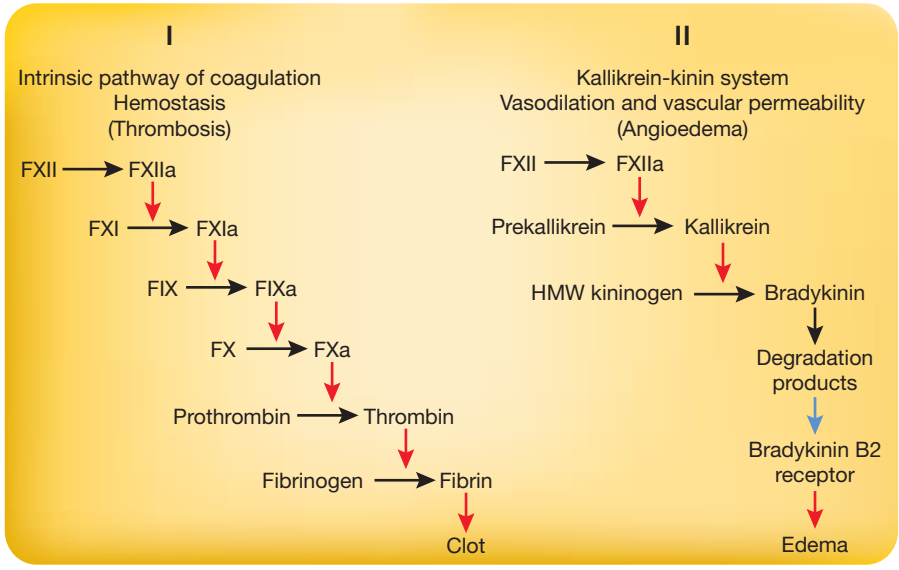

Figure 1. Factor XIIa pathways. The intrinsic pathway of coagulation and the kallikrein-kinin system are both activated downstream of factor XII (FXII).

(I) In the intrinsic pathway, activated FXII (FXIIa) initiates an activation cascade of serine protease enzymes, including factor XIa (FXIa), factor IXa (FIXa), factor Xa (FXa) and thrombin (factor IIa; F2). Thrombin cleaves fibrinogen to form soluble fibrin, which aggregates or polymerizes to form a clot or thrombus.

(II) In the kallikrein-kinin system, FXIIa cleaves high–molecular weight (HMW) kininogen to form bradykinin. Bradykinin is degraded, and the degradation products activate bradykinin B2 receptor (BDKRB2; B2R), leading to edema.

A number of companies are developing inhibitors of the components of these two systems (*see* **Table 1, "Targeting the intrinsic pathway of coagulation and the kallikrein-kinin system"**). Reports in *Science Translational Medicine* and *Blood* provide evidence that FXII and FXIIa can be targeted to prevent clot formation without risk of bleeding.[1,2]

Table 1. Targeting the intrinsic pathway of coagulation and the kallikrein-kinin system. The intrinsic pathway and the kallikrein-kinin system are both activated by factor XIIa. The table below is a selected list of compounds against components of the pathways that are in clinical development or on the market.
Source: BioCentury Archives

Target	Company	Compound	Status	Indication
Factor XI	**Isis Pharmaceuticals Inc.** (NASDAQ:ISIS)	ISIS-FXIRx (antisense oligonucleotide)	Phase II	Block coagulation
Factor IXa	**Regado Biosciences Inc.** (NASDAQ:RGDO)	Pegnivacogin (aptamer)	Phase II	Block coagulation
Factor Xa	**Alchemia Ltd.** (ASX:ACL); **Dr. Reddy's Laboratories Ltd.** (NYSE:RDY)	Fondared fondaparinux (small molecule)	Marketed	Deep vein thrombosis (DVT)
	Bayer AG (Xetra:BAYN); **Almirall S.A.** (Madrid:ALM); **Johnson & Johnson** (NYSE:JNJ)	Xarelto rivaroxaban (small molecule)	Marketed	DVT; venous thromboembolism (VTE); pulmonary embolism (PE); stroke
			Registration	Acute coronary syndrome (ACS)
	Bristol-Myers Squibb Co. (NYSE:BMY); **Pfizer Inc.** (NYSE:PFE)	Eliquis apixaban (small molecule)	Marketed	VTE; stroke
			Registration	DVT
	Daiichi Sankyo Co. Ltd. (Tokyo:4568)	Lixiana edoxaban (small molecule)	Marketed	VTE
			Registration	Atrial fibrillation (AF); stroke; DVT; PE; VTE
	GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	Arixtra fondaparinux (small molecule)	Marketed	DVT
			Approved	ACS; PE; VTE
	Sanofi (Euronext:SAN; NYSE:SNY)	Idraparinux (polysaccharide)	Phase III	DVT; thrombosis with AF
	Portola Pharmaceuticals Inc. (NASDAQ:PTLA)	Betrixaban (small molecule)	Phase III	VTE
			Phase II	Stroke
	TeaRx LLC; **Roche** (SIX:ROG; OTCQX:RHHBY)	TeaRxaban (unknown)	Phase II	Thrombosis; VTE
	Green Cross Corp. (KSE:006280)	GCC4401C (small molecule)	Phase I	VTE; stroke
Thrombin (factor IIa; F2)	**Asahi Kasei Pharma Corp.**	Recomodulin (peptide)	Marketed	Block coagulation
	Bayer	Refludan (biologic)	Marketed	Thrombosis; thrombocytopenia
	Boehringer Ingelheim GmbH	Pradax dabigatran (small molecule)	Marketed	VTE
			Registration	Thrombosis
			Phase II	Coronary artery disease (CAD)
	Eagle Pharmaceuticals Inc. (NASDAQ:EGRX); **The Medicines Co.** (NASDAQ:MDCO)	Ready-to-use argatroban (small molecule)	Marketed	Thrombosis
	The Medicines Co.; **AstraZeneca plc** (LSE:AZN; NYSE:AZN); **Grupo Ferrer Internacional S.A.**	Angiomax bivalirudin (small molecule)	Marketed	ACS; angina angioplasty; percutaneous coronary intervention (PCI); thrombosis; thrombocytopenia
	Mitsubishi Tanabe Pharma Corp. (Tokyo:4508); GSK	Arganova argatroban (small molecule)	Marketed	Blood clots; thrombosis; thrombocytopenia
	AstraZeneca	AZD0837 (small molecule)	Phase II	Thrombosis
	Archemix Corp.; **Arca biopharma Inc.** (NASDAQ:ABIO)	ARC2172 (aptamer)	Phase I	Block coagulation
	Diakron Pharmaceutical Inc.; **Orchid Chemicals & Pharmaceuticals Ltd.** (BSE:524372; NSE:ORCHIDCHEM)	DP-4088 (small molecule)	Phase I	Thrombosis
Factor Xa; F2	**Abbott Laboratories** (NYSE:ABT)	Clivarin reviparin (low–molecular weight heparin (LMWH))	Marketed	DVT
	Leo Pharma A/S; **Celgene Corp.** (NASDAQ:CELG)	Innohep tinzaparin (LMWH)	Marketed	DVT
	Momenta Pharmaceuticals Inc. (NASDAQ:MNTA); **Novartis AG** (NYSE:NVS; SIX:NOVN)	M-enoxaparin (LMWH)	Marketed	DVT; ACS

(Continues on p. 8)

Table 1. Targeting the intrinsic pathway of coagulation and the kallikrein-kinin system (continued).

