

THIS WEEK**ANALYSIS****COVER STORY****1 Bringing patient data into the open**

Two groups have come to the conclusion that breakthroughs in translational medicine require collecting large-scale data on patients, including outcomes, and making those data available to translational researchers. Sage Bionetworks launched a portal through which users can contribute their own health and genomic data for research, and a report from the U.S. National Academy of Sciences is calling for the creation of a national infrastructure for accessing and analyzing open-source patient data.

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By *Joanne Kotz, Senior Editor*

Most translational science efforts focus on integrating the work of academic and industry scientists, and they leave out a critical set of participants: patients. This is problematic because the speed and quality of the feedback between the bench and the bedside is a critical rate-limiting factor for medical progress.

Two groups have come to the conclusion that breakthroughs in translational medicine require collecting data on patients, including outcomes, on a scale never previously attempted and making those data available with appropriate privacy protections to translational researchers.

In both cases, the key challenges will be getting industry and academic buy-in to data sharing and setting up the legal and logistical infrastructures.

Sage Bionetworks [launched a portal this month](#) through which users can contribute their own health and genomic data for research using a newly developed legal framework. Separately, a report from the U.S. **National Academy of Sciences** (NAS) is calling for the creation of a national infrastructure for accessing and analyzing open-source patient data.¹

Pooling patient data to enhance the value of treatment is not a new concept. Indeed, a handful of pharma and payers already are collaborating to share patient information to improve clinical trial design and better evaluate a drug's benefit to patients.

For example, in February 2011, **AstraZeneca plc** announced a collaboration with the HealthCore Inc. outcomes research unit of **WellPoint Inc.** to analyze the effectiveness of marketed therapies to identify gaps in which new medicines are needed. In June 2011, **Sanofi** partnered with **Medco Health Solutions Inc.** to identify subpopulations of patients with the highest medical need to inform patient selection during clinical testing.²

The Sage and NAS efforts are seeking to move the concept to an open-access model in which patient data are collected with appropriate legal and privacy safeguards and pooled anonymously in an open database to aid biomedical research, drug discovery and ultimately clinical care (*see Figure 1, "Open-access model for patient data sharing"*).

"Having come back to academia from industry three years ago, I have been surprised, actually, how little overlap there is between the world of research and the world of clinical care. I think that's to the detriment of patients and what we are trying to accomplish in translational research. With advances like electronic health records and low-cost, high throughput DNA sequencing, there is an opportunity to take advantage of routine episodes of clinical care for biomedical and clinical research. Yet most of the data are not collected, not pooled or never connected to the explosion of molecular data," said Susan Desmond-Hellmann, chancellor of the **University of California**,

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San Francisco and co-chair of the committee that wrote the NAS report.

Desmond-Hellmann was previously president of product development at **Genentech Inc.**, which is now part of **Roche**.

Although the NAS report is nominally about the need to modernize the taxonomy of disease, its real focus is creating a learning healthcare system. This would be achieved by building a national informatics infrastructure over the course of years to decades to make health data and molecular information obtained from individual patients during routine office visits openly available to inform both biomedical research and patient care.

Patient health information would come from electronic health records. Molecular information that could be collected for patients includes genome, epigenome, metabolome and microbiome data.

As for Sage, director John Wilbanks said the purpose of the not-for-profit's proposed project is to put "a lot of data together, get it clean and let the researchers of the world start running on it to make new connections."

These two efforts "represent a great step forward with considerable potential to be highly informative and impactful. By having a resource available that amalgamates genomic, biosensor, phenotypic and other critical data for a very large population of individuals, the whole biomedical research process will be markedly accelerated," Eric Topol, director of the **Scripps Translational Science Institute** and chief academic officer of **Scripps Health**, told SciBX.

Ultimately, said Desmond-Hellmann, the drivers behind these initiatives are "a need to innovate, to lower the cost of health and to challenge ourselves to tap into the explosion of how people use data to completely change how we think about doing R&D in the life sciences."

Getting to the point

According to Desmond-Hellmann, collecting point-of-care patient information is a key aspect of the proposal and is distinct from information currently collected in clinical trials.

Collecting point-of-care information would provide patient data that are more reflective of "real life, including all of us in the community—not a contrived situation," she said. "Even in large clinical studies currently conducted, the numbers of patients are relatively small and miss the power of having huge numbers of patients."

Pfizer Inc.'s David Cox, a member of the committee that wrote the NAS report, told SciBX that longitudinal data with outcomes are critical to advance translational research. "My view is that right now, without access to this kind of information, the entire pharma industry is severely limited in its ability to make new medicines. When you look at what has driven the ability to make novel therapies, in almost every case it is longitudinal

"With advances like electronic health records and low-cost, high throughput DNA sequencing, there is an opportunity to take advantage of routine episodes of clinical care for biomedical and clinical research. Yet most of the data are not collected, not pooled or never connected to the explosion of molecular data."

**—Susan Desmond-Hellmann,
University of California,
San Francisco**

clinical outcome data in clinical samples. Clinical trial data, which is more of a snapshot, is critical, but not sufficient.”

Cox is SVP and CSO of Pfizer’s Applied Quantitative Genotherapeutics Unit.

Once the molecular and health information is assembled, the NAS committee envisions integrating analytical and visualization tools to improve disease classification, facilitate more personalized clinical care and catalyze biomedical research.

The report cited an ongoing UCSF–**Kaiser Permanente** study as proof of concept for collecting additional molecular patient data during the course of routine care as an opt in that is paid for via research funding.

Under the project, which is funded by an NIH grant of about \$25 million, Kaiser patients can elect to have their DNA genotyped. To date, the partners have genotype information for about 200,000 patients. The genetic information is then integrated with self-reported health information, electronic health records and California environmental data and held anonymously in a database—separately from patients’ health records—for analysis by UCSF researchers.

The integrated information enables researchers to look at the natural history of disease. “We can go backwards in time and look at people who have acquired diseases and look at their genetic information, at what medications they were on, at risk behaviors, etc.,” said Desmond-Hellmann.

Two new pilot studies are proposed in the NAS report: “The Million American Genomes Initiative” and “Metabolomic Profiles in Type 2 Diabetes.” No specific steps have been taken to implement them, and how such efforts would be financed has not been decided, said Desmond-Hellmann.

The virtue of patients

Meanwhile, Sage is launching a study in which individual users can anonymously share their health and genomic data for biomedical research.

The first step was creating a legal framework, dubbed the Portable Legal Consent (PLC), which allows users to give broad rights for the use of data on themselves for research purposes. Only a few restrictions apply that create some protections for participants against discrimination and that require open access to publications resulting from the research.

Next up is testing the concept. In a study called “Portable Legal Consent for Common Genomics Research (PLC-CGR),” individuals will be able to

Figure 1. Open-access model for patient data sharing. Two groups are hoping to make patient health and outcome data—and associated genomic and molecular information—openly available to facilitate translational research.

Sage Bionetworks launched a portal through which users can contribute their own health and genomic data, and a report from the U.S. **National Academy of Sciences** is calling for the creation of a national infrastructure for accessing and analyzing open-source patient data.

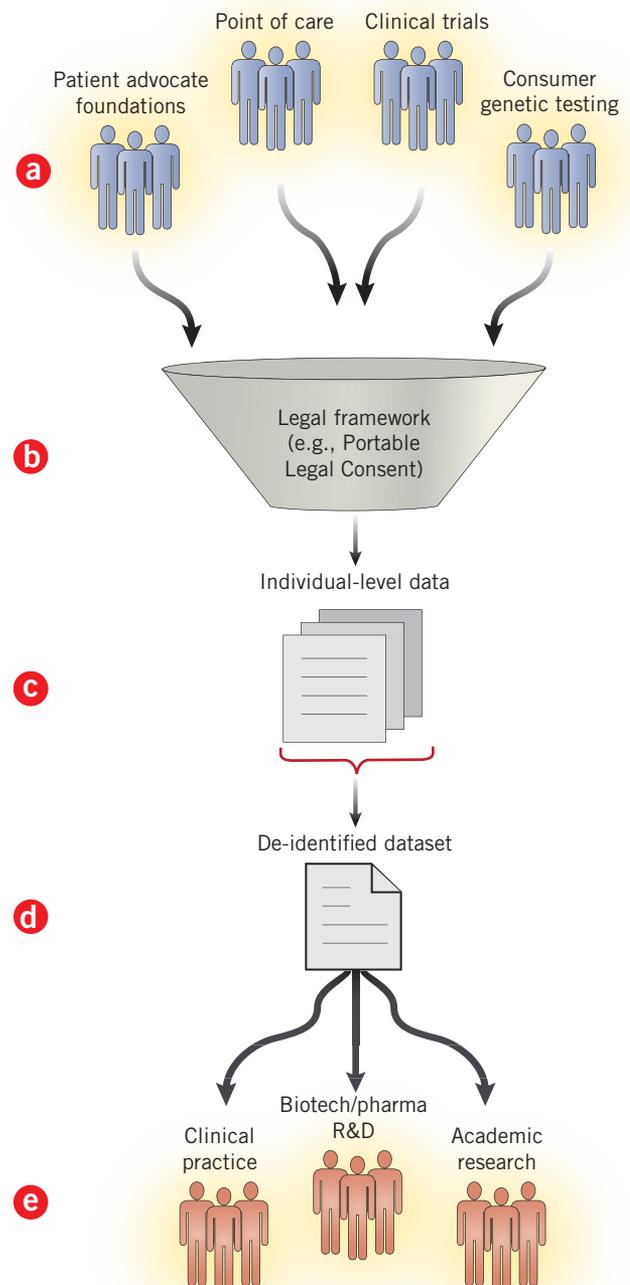
In these models, health and molecular data is collected from clinical trials and routine health visits [a] using a legal framework that protects privacy and ensures appropriate downstream uses [b]. The data from individuals [c] are then de-identified [d] and made available for academic and industry research, as well as ultimately to inform clinical care [e].

deposit data on themselves on the trial’s website, including electronic health records and genomic and lifestyle information. Sage received IRB approval for the study in April and began enrolling participants this month.

Wilbanks told *SciBX* that patients also could submit data from sites such as **PatientsLikeMe** or directly transfer information from clinical trials in which they are enrolled.

He hopes to have 25,000 participants enrolled within a year, a number roughly equal to the size of the Framingham Heart study, and ultimately to have data on a million individuals.

Wilbanks added that some pharmas and biotechs already are considering using PLC as a consent protocol in pilot trials. In this scenario, a company



would run a clinical trial as usual but include an option for participants to upload their individual data to the PLC-CGR site.

“PLC-CGR is making a bold assertion here—that informed consumers can provide portable consent, allowing them to assign consent to researchers rather than for consent be taken from them in individual studies,” said Paul Wicks, R&D director at PatientsLikeMe.

PatientsLikeMe previously ran a study exploring why patients with amyotrophic lateral sclerosis (ALS) chose not to participate in a biomarker study that sought to understand the cause of their disease.³

“Many patients felt they didn’t need to donate blood because during their diagnostic workup they had already had blood taken several times, and these patients assumed that their blood would also be used for research to find a cure. In fact when we told these patients that, no, we would need to take new samples and get separate consent for each new study, they were dissatisfied with the inefficiency of the system,” Wicks said.

Opening up

The primary challenges to the NAS and Sage efforts will be obtaining enough data submissions to enable meaningful analysis of compatible data and convincing academics, payers, health maintenance organizations and biotech and pharma companies to openly share their data.

There are data analysis approaches that “simply can’t work until there’s vast amounts of data. To be blunt, neither Google nor Facebook would make a change to an advertising algorithm with a sample set as small as that used in a Phase III clinical trial. Sage’s goal is to get the sample sizes for clinical data closer to those we use in consumer systems,” said Wilbanks.

He also said completeness of the data will be paramount. For example, in Sage’s study, “if we get a million people enrolled but each only uploads one kind of data—a genotype here, a medical record there—it probably won’t be as useful as getting 25,000 people to upload their genotype, a personal health record and ongoing lifestyle data,” he said.

Ultimately, the success of these efforts will depend heavily on sharing, said Desmond-Hellmann, “and I think it’s hard for academia and it’s hard for industry.

Topol agreed. “The barriers will not likely be most individuals who are asked to provide consent but rather the researchers who are used to keeping the data in their own domain.”

“I think pharma is also in a fantastic position to benefit from” the efforts, noted Desmond-Hellmann. “I would point to what Vertex did in cystic fibrosis by partnering with the **Cystic Fibrosis Foundation**. Can you imagine scouring the earth for 4% of patients with a rare disease? Impossible. That link to the kind of databases that the CF foundation has built up over the years was essential.”

Vertex Pharmaceuticals Inc.’s Kalydeco, which was approved in January, targets a mutation found in about 4% of patients with CF. Vertex took the compound from IND to market in just over five years. The CF Foundation’s registry of patients, which contains genetic information and medical histories, and the foundation’s clinical trial network were key factors in Kalydeco’s rapid development path.

“What I think is really key is increasingly thinking about intellectual property and authorship as being driven by intellectual contribution, not

“If we get a million people enrolled but each only uploads one kind of data—a genotype here, a medical record there—it probably won’t be as useful as getting 25,000 people to upload their genotype, a personal health record and ongoing lifestyle data.”

—John Wilbanks, Sage Bionetworks

by who owns the database,” said Desmond-Hellmann. “I think that patients and patient advocacy groups can drive some of these collaborative behaviors.”

She added: “A lot of different disease-oriented patient advocacy groups, who are increasingly getting into venture philanthropy, are really pushing that if you’d like funding, for example, from the **Multiple Myeloma Research Foundation** (MMRF), you need to share your data.”

In July 2011, the MMRF launched CoMMpass, a 5-year study of 1,000 newly diagnosed MM patients that will connect multiple types of genomic profiling with longitudinal clinical data. The study is supported in part by a precompetitive consortium of industry partners, and the initial data will be made openly available when the portal is launched near the end of this year. Following the portal launch, data will be made available first to members of the precompetitive consortium for five months, then to study investigators for one month and then openly to the clinical and research community every six months throughout the study.

Louise Perkins, CSO of MMRF, told *SciBX* the foundation is building a research portal with tools and interfaces to allow clinicians and researchers to “interact with the data and explore clinical and biological hypotheses.”

One difficulty the MMRF has encountered is the issue of data compatibility. Even genomic information collected by different research teams is not necessarily readily compatible. “Some groups are analyzing 100 genes, some are sequencing exomes, some are only sequencing parts of the exome,” said Perkins.

Perkins said bringing together multiple kinds of molecular information for multiple diseases will not be straightforward. “When one starts talking about collecting data across diseases it becomes very challenging to see the light at the end of the tunnel,” she said.