Target	Company	Compound	Status	Indication
	Pfizer; **Eisai Co. Ltd.** (Tokyo:4523)	Fragmin dalteparin (LMWH)	Marketed	CAD; DVT; ischemia/reperfusion injury; VTE
	Sanofi	Klexane R enoxaparin (LMWH)	Marketed	Unstable angina; non–ST segment elevation myocardial infarction (NSTEMI); DVT; myocardial infarction (MI); VTE
	Amphastar Pharmaceuticals Inc.; **Actavis plc** (NYSE:ACT)	Enoxaparin (LMWH)	Approved	DVT
	Merck & Co. Inc. (NYSE:MRK); **Endotis Pharma**	EP217609 (unknown)	Phase II	Prevent coagulation during extracorporeal circulation (ECC)
	Momenta Pharmaceuticals	M118 (LMWH)	Phase II	ACS
Fibrin	**Genentech Inc.** unit of Roche; Boehringer Ingelheim	Metalyse tenecteplase (biologic: enzyme)	Marketed	MI
			Phase III	Catheter clearance
			Phase II	Stroke
	Fibrex Medical Inc.; **Ikaria Inc.**	FX06MRI (peptide)	Phase II	Ischemia/reperfusion injury
	Grifols S.A. (Madrid:GRF; NASDAQ:GRFS)	Plasmin (biologic: enzyme)	Phase II	Peripheral vascular disease
	BioCryst Pharmaceuticals Inc. (NASDAQ:BCRX)	BCX4161 (small molecule)	Phase II	Hereditary angioedema (HAE)
Kallikrein	**Dyax Corp.** (NASDAQ:DYAX); **Lee's Pharmaceutical Holdings Ltd.** (HKSE:0950); **Sigma-Tau Group**; **taiba Pharma LLC**	Kalbitor ecallantide (peptide)	Marketed	Angioedema; HAE
	Dyax	DX-2930 (antibody)	Phase I	HAE
Bradykinin B2 receptor (BDKRB2; B2R)	Sanofi; **Shire plc** (LSE:SHP; NASDAQ:SHPG)	Firazyr icatibant (small molecule)	Marketed	Angioedema; HAE

Results were published in *Science Translational Medicine*. Scientists from the **Swedish University of Agricultural Sciences** also contributed to the study.

The take-home message, the authors wrote, is that "FXIIa-driven fibrin formation is essential for pathological thrombus formation and propagation but has no function for fibrin formation during 'normal' hemostasis at a site of injury."

In a related paper, a team from Isis Pharmaceuticals and McMaster University led by Jeffrey Weitz also identified factor XII as an anticoagulation target. The group showed that factor XII–directed antisense oligonucleotides (ASOs) protected against catheter-induced thrombosis in rabbits.[2]

Similar results were seen with antisense inhibitors of factor XI, which sits downstream of factor XII (*see* **Figure 1, "Factor XIIa pathways"**) and had previously been shown by Isis to prevent thrombus formation without causing an increase in bleeding in mouse models of stroke.

Weitz is chair of thrombosis and a professor of medicine at McMaster University and executive director of the **Thrombosis and Atherosclerosis Research Institute**.

Results were published in *Blood*.

Factor factory

Renné said that the data on factor XII may change the classical concept of coagulation, which holds that coagulation and bleeding are inextricably bound. Indeed, marketed anticoagulants including warfarin and antiplatelet therapies are used to prevent thrombosis, but they also result in dose-dependent increases in the risk of major bleeding.

Weitz agreed but added that "factor XI may be a better target because thrombin can feed back and activate factor XI, thereby bypassing factor XIIa inhibitors."

He did say that inhibitors of either target could have utility in a broad spectrum of indications.

"We believe that in addition to central venous catheters, other blood-contacting medical devices, such as vascular grafts, mechanical heart valves and left ventricular assist devices, also trigger clotting. Therefore, the ASOs could be used for long-term prevention of clotting for a wide variety of medical devices."

Isis' ISIS-FXIRx, a factor XI–targeted ASO, is in Phase II testing to prevent coagulation without increasing the risk of bleeding in patients undergoing knee replacement surgery. Results are expected this year.

At least one other company thinks that it has found a way to provide anticoagulation without increasing bleeding risk. **XO1 Ltd.**'s ichorcumab, a mAb against an allosteric site on thrombin (factor IIa; F2), is in preclinical development.[5]

CSL holds patents and patent applications covering 3F7, an optimized version of the mAb and FXII inhibition in prevention of thrombi formation. The IP is not currently available for licensing for antithrombotic indications. CSL said that it is focused on inhibiting factor XII to treat hereditary angioedema (HAE) and has an antibody against the target in preclinical development for that indication.

Panousis said that factor XII is also involved in bradykinin-induced edema, which is dysregulated in HAE. CSL markets Berinert, an injectable complement 1 (C1) esterase inhibitor derived from human plasma, to treat HAE.

Donner, A. *SciBX* 7(8); doi:10.1038/scibx.2014.217
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REFERENCES

1. Larrson, M. *et al. Sci. Transl. Med.*; published online Feb. 5, 2014; doi:10.1126/scitranslmed.3006804
   Contact: Thomas Renné, Karolinska Institute, Stockholm, Sweden
   e-mail: thomas@renne.net
2. Yau, J.W. *et al. Blood*; published online Feb. 5, 2014; doi:10.1182/blood-2013-12-540872
   Contact: Jeffrey I. Weitz, Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada
   e-mail: weitzj@taari.ca
3. Renné, T. *et al. Blood* **120**, 4296–4303 (2012)
4. Renné, T. *et al. J. Exp. Med.* **202**, 271–281 (2005)
5. Hansen, S. *BioCentury* **21**(26), A26; July 1, 2013

COMPANIES AND INSTITUTIONS MENTIONED

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Swedish University of Agricultural Sciences, Uppsala, Sweden
Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada
University Medical Center Hamburg-Eppendorf, Hamburg, Germany
University of Wuerzburg, Wuerzburg, Germany
XO1 Ltd., Cambridge, U.K.