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Medco Health Solutions Inc. (NYSE:MHS), Franklin Lakes, N.J.
Multiple Myeloma Research Foundation, Norwalk, Conn.
National Academy of Sciences, Washington, D.C.
PatientsLikeMe, Cambridge, Mass.
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Roche (SIX:ROG; OTCGX:RHHBY), Basel, Switzerland
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GSK completes its Canadian tripod

By Michael J. Haas, Senior Writer

GlaxoSmithKline plc and the not-for-profit Centre for Drug Research and Development have partnered to fund research from academic institutions across Canada. The deal completes a trio of alliances established by the pharma in the last two years to tap promising preclinical research in Canadian academia.

CDRD was founded in 2007 and helps investigators at more than 20 institutions turn their discoveries into investment opportunities for industry by providing access to in-house resources that cover all stages of preclinical drug development, scientific and business expertise and project management skills, president and CEO Karimah Es Sabar told *SciBX*.

CDRD receives funding from the Canadian federal government, the provincial governments of British Columbia and Alberta and companies such as Pfizer Inc. and Johnson & Johnson, which have invested in small-scale projects, and Merck & Co. Inc., which supports a training initiative within CDRD.

Since its founding, CDRD has raised about C\$98 million (US\$95 million), of which 70% comes from public funds and 30% from private industry sources, Es Sabar said.

CDRD's for-profit commercial arm, CDRD Ventures Inc. (CVI), forms strategic alliances with industry and facilitates licensing agreements between industry and CDRD's affiliates.

According to Barry Gee, CDRD's director of communications, the organization's industry partnerships "on the nonprofit CDRD side, such as those by Pfizer and Johnson & Johnson, support smaller, earlier stage projects, whereas those on the for-profit CVI side, such as the GSK collaboration, generally support larger-scale, more advanced projects that are closer to a commercial stage."

"The collaboration will bring GSK's expertise to the projects, and the resources GSK is investing will significantly increase the pool of capital available to take selected projects through the development process," Es Sabar said.

This is CDRD/CVI's second broad-based collaboration with an industry partner. The first—with Roche—was formed last year.

"GSK has always supported innovative R&D in Canada, and we think the potential for very good life sciences research here has been underutilized in terms of its commercial potential," said Rav Kumar, VP at GSK in Canada who is responsible for clinical, regulatory and R&D alliances. "We have been tapping that potential through our collaborations with CQDM, MaRS Innovation and now Vancouver-based CDRD/CVI. We see these partnerships as three legs of a tripod" that span Canadian academia and complement one another.

Last year GSK joined the Quebec Consortium for Drug Discovery (CQDM), which funds precompetitive research at small companies and academic institutions in Quebec province.¹ The pharma also established

a collaboration to cherry-pick early technologies emerging from MaRS, a technology transfer organization that represents 16 partner institutions in Ontario.²

Kumar said a driver of the new deal was CDRD's connections to most major Canadian institutions and a few outside Canada, including the Karolinska Institute; The University of Tokyo's technology transfer organization, **Todai TLO Ltd.**; and the **Lead Discovery Center GmbH**, which is a drug discovery company established by **Max Planck Innovation GmbH** to develop the life sciences research of **Max Planck Society** scientists.

"What appeals to us is not just the assets CDRD has now but that they're always looking for new ones—so we can direct them to therapeutic areas that interest us," such as oncology, inflammation and neurodegeneration, he said.

The collaborators have not yet chosen specific projects, but a committee that includes representatives from CDRD and GSK will meet in the next few

weeks to review CDRD's assets and decide which ones to develop, said Kumar.

Es Sabar added that projects reviewed by the joint CDRD-GSK committee will have already met CDRD's own criteria, such as innovative science, the potential for a solid IP position and commercialization, and readily identifiable questions and experiments that will advance the project.

"CDRD would probably have already done some de-risking by funding additional

experiments so that a candidate project is at a stage that GSK would want to see," Kumar added.

This de-risking is part of CDRD's process for making any asset an attractive investment for industry, Es Sabar said.

The path forward

Kumar said all projects would probably be preclinical and "span the spectrum from a very early stage, where the researchers have explored the biology and begun to identify and validate potential therapeutic targets," to projects that are ready to be put on a development track.

For an early stage project, GSK, CDRD and the researchers will jointly form a development plan that would include defined experiments requiring only a limited level of funding, he said. "GSK would invest in the project at this point, but CDRD might also leverage funding from the government or other organizations, so the investment in such a project wouldn't come from just GSK."

He added that CDRD and/or the academic institution would retain ownership of any existing or new IP associated with early stage projects.

When GSK deems a project ready for a commercial development track, the pharma would do a formal deal with CVI to in-license the IP or spin it out into a new company, Kumar said. GSK has the option to lock in its interest in a project through such a deal at any point in the collaborative process, he said.

Each partner's investments in the collaboration are undisclosed.

Kumar did say GSK has placed no hard limits on its total investment. "As long as the science is innovative and could improve patient outcomes, GSK will be interested in investing in it," he said. "We are committed to CDRD and its model for developing assets, and we plan to be involved with them

"What appeals to us is not just the assets CDRD has now but that they're always looking for new ones—so we can direct them to therapeutic areas that interest us."

—Rav Kumar, GlaxoSmithKline plc

for the long term.”

Es Sabar added that “the funding levels, as well as the respective contributions from CDRD, industry or academic partners, or other leveraged sources such as grants, will be determined on a project-by-project basis.”

She said the length of the collaboration with GSK will depend on the number of projects selected and the level of funding contributed to each from GSK’s initial investment.

Es Sabar noted that CVI’s collaborations with Roche and GSK are similar in terms and how they are managed. “This was specifically done to ensure that both partners are on the same footing and have equal opportunities in regard to the technologies within CDRD. Our ability to work effectively with multiple industry partners is one of the strengths of our model. Any of our future partnerships with industry will be consistent with this established structure.”

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Karolinska Institute, Stockholm, Sweden
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Max Planck Innovation GmbH, Munich, Germany
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Reining in pain

By Lev Osherovich, Senior Writer

University of California, San Francisco researchers have shown that neuronal precursor cells from fetal mouse brains can be transplanted into the spinal cord of adult mice to treat neuropathic pain.¹ The embryonic brain cells are being developed by **Neurona Therapeutics Inc.**, a company founded by several of the San Francisco team members.

The precursor cells come from the medial ganglionic eminence (MGE) region of the embryonic brain. During development MGE cells migrate to distant areas of the brain, form synapses with nearby neurons and mature into γ -aminobutyric acid (GABA)-producing inhibitory neurons, called GABAergic interneurons.

Now, a team led by Allan Basbaum, professor of anatomy at UCSF, has shown that transplanted MGE cells can take root in the spinal cord and adopt an inhibitory function that suppresses neuropathic pain.

“Inhibitory interneuron activity, which normally regulates outflow of pain, is decreased” in patients with neuropathic pain and models of the disease, said Basbaum.

Basbaum said there was prior evidence that inhibitory GABA activity in the spinal cord could suppress the transmission of neuropathic pain. Thus, his team set out to enhance this effect by increasing the number of inhibitory GABAergic neurons within the spinal cord.

“We asked if we could repopulate GABAergic interneurons in the spinal cord with cells from the embryonic cortex,” said Basbaum. “We’ve demonstrated that these cells can integrate into the spinal cord circuitry and normalize GABA production.”

New home

The team began by harvesting MGE cells from the brains of embryonic mice, marking them with transgenic GFP and injecting them into the spinal cords of adult mice. After one month, the cells had migrated throughout the spinal cord region near the injection site and differentiated into mature neurons expressing GABAergic markers.

Fluorescent labels showed that the transplanted neural precursors formed synapses with adjacent spinal cord neurons. MGE-derived neurons in the spinal cord became activated by both normal mechanical stimulation and by painful stimulus, as expected for interneurons with multiple synaptic connections.

Basbaum said there initially was some concern that having too many GABAergic neurons in the spinal cord would create an overly inhibitory environment that would interfere with normal nervous system functions. However, “the transplant normalizes GABA production but doesn’t put it above normal range,” he noted.

Finally, the team assessed the functional effect of the transplant. In a functional assay of neuropathic pain, mice with MGE transplants had less pain avoidance behavior than nontransplanted controls. The MGE cells had no effect in a model of inflammatory pain, which is a distinct form of pain that does not involve dysregulation of GABA signaling.

Data were reported in *Neuron*.

Altogether, the findings suggest MGE transplants can dial down the intensity of sensory signals that drive neuropathic pain.

“In nerve injury, there can be persistent activation of brain circuits, leading to hyperexcitability,” said Cory Nicholas, Neurona CEO and a postdoctoral fellow at UCSF. “This is a peripheral injury but the cells are acting in the spinal cord, inhibiting the pain pathways that are coming up the injured neurons into the CNS.”

Nervy play

A number of neurological conditions are associated with excessive stimulatory signaling in the brain and could be amenable to normalization by MGE-derived GABAergic cells, said Nicholas.

Indeed, prior work by members of the UCSF team and other groups has shown the possibility of using embryonic MGE cells for epilepsy and Parkinson’s disease (PD).²⁻⁴ In all of these cases, the MGE cells were transplanted into the brains of mice rather than into the spinal cord.

Remaining hurdles include determining whether human MGE cells will behave similarly to mouse cells in cell culture and when transplanted into the spinal cord and scaling up the production of human MGE cells to therapeutically useful quantities.

Because human MGE cells would ordinarily need to be harvested from fetal brains, Nicholas said the company has developed a way to make MGE-like cells from human induced pluripotent stem (iPS) cells. The company is now testing those cells in

multiple undisclosed disease models.

Cells derived from iPS cells typically undergo differentiation *in vitro* prior to transplantation. Thus, it remains to be seen whether iPS cell-derived MGE cells will migrate, engraft and function as efficiently as actual MGE cells.

Regardless of the source, Chris Parker, VP and chief commercial officer of **Cellular Dynamics International Inc.**, said getting useful quantities of human MGE cells and scaling up production would probably require identifying markers that distinguish the cells from other semi-differentiated cells of the embryonic cortex.

Cellular Dynamics markets iPS cell-derived cell lines as discovery tools.

Parker noted that one CDI product—the iCell Neuron preparation—is a mixture of iPS cell-derived forebrain neurons that may include some MGE-like cells. He said the company might test whether iCell Neurons can behave like the UCSF team’s primary MGEs in neuropathic pain.

Neurona is funded by grants from the **California Institute for Regenerative Medicine** (CIRM), and Nicholas said the company hopes to raise venture money once it demonstrates the preclinical efficacy of human MGE cells. The company has filed for a patent covering *in vitro* production of MGE cells. UCSF has filed for patents covering the use of MGE cells to treat neuropathic pain, epilepsy and neurodegeneration.

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ADORABLE implants

By Kai-Jye Lou, Staff Writer

Researchers at the **New York University Langone Medical Center** have found a way to ward off a leading cause of joint implant failure.¹ The group has shown that adenosine A_{2A} receptor agonists can block the inflammation and bone destruction that stems from debris particles flaking off the implants. The group now needs to translate the findings into a product that companies can test in the clinic.

Bruce Cronstein, a professor in the Departments of Medicine, Pathology, and Biochemistry and Molecular Pharmacology, said joint implant failure is a bigger problem than in previous decades because the average age of implant recipients today is lower.

“Prosthetic joint implants usually last 10–15 years before they began to fail, so if you put a replacement hip in a 65-year-old patient, it would probably last for the life of that patient,” said Cronstein. “But it’s much more common these days to see joint implants in younger age groups such as 50-year-old patients, and such patients are probably going to need a revision surgery once their first implant fails. The problem is that this surgery is going to be much more difficult to carry out, and the second implant is more likely to fail.”

Factors contributing to the increasing number of joint implant procedures in younger age groups include high obesity rates and increasing demand from patients themselves to improve the quality of their active lives.^{2,3} Moreover, processes that lead to implant failure also could weaken the bone at the site of the implant, which could make subsequent implants more likely to fail.

Cronstein’s group has been looking for ways to prolong the life of the initial implant. The team had previously studied adenosine signaling in rheumatoid arthritis (RA) and focused on the adenosine A_{2A} receptor (ADORA_{2A}) because agonizing it has anti-inflammatory effects.⁴

In November, Cronstein’s team added another puzzle piece with a paper showing that activation of ADORA_{2A} suppressed the formation of osteoclasts, which carry out bone resorption.⁵

The group recognized the overlap between processes that lead to joint implant failure and those modulated by ADORA_{2A}, and thus they sought to determine whether an ADORA_{2A} agonist could help prevent the inflammation and bone destruction triggered by debris particles (*see*

“I think the key concerns going forward are not going to be whether A_{2A} agonists can prevent osteolysis but whether such an agonist could be developed in a manner that will contain or limit its anti-inflammatory effects.”

—Nadim Hallab,
Rush University Medical Center

Figure 1, “Processes that lead to debris particle-induced osteolysis”).

In wild-type mice injected with polymeric particles in a pouch above their skulls, injection of an ADORA_{2A} agonist decreased bone loss, inflammation and osteoclast levels compared with injection of saline. Those effects did not occur in particle-injected *Adora_{2a}* knockout mice treated with the same agonist.

The polymeric particles model debris particles caused by implant wear.

In human bone marrow samples, an ADORA_{2A} agonist inhibited osteoclast differentiation compared with no treatment. Results were published in *Science Translational Medicine*.

“The most interesting aspect of the findings reported in this paper is in identifying a new target for preventing implant failure, as nobody has really explored the role of the adenosine A_{2A} receptor in the debris-induced osteolysis setting,” said Edward Schwarz, director of the Center for Musculoskeletal Research at the **University of Rochester Medical Center**. “What the researchers need to do now is develop a product that would be practical to test in the clinic, such as an oral drug.”

Nadim Hallab, an associate professor at **Rush University Medical Center**, said the findings reveal a clear effect against processes that cause implant loosening and failure.

“I think the key concerns going forward are not going to be whether A_{2A} agonists can prevent osteolysis but whether such an agonist could be developed in a manner that will contain or limit its anti-inflammatory effects,” said Hallab, who also is CEO at **Bioengineering Solutions Inc.** and **Orthopedic Analysis LLC**. “As many of the patients experiencing joint implant failure are in the higher age groups, their immune systems may not be as robust, so persistent systemic immunosuppression from the anti-inflammatory effects could be risky.”

Bioengineering Solutions carries out implant debris analysis and particle production for companies developing prosthetic implants. Orthopedic Analysis tests for metal allergies in prospective implant recipients.

Practical options

Cronstein said his group is working with the **NIH** to translate the findings into a viable product.