(Pluri)potent acid

By Benjamin Boettner, Associate Editor

Academics and companies alike are scrambling—and thus far failing—to reproduce a surprisingly simple method for generating pluripotent mouse stem cells that uses an external stress stimulus to trigger reprogramming. Whether the method simply does not work or just faces initial hurdles similar to those experienced by other induced pluripotent stem cell–generating technologies remains to be seen.

If it does work, the technique offers minimal invasiveness without the need for genetic reprogramming factors, nuclear transfer or small molecules.

A team from the **Brigham and Women's Hospital** and **RIKEN Center for Developmental Biology** reported the generation of pluripotent mouse stem cells by simply exposing somatic cells to low pH.[1]

The state of the art for making induced pluripotent stem (iPS) cells is to introduce pluripotency-promoting genetic elements or combinations of small molecules into differentiated cells.[2,3] In both cases, the transition to iPS cells takes at least two weeks.

The group, led by Charles Vacanti, took genetic manipulation out of the equation and sped up culture times. Based on observations that differentiated plant cells can revert to a stem cell state under stress,[4] the group hypothesized that a similar phenomenon could occur in differentiated animal cells.

The researchers started with hematopoietic cells from newborn mice carrying an *Oct4-GFP* reporter transgene and monitored its expression following different stresses. Oct4 is of one of the core pluripotency factors.

The most effective stressor turned out to be an acidic environment. Mouse hematopoietic cells that were shocked for 30 minutes by low pH and then cultured in neutral medium needed only 7 days to reprogram and activate *Oct4-GFP*.

Other pluripotency markers also were induced, suggesting that the hematopoietic cells had indeed reverted to an embryonic stem cell (ESC)-like state. The group named the resulting cells stimulus-triggered acquisition of pluripotency (STAP) cells.

In vitro differentiation and *in vivo* teratoma formation assays showed that STAP cells gave rise to cell types representing all three germ layers, one of the hallmarks of pluripotency. When injected into early embryonic blastocysts, STAP cells turned into all tissues of the developing chimeric animals and the germ line.

One initial caveat of using STAP cells was their limited self-renewal and proliferation capacity. As a remedy, Vacanti's team added adrenocorticotropic hormone (ACTH) and leukemia inhibitory factor (LIF) to STAP cell cultures. ACTH and LIF help propagate mouse ESCs; indeed, adding the two molecules enabled expansion of STAP cell–derived cell lines.

The findings were reported in *Nature*.

Some of the same authors published a companion article describing how STAP cells cultured in medium containing fibroblast growth factor 4 (FGF4) instead of ACTH and LIF produced cells with the characteristics of placental tissues *in vivo*.[5]

"Reprogramming seems to be part of a physiological response to damage, probably to initiate tissue regeneration," said Manuel Serrano, a group leader at the **Spanish National Cancer Research Centre** (CNIO).

Serrano's group recently reprogrammed adult cells to pluripotent cells in living mice.[6]

"Our findings may mimic Mother Nature's approach to repairing injured tissue," said Vacanti, who is a professor at **Harvard Medical School** and chair of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women's Hospital.

Ian Wilmut, professor emeritus and chairman of the **MRC Centre for Regenerative Medicine**, said, "Assuming that the results can be replicated, the authors will have created very important new opportunities in research to understand the molecular basis of cell fate. In the longer term, the findings may also herald new approaches to cell therapy."

"Assuming that the results can be replicated, the authors will have created very important new opportunities in research to understand the molecular basis of cell fate. In the longer term, the findings may also herald new approaches to cell therapy."

—Ian Wilmut, MRC Centre for Regenerative Medicine

Play it again

Shortly after publication, other researchers raised questions related to the data reported in the papers and the overall reproducibility of the method of generating STAP cells. RIKEN and *Nature* have launched investigations.

"There has been a significant amount of interest, speculation and scrutiny since our STAP cell papers were published in *Nature*," said Vacanti. "I understand that questions have been raised around certain images that were used in the publication. I believe that these concerns are a result of minor errors that occurred in the manuscript editing process and do not affect the overall content of the published reports, the scientific data or the conclusions."

Jacob Hanna, a principal investigator at the **Weizmann Institute of Science** who is focused on pluripotency, said that his team has been trying without success to reproduce the method. However, he added that if replicated by his or another lab, the findings would be extremely exciting for the stem cell field.

Wilmut said that the media reports of irreproducibility were "disappointing because it seems to be such a simple procedure, but those of us with experience of laboratory work with cells know that it is actually quite common. There may be small differences in the way in which the protocol is applied which prejudice the outcome."

Chris Parker, VP and CCO at **Cellular Dynamics International Inc.**, and Matthew Vincent, director of business development at **Advanced Cell Technology Inc.**, said that their respective companies are going to test the STAP cell–generating methodology.

Parker noted that there originally were problems in reproducing the first iPS cell–generating procedures. He thinks that STAP cell generation could get over this initial technical hurdle once the protocol's details are worked out.

Firming up the biology

Even if the reproducibility issue is laid to rest, there needs to be more research on the molecular and cellular mechanisms that initiate the transition to STAP cells and on the epigenetic state of the STAP cells.

In addition, Parker said that "it will be important to find out whether this can be done with human cells. Mouse cells are very malleable, and human cells are often more difficult to manipulate."

"It will be important to find out whether this can be done with human cells. Mouse cells are very malleable, and human cells are often more difficult to manipulate."
—Chris Parker, Cellular Dynamics International Inc.

Cellular Dynamics produces iPS cell–derived cells for disease modeling, drug discovery and regenerative medicine.

Both Serrano and Hanna wanted to see a comparison between the transcriptional and epigenetic changes during STAP cell generation and those seen during iPS cell generation.

"The findings raise the question from what cellular context pluripotency in STAP cells arises," said Hanna. "We always think of transcription factors acting upstream, but these data say this state can also be induced without ectopic expression of transcription factors and beg the question of how cellular stresses affect chromatin and epigenetic imprinting."

"Given that nothing is known about the early events that are initiated by low pH treatment, coming up with informative measurements will be much more difficult than the analysis of defined transcriptional and genomic changes after the activation of pluripotency factors. The analytical net has to be broadened," said Parker.

Hans Keirstead, president and CEO of **California Stem Cell Inc.**, agreed that the underlying biology of STAP cells needs to be fleshed out. He also wanted to know more about the batch-to-batch consistency of STAP cells.