One idea, he said, is to incorporate an ADORA_{2A} agonist into the cement used to fix an implant in place or as a device coating on the

(Continues on p. 9)

(Continued from “Reining in pain,” p. 7)

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Contact: Allan Basbaum, same affiliation as above e-mail: allan.basbaum@ucsf.edu
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COMPANIES AND INSTITUTIONS MENTIONED

California Institute for Regenerative Medicine, San Francisco, Calif.
Cellular Dynamics International Inc., Madison, Wis.
Neurona Therapeutics Inc., San Francisco, Calif.
University of California, San Francisco, San Francisco, Calif.

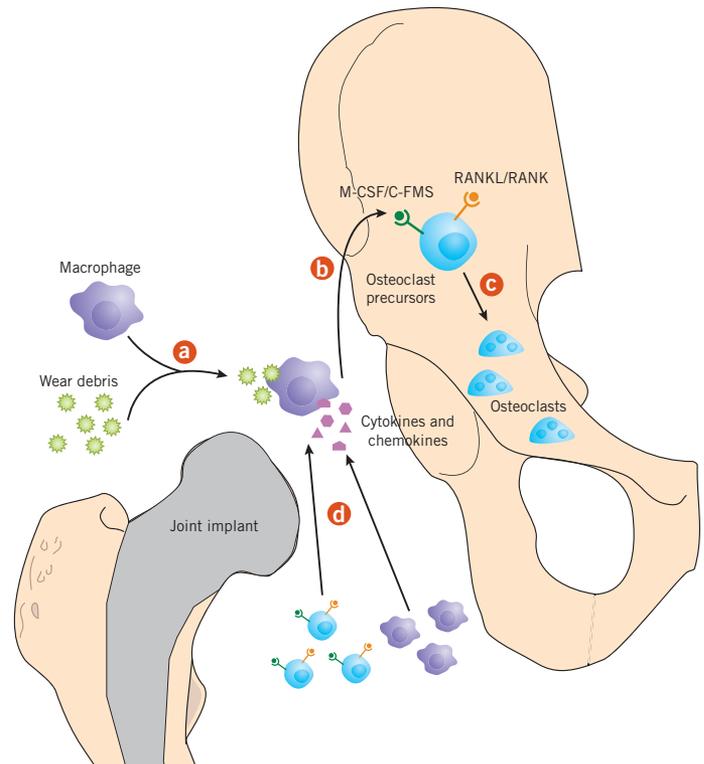
Figure 1. Processes that lead to debris particle–induced osteolysis. As joint implants wear, debris triggers processes that lead to inflammation and osteolysis. Together, these processes cause the implant to loosen and fail.

Macrophages are the primary target of debris particles from an implant. These cells take up debris via phagocytosis and secrete cytokines and chemokines in response [a]. One of these secreted cytokines, macrophage colony-stimulating factor 1 (CSF1; M-CSF), activates colony-stimulating factor 1 receptor (CSF1R; C-FMS; CD115) on osteoclast precursors [b].

When M-CSF is present with another factor, receptor activator of NF- κ B ligand (RANKL; TNFSF11), osteoclast precursors differentiate into bone-resorbing osteoclasts [c]. RANKL activates tumor necrosis factor receptor superfamily member 11a (TNFRSF11A; RANK; CD265) and is produced by other cells such as T lymphocytes.

In addition to promoting osteoclast generation, the cytokines and chemokines secreted by the macrophage also attract additional macrophages, osteoclast precursors and other proinflammatory cells to the area [d].

As reported in Mediero *et al.*, adenosine A_{2A} receptor (ADORA $_{2A}$) agonists can block the inflammation- and osteolysis-promoting effects of wear debris particles and thus have the potential to prevent joint implant failure.



implant itself.

“The nice thing about adenosine A_{2A} agonists is they are generally not very heat labile and will probably survive the cement setting process, which is an exothermic event,” Cronstein told *SciBX*. “As for developing a long-term coating for the prosthetic itself, that is going to require more ingenuity.”

Hallab said the success of either approach will hinge on the ability to develop a product that retains its activity after 10–15 years. “Nearly all implants are still doing fine at 5 years, and it’s the problems that begin after 10–15 years that need to be addressed,” he said.

Schwarz added that companies developing medical implants have no appetite for the risks associated with developing a long-term coating for joint implants and will not want to run a 10-year clinical trial to evaluate the safety and efficacy of such a product.

“These companies have shied away from long-term coatings because they won’t know the long-term effects until much later and could be liable if the coating does end up causing problems,” he said. “At this time, implant companies are only considering coatings with short half-lives, such as antimicrobial coatings.”

Thus, Schwarz thinks the focus instead should be on patients who are showing signs of implant failure but are not candidates for a revision surgery or those who choose not to have such a surgery. “An oral A_{2A} agonist could be beneficial and help delay implant failure in such patients,” he told *SciBX*.

Yousef Abu-Amer, a professor in the Department of Orthopedics and the Department of Cell Biology and Physiology at the **Washington University in St. Louis School of Medicine**, said it will be important to determine how tissue-specific deletion of ADORA $_{2A}$ affects various cellular compartments and to identify the molecular mechanism by which the receptor regulates osteoclasts. He noted that such studies could provide the researchers with useful insights on specificity, drug design and potential side effects.

He also said it will be important to study the effects of candidate agonists on fracture repair, bone formation and integration of an implant with bone and to carry out studies that evaluate both systemic and local application.

At least one orally delivered ADORA $_{2A}$ agonist is in clinical trials. BVT.115959, which is being developed by **CBT Development Ltd.**, **Ergomed Group** and **Swedish Orphan Biovitrum AB**, is in Phase II testing to treat diabetic neuropathic pain.

Moreover, at least three injectable ADORA $_{2A}$ agonists have already progressed into or through the clinic as vasodilators for use in myocardial perfusion imaging (MPI). These include **Lexiscan regadenoson**, which is marketed by **Gilead Sciences Inc.** and **Astellas Pharma Inc.**; **Pfizer Inc.**’s **binodenoson**, which is in registration; and **Forest Laboratories Inc.**’s **apadenoson**, which is in Phase III testing.

Last month, a team at the **University of California, San Francisco** published data showing that ADORA $_{2A}$ agonists could promote β cell regeneration, suggesting a potential application in diabetes.^{6,7}

“It’s much more common these days to see joint implants in younger age groups such as 50-year-old patients, and such patients are probably going to need a revision surgery once their first implant fails.”

**—Bruce Cronstein,
New York University Langone
Medical Center**

NYU has a patent covering medical implants containing adenosine receptor agonists and methods for inhibiting medical implant loosening. The work is available for licensing from the university's Office of Industrial Liaison.

Lou, K.-J. *SciBX* 5(25); doi:10.1038/scibx.2012.647
Published online June 21, 2012

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Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Bioengineering Solutions Inc., Oak Park, Ill.
CBT Development Ltd., Cambridge, U.K.
Ergomed Group, Frankfurt, Germany
Forest Laboratories Inc. (NYSE:FRX), New York, N.Y.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
National Institutes of Health, Bethesda, Md.
New York University Langone Medical Center, New York, N.Y.
Orthopedic Analysis LLC, Chicago, Ill.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Rush University Medical Center, Chicago, Ill.
Swedish Orphan Biovitrum AB (SSE:SOBI), Stockholm, Sweden
University of California, San Francisco, Calif.
University of Rochester Medical Center, Rochester, N.Y.
Washington University in St. Louis School of Medicine, St. Louis, Mo.