"Often, stem cells in the lab have great heterogeneity in proliferation rates and differentiation biases. A lot of reprogrammed cells are stable short term, but in longer-term, specific culture conditions [they] halt in their differentiation paths, lose lineage identity or even become neoplastic," he said. "These problems are pronounced in larger-scale cultures as part of manufacturing processes that require batch-to-batch consistency."

Vincent said that once sufficiently validated, STAP cells might help establish additional animal models that are hard to efficiently generate, such as dogs.

Vacanti acknowledged that generating STAP cells is unlikely to be a cookie-cutter approach. "In newborn mouse lymphocytes, low pH was most effective at creating STAP cells. However, I believe that the efficacy of different stresses in causing this reversion in mature, fully differentiated cells will vary with the specific cell type and species," he said. "A combination of sublethal stressful treatments that seriously injure specific mature cell types could ultimately be the most effective for causing them to revert to stemness."

Brigham and Women's Hospital has filed for a patent covering the technology. The IP is unlicensed.

Note added in proof: At press time, Vacanti told SciBX *that one of the coauthors on the* Nature *paper who had originally done a lot of the work with the* Oct4-GFP *mice also seemed to have trouble replicating the findings. Vacanti's scientific director met with the coauthor to review the technique he was using and generate STAP cells in the coauthor's laboratory.*

"We learned that there are some very specific facets to the technique that evidently are not perfectly obvious to the reader," said Vacanti. "If our protocol is strictly followed, the STAP cells can easily be generated. If, however, some seemingly minor steps are omitted or not performed precisely, STAP cells generating Oct4 *are not generated. Consequently, we are in the process of setting up a 'Vacanti Lab/STAP cells' Web site that contains the precise protocols in sufficient detail for anyone to generate* Oct4^{+} *STAP cells from mature cells acquired from young animals as well as from fully mature adults."*

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REFERENCES

1. Obokata, H. *et al. Nature*; published online Jan. 29, 2014; doi:10.1038/nature12968
   Contact: Charles A. Vacanti, Harvard Medical School, Boston, Mass.
   e-mail: cvacanti@partners.org
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   e-mail: obokata@cdb.riken.jp
2. Takahashi, K. & Yamanaka, S. *Cell* **126**, 663–676 (2006)
3. Hou, P. *et al. Science* **341**, 651–654 (2013)
4. Thorpe, T.A. *Mol. Biotechnol.* **37**, 169–180 (2007)
5. Obokata, H. *et al. Nature* **505**, 676–680 (2014)
6. Abad, M. *et al. Nature* **502**, 340–345 (2013)

COMPANIES AND INSTITUTIONS MENTIONED

Advanced Cell Technology Inc. (OTCBB:ACTC), Santa Monica, Calif.
Brigham and Women's Hospital, Boston, Mass.
California Stem Cell Inc., Irvine, Calif.
Cellular Dynamics International Inc. (NASDAQ:ICEL), Madison, Wis.
Harvard Medical School, Boston, Mass.
MRC Centre for Regenerative Medicine, Edinburgh, U.K.
RIKEN Center for Developmental Biology, Kobe, Japan
Spanish National Cancer Research Centre, Madrid, Spain
Weizmann Institute of Science, Tel Aviv, Israel