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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
Cancer				
Breast cancer	CC chemokine receptor 5 (CCR5; CD195)	<p><i>In vitro</i> and mouse studies suggest CCR5 antagonists could help prevent breast cancer metastasis. In a genetic study of human breast cancer specimens, HER2 (EGFR2; ERBB2; neu)-positive and basal breast cancer subtypes had greater expression of chemokine CC motif ligand 5 (RANTES; CCL5) and CCR5 than other breast cancer subtypes. In breast cancer cells, the CCR5 inhibitor Selzentry maraviroc decreased cell invasion compared with vehicle. In a mouse model of breast cancer, Selzentry decreased pulmonary metastasis compared with vehicle control. Next steps include determining the role of CCR5 in the metastasis of other cancers.</p> <p>Pfizer Inc. markets Selzentry to treat HIV/AIDS. At least five other companies have CCR5 antagonists in clinical and preclinical testing to treat HIV/AIDS.</p> <p>SciBX 5(25); doi:10.1038/scibx.2012.648 Published online June 21, 2012</p>	Patent application filed; available for licensing	<p>Velasco-Velazquez, M. <i>et al. Cancer Res.</i>; published online May 25, 2012; doi:10.1158/0008-5472.CAN-11-3917 Contact: Richard G. Pestell, Thomas Jefferson University, Philadelphia, Pa. e-mail: richard.pestell@jefferson.edu</p>
Cancer	Ataxia telangiectasia mutated (ATM); c-Met proto-oncogene (MET; HGFR); p53	<p>Computational pathway analysis and a cell-based genomewide small hairpin RNA screen suggest inhibition of ATM or MET could improve the efficacy of the small molecule p53 pathway activator Nutlin-3 in cancer. In a 3D multicellular tumor spheroid model, Nutlin-3 plus an ATM or MET inhibitor completely ablated all tumor spheroids, whereas Nutlin-3 alone only decreased spheroid growth. Next steps could include testing the combination therapies in mouse models of cancer.</p> <p>R7112, a nutlin Mdm2 p53 binding protein homolog (MDM2; HDM2) antagonist from Roche, is in Phase I trials to treat cancer.</p> <p>SciBX 5(25); doi:10.1038/scibx.2012.649 Published online June 21, 2012</p>	Patent and licensing status unavailable	<p>Sullivan, K.D. <i>et al. Nat. Chem. Biol.</i>; published online June 3, 2012; doi:10.1038/nchembio.965 Contact: Joaquín M. Espinosa, University of Colorado at Boulder, Boulder, Colo. e-mail: joaquin.espinosa@colorado.edu</p>
Cancer	BCL2-associated X protein (BAX)	<p>An <i>in vitro</i> and cell culture study identified a small molecule activator of the proapoptotic B cell lymphoma 2 (BCL-2; BCL2) family member BAX that could help treat cancer. Computational screening identified a lead molecule, BAM7, that <i>in vitro</i> displaced a BAX-activating peptide with an IC₅₀ of 3.3 μM. In mouse fibroblasts, BAM7 induced a Bax conformational change associated with Bax activation and increased apoptosis compared with vehicle. Next steps include screening the cell-killing activity of BAM7 in diverse cancer cell types and optimizing the medicinal chemistry of the molecule. At least six companies have antagonists of the antiapoptotic BCL2 family members in preclinical or clinical testing in cancer.</p> <p>SciBX 5(25); doi:10.1038/scibx.2012.650 Published online June 21, 2012</p>	Patent application filed; available for licensing	<p>Gavathiotis, E. <i>et al. Nat. Chem. Biol.</i>; published online May 27, 2012; doi:10.1038/nchembio.995 Contact: Loren D. Walensky, Dana-Farber Cancer Institute, Boston, Mass. e-mail: loren_walensky@dfci.harvard.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Liver cancer	Guanine nucleotide binding protein β -polypeptide 2-like 1 (GNB2L1; RACK1)	Patient sample and mouse studies suggest inhibiting RACK1 could help treat hepatocellular carcinoma (HCC). In paired liver tissue samples, RACK1 mRNA levels in HCC were higher than those in matched normal tissue ($p < 0.001$). In a mouse xenograft model of HCC, small hairpin RNA-mediated knockdown of RACK1 decreased tumor growth compared with no knockdown. Also in the model, shRNA against RACK1 plus doxorubicin chemotherapy decreased tumor growth compared with either agent alone. Next steps could include screening for and testing small molecule RACK1 inhibitors in HCC models. SciBX 5(25); doi:10.1038/scibx.2012.651 Published online June 21, 2012	Patent and licensing status unavailable	Ruan, Y. <i>et al. J. Clin. Invest.</i> ; published online June 1, 2012; doi:10.1172/JCI58488 Contact: Jianxin Gu, Gene Research Center, Shanghai Medical College of Fudan University, Shanghai, China e-mail: jxgu@shmu.edu.cn
Lung cancer	Forkhead box O1 (FOXO1); epidermal growth factor receptor (EGFR)	Studies in cell culture and in mice suggest trifluoperazine hydrochloride (TFP) could help restore the sensitivity of lung cancer to EGFR-targeting therapies. The FDA-approved antipsychotic and antiemetic TFP is a known dopamine receptor antagonist and also inhibits FOXO1 nuclear export. In cultured cells treated with the EGFR inhibitor Tarceva erlotinib, cells sensitive to the drug showed greater levels of nuclear FOXO1 and apoptosis than erlotinib-resistant cells. In mice with Tarceva-resistant tumors, TFP plus Tarceva increased levels of nuclear FOXO1 and tumor regression compared with Tarceva alone. Next steps include clinical trials and testing the combination using other EGFR-targeting therapies in other cancers. Tarceva is marketed by Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd. and Roche for non-small cell lung cancer (NSCLC) and pancreatic cancer. SciBX 5(25); doi:10.1038/scibx.2012.652 Published online June 21, 2012	Patent application filed; available for licensing	Sangodkar, J. <i>et al. J. Clin. Invest.</i> ; published online June 1, 2012; doi:10.1172/JCI62058 Contact: Goutham Narla, Case Western Reserve University and University Hospitals, Cleveland, Ohio e-mail: goutham.narla@mssm.edu
Lymphoma	MAP kinase kinase 7 (MAP3K7; TAK1)	<i>In vitro</i> studies suggest TAK1 inhibitors could help treat lymphoma. In primary lymphoma cells, TAK1 levels were higher than those in peripheral blood monocytes from healthy control subjects. In primary lymphoma cells, TAK1 small interfering RNA and/or the TAK1 inhibitor AZ-TAK1 induced apoptosis but had no effect on the survival of peripheral blood monocytes from healthy controls. Future studies could include testing TAK1 inhibitors in animal models of lymphoma. AZ-TAK1 is a research compound. SciBX 5(25); doi:10.1038/scibx.2012.653 Published online June 21, 2012	Patent and licensing status unavailable	Buglio, D. <i>et al. Blood</i> ; published online May 30, 2012; doi:10.1182/blood-2011-07-369397 Contact: Anas Younes, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: ayounes@mdanderson.org
Endocrine/metabolic disease				