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)	Endothelin 1 (EDN1; ET1); endothelin receptor	*In vitro* and mouse studies suggest antagonizing ET1 or endothelin receptor could help promote remyelination in MS. In an *in vitro* model of demyelination, ET1 decreased differentiation of myelination-promoting oligodendrocytes compared with saline. In a mouse model of demyelination, genetic depletion of *Et1* in astrocytes increased the number of mature oligodendrocytes in lesions compared with normal *Et1* expression. In the mice, pharmacological inhibition of endothelin receptor decreased notch signaling in oligodendrocytes and increased the number of mature oligodendrocytes and levels of myelin compared with saline treatment. Next steps could include testing whether endothelin receptor antagonists can improve recovery and repair of the CNS in additional indications and understanding the relationship between ET1 and notch signaling. At least six endothelin receptor antagonists are marketed to treat pulmonary arterial hypertension (PAH) and various additional indications. ***SciBX* 7(8); doi:10.1038/scibx.2014.219** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Hammond, T.R. *et al. Neuron*; published online Feb. 5, 2014; doi:10.1016/j.neuron.2013.11.015 **Contact:** Vittorio Gallo, Children's National Medical Center, Washington, D.C. e-mail: vgallo@cnmcresearch.org
Multiple sclerosis (MS)	Not applicable	Mouse studies suggest ganciclovir inhibits activated microglia proliferation and could be used to prevent progression of MS. Activated microglia are associated with neuroinflammation and are indicative of disease activity in MS. In a mouse model of experimental autoimmune encephalomyelitis (EAE), ganciclovir prevented development of EAE and decreased both T cell infiltration and activated microglia proliferation in the brain compared with vehicle without causing general immune suppression. In mice, a radiolabeled analog of penciclovir, which has a similar structure to ganciclovir, accumulated in the brain of EAE mice but not healthy mice. Next steps include understanding how ganciclovir modulates microglia and neuroinflammation and performing a SAR study to find more potent analogs. ***SciBX* 7(8); doi:10.1038/scibx.2014.220** **Published online Feb. 27, 2014**	Unpatented; licensing status not applicable	Ding, Z. *et al. J. Exp. Med.*; published online Feb. 3, 2014; doi:10.1084/jem.20120696 **Contact:** Tony Wyss-Coray, Stanford University School of Medicine, Stanford, Calif. e-mail: twc@stanford.edu **Contact:** Jian Luo, same affiliation as above e-mail: jianl@stanford.edu
Cancer				
Cancer	IL-9	*In vitro* and mouse studies suggest adoptive transfer of IL-9-producing T cells (Tc9) could help treat cancer. $CD8^+$ T cells cultured in Tc9-polarizing conditions produced IL-9 and had lower cytotoxic activity against cancer cells *in vitro* than $CD8^+$ cytotoxic T cells (Tc1) typically used for adoptive transfer therapy. However, in mice with established melanoma tumors, adoptive transfer of Tc9 cells led to greater Il-9 production, cellular persistence and antitumor activity than adoptive transfer of Tc1 cells. Next steps include testing tumor-specific Tc9 cells in various cancer types. ***SciBX* 7(8); doi:10.1038/scibx.2014.221** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Lu, Y. *et al. Proc. Natl. Acad. Sci. USA*; published online Jan. 27, 2014; doi:10.1073/pnas.1317431111 **Contact:** Qing Yi, Cleveland Clinic, Cleveland, Ohio e-mail: yiq@ccf.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Tubulin	*In vitro* and mouse studies suggest a new class of tubulin inhibitors could help treat cancer. Chemical synthesis and *in vitro* testing of 4-(*N*-cycloamino)quinazolines identified a lead compound that inhibited tubulin polymerization at a low micromolar IC_{50} value and inhibited growth of several human cancer lines, including a vincristine-resistant mouth carcinoma, at nanomolar GI_{50} values. In mice bearing xenograft breast tumors, the compound decreased tumor growth compared with vehicle. Ongoing work includes optimizing the lead compound and testing it in mouse models of other cancers. The tubulin inhibitor vincristine is a generic chemotherapeutic. ***SciBX*** **7(8); doi:10.1038/scibx.2014.222** **Published online Feb. 27, 2014**	Patent application filed by the Beijing Institute of Pharmacology and Toxicology; available for licensing or partnering	Wang, X.-F. *et al. J. Med. Chem.*; published online Feb. 6, 2014; doi:10.1021/jm4016526 **Contact:** Lan Xie, Beijing Institute of Pharmacology and Toxicology, Beijing, China e-mail: lanxie4@gmail.com **Contact:** Kuo-Hsiung Lee, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: khlee@unc.edu
Multiple myeloma (MM)	Serglycin (SRGN)	*In vitro* and mouse studies suggest inhibiting SRGN could help treat MM. In human MM cells, shRNA knockdown of SRGN inhibited adhesion to bone marrow stromal cells. In immunodeficient mice, tumor growth and vasculature development were decreased following subcutaneous injection of MM cells expressing SRGN shRNA compared with injection of cells expressing control shRNA. Next steps could include developing an SRGN inhibitor. ***SciBX*** **7(8); doi:10.1038/scibx.2014.223** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Purushothaman, A. & Toole, B.P. *J. Biol. Chem.*; published online Jan. 8, 2014; doi:10.1074/jbc.M113.532143 **Contact:** Anurag Purushothaman, The University of Alabama at Birmingham, Birmingham, Ala. e-mail: anuragp@uab.edu
Cardiovascular disease				
Blood coagulation	Factor XI; factor XII	Rabbit studies suggest antisense oligonucleotides (ASOs) that knock down expression of *factor XI* or *factor XII* can be used to prevent contact-induced coagulation. In rabbits with a catheter, ASOs targeting *factor XI* or *factor XII* prolonged catheter occlusion more than twofold compared with scrambled oligonucleotide or an ASO targeting *factor VII*. Next steps include using ASOs to determine the relative contribution of the contact and extrinsic coagulation pathways to clotting in animal models of thrombosis. Isis Pharmaceuticals Inc. has an ASO targeting factor XI in Phase II testing to prevent coagulation (*see* **The XII factor, page 6**). ***SciBX*** **7(8); doi:10.1038/scibx.2014.224** **Published online Feb. 27, 2014**	Patent and licensing status undisclosed	Yau, J.W. *et al. Blood*; published online Feb. 5, 2014; doi:10.1182/blood-2013-12-540872 **Contact:** Jeffrey I. Weitz, Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada e-mail: weitzj@taari.ca
Blood coagulation	Factor XII	Mouse and rabbit studies suggest an anti–factor XII antibody can help prevent some forms of coagulation without increasing risk of bleeding. An *in vitro* screen of a human Fab–based phage antibody library identified 3F7, which inhibited factor XII proteolytic activity with an IC_{50} of 13 nM. In mice, 3F7 protected against thrombosis and dose-dependently decreased time to occlusion compared with control antibody. 3F7 did not increase blood loss compared with saline in tail-bleeding assays. In a rabbit model of extracorporeal membrane oxygenation, 3F7 provided thromboprotection comparable to that of heparin and did not prolong bleeding or impair wound site homeostasis. Next steps include optimizing the antibody for use in humans and preparing for a Phase I trial in hereditary angioedema, which is associated with mutations in the gene encoding factor XII (*see* **The XII factor, page 6**). ***SciBX*** **7(8); doi:10.1038/scibx.2014.225** **Published online Feb. 27, 2014**	Patented by CSL Ltd.; available for licensing	Larsson, M. *et al. Sci. Transl. Med.*; published online Feb. 5, 2014; doi:10.1126/scitranslmed.3006804 **Contact:** Thomas Renné, Karolinska Institute, Stockholm, Sweden e-mail: thomas@renne.net