Diabetes	G protein-coupled receptor 21 (GPR21)	Mouse studies suggest inhibiting GPR21 could help treat or prevent type 2 diabetes. <i>Gpr21</i> knockout mice had greater insulin and glucose tolerance and lower hepatic glucose production, proinflammatory cytokines and macrophages in adipose tissue than wild-type mice. Next steps include identifying GPR21 inhibitors. SciBX 5(25); doi:10.1038/scibx.2012.654 Published online June 21, 2012	Findings unpatented; unlicensed	Osborn, O. <i>et al. J. Clin. Invest.</i> ; published online June 1, 2012; doi:10.1172/JCI61953 Contact: Jerrold M. Olefsky, University of California, San Diego, La Jolla, Calif. e-mail: jolefsky@ucsd.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Obesity	Agouti related protein (AGRP); forkhead box O1 (FOXO1); G protein-coupled receptor 17 (GPR17)	Mouse and <i>in vitro</i> studies suggest inhibiting FOXO1-GPR17 signaling could help treat obesity. In mice, a <i>Foxo1</i> deficiency in <i>Agrp</i> -expressing neurons decreased food intake and body fat mass and increased energy homeostasis compared with normal <i>Foxo1</i> expression. In those mouse <i>Agrp</i> -expressing neurons, expression profiling suggested <i>Foxo1</i> targeted <i>Gpr17</i> . In wild-type mice, intracerebroventricular injection of a <i>Gpr17</i> antagonist decreased food intake compared with saline injection. Next steps include developing a brain-penetrant <i>Gpr17</i> antagonist and testing whether it can affect appetite.	Patent pending covering GPR17-based approaches to obesity and diabetes; available for licensing from Columbia University Contact: Cynthia Lang, Columbia University, New York, N.Y. e-mail: cl2040@columbia.edu	Ren, H. <i>et al. Cell</i> ; published online June 8, 2012; doi:10.1016/j.cell.2012.04.032 Contact: Domenico Accili, Columbia University, New York, N.Y. e-mail: da230@columbia.edu
SciBX 5(25); doi:10.1038/scibx.2012.655 Published online June 21, 2012				
Infectious disease				
Ebola	Ebola glycoprotein GP1; Ebola glycoprotein GP2	Nonhuman primate studies suggest a mAb-based treatment could help improve survival after an Ebola infection. Ebola Zaire strain-specific mAb (ZMab) is a combination of three murine mAbs that target Ebola glycoprotein G1, G2 and a precursor of G1 and G2 called GP. ZMab given in 3 doses 3 days apart protected all 4 cynomolgus macaques from death when treatment began at 24 hours after lethal challenge with Ebola virus. When treatment began at 48 hours after lethal challenge, 2 of 4 macaques survived. Next steps include establishing the commercial scale manufacture of GMP ZMabs and completing safety, biodistribution and toxicology studies.	Patent application filed; licensed to Defyrus Inc.	Qiu, X. <i>et al. Sci. Transl. Med.</i> ; published online June 13, 2012; doi:10.1126/scitranslmed.3003876 Contact: Gary P. Kobinger, University of Manitoba, Winnipeg, Manitoba, Canada e-mail: gary.kobinger@phac-aspc.gc.ca
SciBX 5(25); doi:10.1038/scibx.2012.656 Published online June 21, 2012				
HIV/AIDS	Platelet factor 4 (PF4; CXCL4)	Cell culture studies suggest CXCL4 could help prevent HIV replication. In a cell culture assay of HIV replication, CXCL4 decreased attachment and entry of the virus to host cells and lowered the rate of viral replication compared with vehicle controls. <i>In vitro</i> , CXCL4 bound to the envelope glycoprotein HIV gp120. Next steps include structural studies of the CXCL4-gp120 interaction to aid the rational design of molecules that mimic CXCL4 binding to HIV and prevent or treat HIV infection.	Patent pending; available for licensing	Auerbach, D.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 29, 2012; doi:10.1073/pnas.1207314109 Contact: Paolo Lusso, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. e-mail: plusso@niaid.nih.gov Contact: Anthony S. Fauci, same affiliation as above e-mail: afauci@niaid.nih.gov
SciBX 5(25); doi:10.1038/scibx.2012.657 Published online June 21, 2012				
Inflammation				
Atopic dermatitis	Periostin (POSTN)	<i>In vitro</i> and mouse studies suggest blocking POSTN could help treat atopic dermatitis. In a mouse model of house dust mite-induced allergic skin inflammation, knockout of <i>Postn</i> suppressed swelling and fibrosis. In patients with atopic dermatitis, the level of POSTN expression in the dermis correlated with disease severity. Next steps include developing a neutralizing antibody against POSTN.	Patent application filed; available for licensing	Masuoka, M. <i>et al. J. Clin. Invest.</i> ; published online June 11, 2012; doi:10.1172/JCI58978 Contact: Kenji Izuhara, Saga Medical School, Saga, Japan e-mail: kizuhara@cc.saga-u.ac.jp
SciBX 5(25); doi:10.1038/scibx.2012.658 Published online June 21, 2012				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Inflammation	Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP); toll-like receptor 4 (TLR4); TLR2; tumor necrosis factor- α (TNF- α); IL-6	<i>In vitro</i> and mouse studies suggest Tirap-derived peptides could help treat inflammatory disease. In primary mouse macrophages, Tirap-derived peptides blocked Tlr4 and/or Tlr2 signaling to decrease lipopolysaccharide (LPS)-induced production of proinflammatory cytokines compared with an inactive control peptide. In mice pretreated with the Tirap-derived peptides, compared with mice pretreated with control peptide, LPS injection decreased serum levels of proinflammatory Tnf- α and Il-6. Ongoing work includes testing Tirap-derived and other Tir-derived peptides in mouse models of sepsis. SciBX 5(25); doi:10.1038/scibx.2012.659 Published online June 21, 2012	Patent application filed by the University of Maryland; TIRAP- and TIR-derived peptides available for licensing or partnering	Couture, L.A. <i>et al. J. Biol. Chem.</i> ; published online May 30, 2012; doi:10.1074/jbc.M112.360925 Contact: Vladimir Y. Toshchakov, University of Maryland School of Medicine, Baltimore, Md. e-mail: vtoshchakov@som.umaryland.edu
Neurology				
Alzheimer's disease (AD)	β -Amyloid (A β)	<i>In vitro</i> assays suggest conjugates of benzothiazole-based molecules and Cu ²⁺ chelators could help treat AD. Cu ²⁺ accelerates A β plaque aggregation. In cell-based assays, a conjugate of a benzothiazole-based compound that recognizes A β and a salicylaldehyde-based Cu ²⁺ chelator prevented Cu ²⁺ -induced aggregation and self-assembly of A β plaques and increased cell viability compared with no treatment. Ongoing studies are testing the new compounds in mouse models of AD. SciBX 5(25); doi:10.1038/scibx.2012.660 Published online June 21, 2012	Patent application filed; unavailable for licensing	Geng, J. <i>et al. J. Med. Chem.</i> ; published online June 4, 2012; doi:10.1021/jm3003813 Contact: Xiaogang Qu, Changchun Institute of Applied Chemistry, Changchun, China e-mail: xqu@ciac.jl.cn
Nerve damage	Sterile α and TIR motif containing 1 (SARM1)	<i>In vitro</i> , fly and mouse studies suggest inhibiting SARM1 could help prevent axon loss after injury. A <i>Drosophila</i> screen identified loss-of-function mutations in the fly homolog of <i>Sarm1</i> that protected <i>ex vivo</i> axons from postinjury degeneration. In axotomized mice, <i>Sarm1</i> knockout decreased and delayed axon degeneration compared with normal <i>Sarm1</i> expression. In the <i>Sarm1</i> ^{-/-} mice, 61.2% of axons were protected from degeneration after induction of sciatic nerve lesions. Next steps include identifying ways to block SARM1 function in humans. SciBX 5(25); doi:10.1038/scibx.2012.661 Published online June 21, 2012	Patent applications filed; available for licensing	Osterloh, J.M. <i>et al. Science</i> ; published online June 7, 2012; doi:10.1126/science.1223899 Contact: Marc R. Freeman, University of Massachusetts Medical School, Worcester, Mass. e-mail: marc.freeman@umassmed.edu