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes; obesity	CD40; tumor necrosis factor receptor–associated factor 6 (TRAF6)	Mouse studies suggest inhibiting CD40 signaling through the TRAF6 adaptor protein could help treat metabolic disorders. In a mouse model of diet-induced obesity, selective mutation of Cd40 binding sites specific for Traf2, Traf3 and Traf5 adaptor proteins increased adipose tissue inflammation, insulin resistance and steatosis, and mutation of Cd40 binding sites for Traf6 or a small molecule inhibitor of the Cd40-Traf6 interaction decreased metabolic dysfunctions compared with no CD40 mutation or with vehicle. Next steps include testing the small molecule inhibitor in large animal studies. ***SciBX* 7(8); doi:10.1038/scibx.2014.226** **Published online Feb. 27, 2014**	Patent application filed; unlicensed	Chatzigeorgiou, A. *et al. Proc. Natl. Acad. Sci. USA*; published online Feb. 3, 2014; doi:10.1073/pnas.1400419111 **Contact:** Esther Lutgens, University of Amsterdam, Amsterdam, the Netherlands e-mail: e.lutgens@amc.uva.nl **Contact:** Triantafyllos Chavakis, Dresden University of Technology, Dresden, Germany e-mail: triantafyllos.chavakis@uniklinikum-dresden.de **Contact:** Andrew V. Schally, Veterans Affairs Medical Center, Miami, Fla. e-mail: andrew.schally@va.gov
Infectious disease				
Tuberculosis	Chemokine CXC motif ligand 5 (CXCL5; ENA78); CXC chemokine receptor 2 (CXCR2; IL8RB)	Mouse studies suggest inhibiting the CXCL5-CXCR2 interaction could help treat tuberculosis. In mouse models of tuberculosis, levels of lung alveolar Cxcl5 and its receptor Cxcr2 on polymorphonuclear leukocytes (PMNs) correlated with the aerosol dose of *Mycobacterium tuberculosis* used to establish infection. In the models, deficiency in *Cxcl5* decreased lung levels of proinflammatory cytokines, and deficiency in *Cxcl5* or *Cxcr2* decreased recruitment of PMNs to infected lung tissue and increased survival compared with what was seen in wild-type controls. Future studies could include testing small molecule inhibitors of CXCR2 or CXCL5 in the models. Dompe Farmaceutici S.p.A. has reparixin, an inhibitor of CXCR1 and CXCR2, in Phase III testing to prevent graft dysfunction after islet cell transplantation in type 1 diabetics, Phase II/III testing to prevent liver transplant rejection and Phase II trials to prevent renal transplant rejection. AstraZeneca plc has AZD5069, a CXCR2 antagonist, in Phase II testing to treat asthma and chronic obstructive pulmonary disease (COPD). Ligand Pharmaceuticals Inc. and Merck & Co. Inc. have navarixin (MK-7123; SCH 527123), a CXCR2 antagonist, in Phase II testing to treat COPD. ***SciBX* 7(8); doi:10.1038/scibx.2014.227** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Nouailles, G. *et al. J. Clin. Invest.*; published online Feb. 10, 2014; doi:10.1172/JCI72030 **Contact:** Stefan H.E. Kaufmann, Max Planck Institute for Infection Biology, Berlin, Germany e-mail: kaufmann@mpiib-berlin.mpg.de **Contact:** Geraldine Nouailles, same affiliation as above e-mail: geraldine.nouailles@charite.de
Tuberculosis	Not applicable	*In vitro* and mouse studies have identified spectinomycin analogs that could help treat tuberculosis. *In vitro*, semisynthetic spectinomycin analogs called spectinamides were created using structure-based design and inhibited mycobacterial ribosomal protein synthesis. The compounds were active against a panel of *Mycobacterial tuberculosis* including multidrug-resistant and extensively drug-resistant strains and were not cleared by the *M. tuberculosis* Rv1258c efflux pump. In mouse models of acute and chronic *M. tuberculosis* infection, the most potent analogs decreased lung bacterial burden and increased survival better than saline and as well as or better than marketed drugs. Next steps include safety and toxicology studies on the lead molecule. ***SciBX* 7(8); doi:10.1038/scibx.2014.228** **Published online Feb. 27, 2014**	Patent application filed; licensed to Microbiotix Inc.	Lee, R.E. *et al. Nat. Med.*; published online Jan. 26, 2014; doi:10.1038/nm.3458 **Contact:** Richard E. Lee, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: richard.lee@stjude.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Neuropathy	Glial cell line–derived neurotrophic factor family receptor α1 (GFRA1)	Studies in mice suggest a small molecule positive modulator of GFRA1 could be useful for treating small fiber peripheral neuropathy. In mice with neuropathy resulting from reduced glial cell–derived neurotrophic factor (GDNF) levels or diabetes, topical application of a positive GFRA1 modulator called XIB4035 increased thermal nociception compared with application of vehicle. Next steps include preclinical toxicology studies. ***SciBX*** **7(8); doi:10.1038/scibx.2014.229** **Published online Feb. 27, 2014**	Patented; available for licensing	Hedstrom, K.L. *et al. Proc. Natl. Acad. Sci. USA*; published online Jan. 21, 2014; doi:10.1073/pnas.1308889111 **Contact:** Gabriel Corfas, Harvard Medical School, Boston, Mass. e-mail: gabriel.corfas@childrens.harvard.edu
Pain	Potassium channel K2p10.1 (KCNK10; TREK-2)	Cell culture and mouse studies suggest increasing TREK-2 activity could help treat neuropathic pain. In rats, Trek-2 was expressed in dorsal root ganglion C-fiber nociceptors. In cultured rat dorsal root ganglion neurons, *Trek-2* siRNA increased C-fiber membrane depolarization, which is associated with spontaneous nerve firing and pain, compared with scrambled siRNA. In a rat model of neuropathic pain, *Trek-2* siRNA decreased the pain response compared with scrambled siRNA. Next steps include screening for TREK-2 activators. ***SciBX*** **7(8); doi:10.1038/scibx.2014.230** **Published online Feb. 27, 2014**	Unpatented; licensing status not applicable	Acosta, C. *et al. J. Neurosci.*; published online Jan. 22, 2014; doi:10.1523/JNEUROSCI.4528-13.2014 **Contact:** Sally N. Lawson, University of Bristol, Bristol, U.K. e-mail: sally.lawson@bristol.ac.uk
Spinal cord injury (SCI)	Periostin (POSTN)	*In vitro* and rat studies suggest POSTN could promote axon regeneration after SCI. In cultured neurons from the dorsal root ganglia or the cerebellar granules of rats, POSTN increased neurite outgrowth compared with no treatment. Transplant of astrocytes differentiated *in vitro* with bone morphogenetic protein 4 (BMP4) has previously been shown to promote axon growth and motor function; however, in a rat model of SCI, transplant of *Postn*-deficient astrocytes differentiated with BMP4 did not promote axon growth, indicating that Postn is necessary for axon regeneration. Next steps could include determining whether POSTN is sufficient to promote axon growth *in vivo* and identifying neural receptors for POSTN. ***SciBX*** **7(8); doi:10.1038/scibx.2014.231** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Shih, C.-H. *et al. J. Neurosci.*; published online Feb. 12, 2014; doi:10.1523/JNEUROSCI.2947-13.2014 **Contact:** Christoph Pröschel, University of Rochester, Rochester, N.Y. e-mail: chris_proschel@urmc.rochester.edu
Various				
Cancer; inflammation	IL-6; IL-6 signal transducer (IL-6ST; gp130; CD130); IL-6 receptor (CD126)	*In vitro* studies suggest a modified aptamer that inhibits IL-6 could help treat cancer or inflammation. Slow off-rate modified aptamers (SOMAmers) identified using systematic evolution of ligands by exponential enrichment (SELEX) technology had subnanomolar binding affinity and inhibitory potency against IL-6. A lead SOMAmer inhibited IL-6 activity at a concentration comparable to that of the anti-IL-6 antibody Actemra tocilizumab in human myeloma cells and inhibited cell proliferation better than Actemra in human glioma and liver cancer cells. Crystallization of a high-affinity SOMAmer in complex with IL-6 showed that the inhibitor interacts with the binding site for CD126 and gp130. Next steps could include testing the inhibitors in disease models. SomaLogic Inc. and Otsuka Pharmaceutical Co. Ltd. are developing the SOMAmers. Chugai Pharmaceutical Co. Ltd., Roche and its Genentech Inc. unit market Actemra to treat arthritis. Johnson & Johnson has the IL-6 mAb siltuximab in registration to treat multicentric Castleman's disease (MCD) and in Phase II testing to treat multiple myeloma (MM) and prostate cancer. At least 18 other companies have IL-6 or CD126 inhibitors or antibodies in Phase III or earlier testing to treat cancer or inflammatory diseases. ***SciBX*** **7(8); doi:10.1038/scibx.2014.232** **Published online Feb. 27, 2014**	Patent and licensing status unavailable for both studies	Gupta, S. *et al. J. Biol. Chem.*; published online Jan. 12, 2014; doi:10.1074/jbc.M113.532580 **Contact:** Daniel J. Schneider, SomaLogic Inc., Boulder, Colo. e-mail: dschneider@somalogic.com Gelinas, A.D. *et al. J. Biol. Chem.*; published online Jan. 12, 2014; doi:10.1074/jbc.M113.532697 **Contact:** Nebojsa Janjic, SomaLogic Inc., Boulder, Colo. e-mail: njanjic@somalogic.com

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
Assay & screens			
An antibody specific to an oxidized form of apolipoprotein A-1 (APOA1) to diagnose atherosclerosis	An antibody specific for oxidized, dysfunctional APOA1 complexes could be used to diagnose atherosclerosis. The mAb r8B5.2 was developed against a form of APOA1 that contains an oxidized Trp-72 residue (oxTrp72-APOA1). In mice, injection of oxTrp72-APOA1, but not injection of normal APOA1, impaired formation of cholesterol-containing high-density lipoprotein complexes, suggesting the oxidized variant promotes atherosclerosis. In blood samples from a 627-patient cohort, use of r8B5.2 showed that absolute levels of oxTrp72-APOA1 and ratios of oxTrp72-APOA1 to total APOA1 were associated with elevated cardiovascular disease risk. Next steps include further studying the prognostic value of the antibody in prospective studies and investigating what interventions modulate levels of oxTrp72-APOA1. ***SciBX* 7(8); doi:10.1038/scibx.2014.233** **Published online Feb. 27, 2014**	Patent applications filed; IP covering a diagnostic test with r8B5.2 licensed to Cleveland HeartLab Inc.	Huang, Y. *et al. Nat. Med.*; published online Jan. 26, 2014; doi:10.1038/nm.3459 **Contact:** Stanley L. Hazen, Cleveland Clinic, Cleveland, Ohio e-mail: hazens@ccf.org
Tissue-specific T cell receptor (TCR) sequencing to evaluate immune response to therapeutic HPV vaccines	Tissue-specific TCR sequencing could be used to evaluate immune responses to therapeutic HPV vaccines. In cervical samples, patients with HPV receiving a therapeutic HPV16 vaccine had about a threefold increase of $CD8^+$ T cell infiltration into lesions compared with unvaccinated individuals. The vaccinated patients had activated effector memory T cells and tertiary lymphoid structures, which correlated with favorable prognosis. High throughput sequencing showed that TCRs in cervical tissue were not very prevalent in peripheral blood, suggesting monitoring lesion-specific T cell responses might give a better indication of vaccine immunogenicity. Next steps could include using the method to monitor vaccinated patients with HPV in order to determine if therapeutic resection is needed. ***SciBX* 7(8); doi:10.1038/scibx.2014.234** **Published online Feb. 27, 2014**	Patent application pending; available for licensing	Maldonado, L. *et al. Sci. Transl. Med.*; published online Jan. 29, 2014; doi:10.1126/scitranslmed.3007323 **Contact:** Cornelia L. Trimble, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: ctrimbl@jhmi.edu
Chemistry			
Sponge-associated *Entotheonella* bacteria as a resource for bioactive natural products	Sponge-associated *Entotheonella* bacteria could provide a source of biologically active natural products. Fractionation and sequencing of bacteria associated with the marine sponge *Theonella swinhoei* identified unculturable *Entotheonella* bacterial species that encoded diverse natural product biosynthetic pathways that could produce numerous polyketides and other peptides. Several biosynthetic pathways were functionally validated through expression in *Escherichia coli*. Next steps include developing production systems for encoded compounds. ***SciBX* 7(8); doi:10.1038/scibx.2014.235** **Published online Feb. 27, 2014**	Patent application filed covering genes encoding cytotoxic polytheonamide peptides; available for licensing	Wilson, M.C. *et al. Nature*; published online Jan. 29, 2014; doi:10.1038/nature12959 **Contact:** Jörn Piel, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: jpiel@ethz.ch
Computational models			
Computational modeling to aid epitope-focused vaccine design	*In silico*, *in vitro* and primate studies suggest computational modeling could aid epitope-focused vaccine design. Computational design and screening identified stable epitope-presenting protein scaffolds that mimicked an epitope in the respiratory syncytial virus fusion protein (RSV F protein) and specifically bound the RSV neutralizing antibody motavizumab with comparable affinity to the natural epitope. Vaccination with the scaffolds induced neutralizing antibodies in 12 of 16 rhesus macaques. Next steps could include optimizing the vaccines for magnitude and durability of neutralizing responses. AstraZeneca plc discontinued development of the humanized anti–RSV F mAb motavizumab for RSV prophylaxis in 2010. ***SciBX* 7(8); doi:10.1038/scibx.2014.236** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Correia, B.E. *et al. Nature*; published online Feb. 5, 2014; doi:10.1038/nature12966 **Contact:** William R. Schief, University of Washington, Seattle, Washington e-mail: schief@scripps.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
Cyclodextrin encapsulation of hydrophobic drugs to enable liposome loading	Pre-encapsulation of hydrophobic drugs in cyclodextrin could improve delivery by enabling loading into liposomes. Hydrophobic drugs encapsulated in cyclodextrin, which has a hydrophobic core and hydrophilic exterior, increased drug loading into liposomes compared with hydrophobic drugs that were not encapsulated. In mouse colon cancer xenograft models, injection of liposomes loaded with encapsulated hydrophobic cancer drugs decreased tumor growth compared with empty liposomes or free drug without adverse effects. The cancer drugs had previously failed clinical testing because of toxicity issues. Next steps could include testing the platform with additional cancer therapeutics. ***SciBX* 7(8); doi:10.1038/scibx.2014.237** **Published online Feb. 27, 2014**	Patent and licensing status unavailable	Sur, S. *et al. Proc. Natl. Acad. Sci. USA*; published online Jan. 28, 2014; doi:10.1073/pnas.1324135111 **Contact:** Bert Vogelstein, The Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: bertvog@gmail.com
Drug platforms			
Dermo-epithelial skin grafts prevascularized with functional lymphatic and blood capillaries	Autologous skin substitutes supported by a functional lymphatic and blood vasculature could be used to improve transplant success after dermal injury. Coculturing of human keratinocytes, blood endothelial cells and lymphatic endothelial cells with fibroblasts in fibrin- or collagen-containing hydrogels reconstituted a skin graft containing blood and lymphatic vessels. When transplanted onto the wounded backs of immunodeficient rats, the grafts gave rise to a stratified epidermis with blood and lymphatic microvessels that functionally integrated with host microvessels. Next steps include preclinical testing of the prevascularized skin grafts in immunocompetent large animal models to evaluate toxicity and efficacy. ***SciBX* 7(8); doi:10.1038/scibx.2014.238** **Published online Feb. 27, 2014**	Patent application filed; not yet available for licensing	Marino, D. *et al. Sci. Transl. Med.*; published online Jan. 29, 2014; doi:10.1126/scitranslmed.3006894 **Contact:** Ernst Reichmann, University Children's Hospital Zurich, Zurich, Switzerland e-mail: ernst.reichmann@kispi.uzh.ch