Stroke	Thrombin (Factor IIa; F2)	Rat studies suggest detecting thrombin activity in the brain could help diagnose stroke and inhibiting thrombin during stroke could help reduce neurovascular damage. In a rat middle cerebral artery occlusion stroke model, an antithrombin antibody detected thrombin in regions of severe vascular disruption, whereas thrombin was not detected in less damaged areas. In the same model, intra-arterial infusion of thrombin increased vascular permeability and damage and impaired memory and learning, whereas a thrombin inhibitor decreased vascular disruption. Next steps include developing a probe to diagnose thrombin-associated conditions. SciBX 5(25); doi:10.1038/scibx.2012.662 Published online June 21, 2012	Probes patented; licensing status undisclosed	Chen, B. <i>et al. J. Neurosci.</i> ; published online May 30, 2012; doi:10.1523/JNEUROSCI.0369-12.2012 Contact: Bo Chen, Cedars-Sinai Medical Center, Los Angeles, Calif. e-mail: bochen.neuro@gmail.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
Chemistry			
Combinatorial chemistry method for identifying boronic acid-based inhibitors of oxygenase enzymes	A combinatorial chemistry method for identifying boronic acid-based inhibitors of oxygenase enzymes could help identify new therapeutic leads. In the method, a boronate-based ligand is mixed with multiple alcohols to create a library of boronate esters, from which protein ligands are identified by mass spectrometry. The method identified molecules that bound hypoxia-inducible factor prolyl hydroxylase 2 (EGLN1; HIF-PH2; PHD2), an enzyme implicated in cancer. In human cells, a derivative of one of the identified ligands inhibited PHD2 to upregulate hypoxia-inducible factor 1 α (HIF1A; HIF1- α). Next steps include testing derivatives of the PHD2 inhibitors in animal models and identifying inhibitors of other human and bacterial oxygenases.	Methodology unpatented; patent applications filed on PHDs as therapeutic targets; available for licensing or partnering	Demetriades, M. <i>et al. Angew. Chem. Int. Ed.</i> ; published online May 25, 2012; doi:10.1002/anie.201202000 Contact: Christopher J. Schofield, University of Oxford, Oxford, U.K. e-mail: christopher.schofield@chem.ox.ac.uk Contact: Esther C.Y. Woon, National University of Singapore, Singapore e-mail: phaewcy@nus.edu.sg
SciBX 5(25); doi:10.1038/scibx.2012.663 Published online June 21, 2012			
Disease models			
A mouse model of Gleevec-resistant gastrointestinal stromal tumors (GISTs) could aid the identification of new therapies	A mouse model of Gleevec-resistant GIST could help identify new GIST therapies. The mouse was engineered to express a <i>stem cell factor receptor tyrosine kinase (c-Kit; Kit; Cd117)</i> mutation that promoted oncogenesis as well as a second <i>Kit</i> mutation that mediated Gleevec resistance. In the double mutant mice, Gleevec did not decrease Kit activity compared with vehicle or inhibit GIST proliferation, whereas Sutent sunitinib did. Next steps include conducting mechanistic studies of oncogenic signaling in this model and evaluating targets downstream of the double-mutant KIT receptor. Novartis AG markets Gleevec imatinib for gastrointestinal cancer and other cancers. Pfizer Inc. markets Sutent for gastrointestinal, pancreatic and renal cancers.	Unpatented; available for licensing	Bosbach, B. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 31, 2012; doi:10.1073/pnas.1115240109 Contact: Peter Besmer, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: p-besmer@ski.mskcc.org
SciBX 5(25); doi:10.1038/scibx.2012.664 Published online June 21, 2012			
<i>In vitro</i> microvasculature network model	An <i>in vitro</i> model of organ microvasculature could be useful for identifying compounds that target the vasculature to treat cardiovascular diseases. An <i>in vitro</i> microvasculature network that modeled the <i>in vivo</i> morphology and stability of live vasculature was formed by using soft lithography to seed endothelial cells on type I collagen. In the model, provasculature stimulators led to angiogenic sprouting from the vessels. Also in the model, blood flowed through the vessels without adhering to the endothelial surface or causing thrombosis, whereas with prothrombotic stimulation of the vessels, platelets adhered to the endothelial surface and aggregated. Next steps include large-scale production of the microvessels.	Patent application filed; unlicensed	Zheng, Y. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 29, 2012; doi:10.1073/pnas.1201240109 Contact: Abraham D. Stroock, Cornell University, Ithaca, N.Y. e-mail: ads10@cornell.edu Contact: Ying Zheng, University of Washington, Seattle, Wash. e-mail: yingzy@uw.edu
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This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Mouse model of human mucosa associated lymphoma tissue (MALT) lymphoma	<p>A MALT lymphoma model could be used to test therapeutics for the disease. In mice, transgenic expression of human <i>mucosa associated lymphoid tissue lymphoma translocation gene 1</i> (<i>MALT1</i>) in hematopoietic progenitor cells led to the formation of tumors with clinical, biological and molecular characteristics of human MALT lymphomas. In lymphoma cells isolated from the mouse model, a MALT1 inhibitor decreased viability compared with no treatment. Next steps could include using the model to test inhibitors of MALT lymphoma therapeutic targets.</p> <p>SciBX 5(25); doi:10.1038/scibx.2012.666 Published online June 21, 2012</p>	Patent application filed for mouse model; available for licensing	<p>Vincente-Dueñas, C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online June 11, 2012; doi:10.1073/pnas.1204127109</p> <p>Contact: Jose A. Martinez-Climent, University of Navarra, Pamplona, Spain e-mail: jamcliment@unav.es</p> <p>Contact: Isidro Sanchez-Garcia, Spanish National Research Council and the University of Salamanca, Salamanca, Spain e-mail: isg@usal.es</p>
Drug delivery			
Vaginal delivery of antiviral-loaded mucos-penetrating particles (MPPs)	<p>Vaginal delivery of antiviral-loaded MPPs could be used to prevent viral infections. In mice receiving intravaginal delivery of particles, MPPs showed uniform distribution over the vaginal epithelium and 60% were retained in the vaginal tract after 6 hours without causing inflammation, whereas conventional nanoparticles aggregated in the vaginal mucosa surface, had 10% retention and caused subsequent inflammation. In mice pretreated with acyclovir monophosphate (ACVp)-loaded MMPs 1 hour before herpes simplex virus (HSV) challenge, 50% became infected compared with 88% of mice pretreated with soluble ACVp. Next steps include testing tenofovir-loaded MPPs in mice to prevent HIV infection.</p> <p>Acyclovir is a generic used to treat HSV infection. Gilead Sciences Inc. markets the reverse transcriptase inhibitor Viread tenofovir disoproxil fumarate to treat HIV infection. Kala Pharmaceuticals Inc. is developing MPPs to improve the delivery of drugs to mucosal organs.</p> <p>SciBX 5(25); doi:10.1038/scibx.2012.667 Published online June 21, 2012</p>	Patented in Europe and patent pending in U.S.; licensed to Kala Pharmaceuticals	<p>Ensign, L.M. <i>et al. Sci. Transl. Med.</i>; published online June 13, 2012; doi:10.1126/scitranslmed.3003453</p> <p>Contact: Justin Hanes, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: hanes@jhu.edu</p>

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