Lipopeptide nanoparticles (LPNs) for potent *in vivo* delivery of siRNA selectively to hepatocytes	Rodent and nonhuman primate studies suggest LPNs could be used to deliver siRNAs selectively to hepatocytes. Synthetic lipoamino acid derivatives formulated in nanoparticles with siRNA were screened in mice for target gene knockdown in the liver, yielding a lead LPN containing a dilysine-derived diketopiperazine core and four amino acid, alcohol-based lipid tails. In mice, siRNAs targeting three widely expressed genes delivered with the lead LPN led to selective gene silencing in hepatocytes. In nonhuman primates, i.v. injection of siRNA targeting *transthyretin* (*TTR*) formulated in the lead LPN led to knockdown of *TTR* mRNA with an ED_{50} of ~0.002 mg/kg. Next steps could include further elucidating the mechanism of LPN uptake by hepatocytes. ***SciBX* 7(8); doi:10.1038/scibx.2014.239** **Published online Feb. 27, 2014**	Patent filed; available for licensing from Alnylam Pharmaceuticals Inc.	Dong, Y. *et al. Proc. Natl. Acad. Sci. USA*; published online Feb. 10, 2014; doi:10.1073/pnas.1322937111 **Contact:** Daniel G. Anderson, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: dgander@mit.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Stimulus-triggered acquisition of pluripotency (STAP) cells derived from adult mouse somatic cells	Methods to generate mouse STAP cells by exposure to low pH could lead to the production of stem cells for use in human regenerative medicine. In culture, differentiated mouse $Cd45^+$ blood cells and a variety of other somatic cells treated with low pH reverted to a pluripotent state after 7 days. In chimeric mice, STAP cells gave rise to all three germ layers and germ cells. In culture, adrenocorticotropic hormone (Acth)- and leukemia inhibitory factor (Lif)-containing medium induced proliferation of STAP stem cells, whereas in medium used for their generation, STAP cells had limited self-renewal capacity. In a second study, STAP cells cultured with fibroblast growth factor 4 (Fgf4) were converted into trophoblast stem cell–like cells that led to generation of extra-embryonic tissue and embryonic tissue when injected into blastocysts. Ongoing work includes testing the potential of the method to revert cells derived from primates and humans to an embryonic stem cell–like state (*see* **(Pluri)potent acid, page 10**). *SciBX* 7(8); doi:10.1038/scibx.2014.240 Published online Feb. 27, 2014	For the first study, patent applications for STAP cell–generating methodology filed; licensing status undisclosed For the second study, patent and licensing information unavailable	Obokata, H. *et al. Nature*; published online Jan. 29, 2014; doi:10.1038/nature12968 **Contact:** Charles A. Vacanti, Harvard Medical School, Boston, Mass. e-mail: cvacanti@partners.org **Contact:** Haruko Obokata, RIKEN Center for Developmental Biology, Kobe, Japan e-mail: obokata@cdb.riken.jp Obokata, H. *et al. Nature*; published online Jan. 29, 2014; doi:10.1038/nature12969 **Contact:** Teruhiko Wakayama, RIKEN Center for Developmental Biology, Kobe, Japan e-mail: teru@cdb.riken.jp **Contact:** Yoshiki Sasai, same affiliation as above e-mail: yoshikisasai@cdb.riken.jp **Contact:** Haruko Obokata, same affiliation as above e-mail: obokata@cdb.riken.jp
Markers			
An inflammatory cytokine signature to improve diagnosis of endometriosis	*In vitro* and *in silico* studies suggest an inflammatory cytokine signature could be used to diagnose endometriosis and identify new targets to treat the disease. In peritoneal aspirates from women, elevated concentrations of 13 cytokines comprised an inflammatory signature in patients with endometriosis. In *in silico* analyses, c-Jun N-terminal kinase (JNK) transcription factor binding sites were enriched in genes associated with the cytokine signature. In cultured macrophages with elevated levels of the 13 cytokines, inhibition of JNK and MAP kinase kinase 1 (MAP2K1; MEK1) decreased cytokine secretion compared with vehicle treatment or inhibition of unrelated kinases. Next steps could include extending the approach to more indications and determining whether interfering with the cytokine signature can help treat endometriosis. Xigen S.A. and Auris Medical AG have D-JNKI-1 (AM-111; XG-102), a JNK inhibitor, in Phase II testing to treat hearing loss. The compound is also in Phase I testing to treat stroke. Opko Health Inc. and The Scripps Research Institute have the JNK inhibitor SR-3306 in preclinical development to treat Parkinson's disease (PD). Japan Tobacco Inc. and GlaxoSmithKline plc market the MEK inhibitor Mekinist trametinib to treat melanoma and have the compound in Phase I/II testing to treat additional cancers. *SciBX* 7(8); doi:10.1038/scibx.2014.241 Published online Feb. 27, 2014	Patent and licensing status unknown	Beste, M.T. *et al. Sci. Transl. Med.*; published online Feb. 5, 2014; doi:10.1126/scitranslmed.3007988 **Contact:** Linda G. Griffith, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: griff@mit.edu
Categorization of breast cancers based on expression of vitamin D receptor (VDR), androgen receptor and estrogen receptor	A breast cancer classification system based on expression of three nuclear hormone receptors could help guide prognosis and treatment of the disease. An analysis of normal luminal breast cell differentiation identified four luminal breast cancer categories based on the bimodal expression of VDRs, androgen receptors and estrogen receptors. In samples from patients with breast cancer, the categories correlated with disease outcome, with tumors that did not express the receptors (HR0) having the worst prognosis and tumors expressing all three receptors (HR3) having the best. Next steps include using the system to develop a prognostic test. *SciBX* 7(8); doi:10.1038/scibx.2014.242 Published online Feb. 27, 2014	Patent application filed; available for licensing as a diagnostic or prognostic test	Santagata, S. *et al. J. Clin. Invest.*; published online Jan. 27, 2014; doi:10.1172/JCI70941 **Contact:** Sandro Santagata, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. e-mail: ssantagata@partners.org

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Targets and compounds