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By **Tim Fulmer**, Senior Writer

Three academic teams have independently developed techniques for *in vivo* detection of cancer stem cells in mouse solid tumors.<sup>1-3</sup> The methods could be useful as next-generation target discovery platforms and as screens for compounds that hit cancer stem cells.

Cancer stem cells (CSCs) in solid tumors were first identified in 2003 when researchers at the **University of Michigan Medical School** identified them in a mouse xenograft model of human breast cancer.<sup>4</sup> The group's method relied on transplanting human tumor cells into immunodeficient animals—a biological context that is dramatically different from the cells' tumor niche in humans.

Subsequently, the same method was used by a variety of labs to identify CSCs in many solid cancers, including colon, brain, skin, and head and neck cancers.<sup>5</sup>

However, until now it has remained unclear whether the identified cells actually functioned as CSCs in an intact human or mouse tumor.<sup>6,7</sup>

Thus, three academic teams independently set out to design cleaner approaches that directly detect CSCs in tumor tissue without the need for transplantation. The trio of methods all converged on similar strategies that combined genetic techniques and fluorescent imaging.

Each group began with a mouse model of solid cancer that was genetically altered to express a fluorescent protein in its tumor tissue.

A team led by Benjamin Simons and Cédric Blanpain engineered a mouse model of chemically induced skin cancer to express yellow fluorescent protein in basal tumor epithelial cells. Luis Parada and colleagues created a mouse model of glioma that expressed GFP in glioma cells. A team led by Hans Clevers created a mouse model of intestinal cancer that expressed GFP or one of its three derivatives in leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5; Gpr49)-positive intestinal adenoma cells.

In all cases, the mice developed cancer. Histological analysis of tumor tissue at various time points of disease progression allowed the researchers to trace the fluorescence signal as tumor cell lineages proliferated.

All three studies identified a subset of fluorescently labeled cancer cells that were proposed to be CSCs based on their ability to self-renew and give rise to other tumor cell types, including proliferating progenitor cells and terminally differentiated cells.

The study by Clevers and colleagues was published in *Science*. The other two studies were published in *Nature*.

Simons is professor of theoretical physics and the physics of

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medicine at the **University of Cambridge**. Blanpain is a professor in the Interdisciplinary Research Institute at the **Free University of Brussels**. Parada is chair of the Department of Developmental Biology at **The University of Texas Southwestern Medical Center**. Clevers is professor of molecular genetics at the **Hubrecht Institute**.

**Of mice and CSCs**

The lineage-tracing methods used in the three papers “give very strong support to the cancer stem cell concept and are notable for avoiding the limitations of the transplantation methods, which gave rise to skepticism about the existence of cancer stem cells in solid cancers,” said Max Wicha, who published the 2003 paper that first used the transplantation method to identify breast CSCs.

He is director of the **University of Michigan Comprehensive Cancer Center** and professor of internal medicine and oncology at the University of Michigan Medical School.

“The advance here is that we can identify cancer stem cells in an intact tumor and tumor microenvironment, which could better reflect tumor biology than transplanting tumor cells into immunocompromised mice,” said Wicha.

However, he said that compared with the xenograft transplantation and cell culture methods currently used by CSC researchers, the lineage-tracing methods are more complex and perhaps not as straightforward to use. “At least in their current form, these new methods do not seem to be practical enough for use as discovery platforms and screens,” he said.

Wicha is a cofounder of **OncoMed Pharmaceuticals Inc.**, which develops therapeutic antibodies that target pathways dysregulated

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in CSCs. The company's lead compound, OMP-21M18, is in Phase I testing to treat non-small cell lung cancer (NSCLC) and pancreatic cancer in combination with chemotherapy. The mAb blocks delta-like 4 (DLL4), an activator of the Notch pathway in CSCs.

OncoMed's discovery and screening platform uses human tumor xenograft mice to identify CSC targets and test therapeutic mAbs.

In his own research, Wicha is combining CSC-targeting agents with antiangiogenic therapies. Earlier this year, he published data in the *Proceedings of the National Academy of Sciences* showing that antiangiogenic mAbs increase CSC proliferation in mouse models of breast cancer.<sup>8</sup>

Because the lineage-tracing methods allow study of intact tumors, "we may finally be able to determine what role cancer stem cells play in the initial events of tumor formation and how those cells drive tumor progression," said Mick Bhatia. "That information could reveal periods of tumor progression when cancer stem cells are more susceptible to therapy."

Bhatia is professor of biochemistry and biomedical sciences at **McMaster University** and director of the **Stem Cell and Cancer Research Institute at McMaster University**. He cofounded **Actium Research Inc.**, which has licensed a human cancer stem cell discovery platform from McMaster. The platform is based on a human pluripotent stem cell line that has CSC properties including self-renewal and loss of differentiation capacity.<sup>9</sup>

Earlier this year, Bhatia and colleagues published in *Cell* that the platform had identified the small molecule dopamine receptor antagonist thioridazine as a CSC-targeting molecule.<sup>10</sup>

**Verastem Inc.**, another company in the CSC space, also uses a cell culture platform as part of its screens of compounds that block proliferation of CSCs.<sup>11</sup> The platform is based on an immortalized human breast epithelial cell line that is genetically modified to undergo the epithelial-mesenchymal transition (EMT), a process that imparts self-renewal capability similar to that of CSCs.

In 2009, Verastem cofounder Robert Weinberg published in *Cell* that the screen identified the antibiotic salinomycin as an inhibitor of breast CSCs.<sup>12</sup> In 2012, the company presented additional data at the **American Association for Cancer Research** meeting in Chicago showing that salinomycin inhibited wingless-type MMTV integration site (WNT) family member signaling, a pathway known to be dysregulated in CSCs. However, the company announced earlier this year that it has put development of salinomycin on hold and is seeking to discover next-generation WNT inhibitors.

Verastem also has a preclinical program targeting focal adhesion kinase (FAK) to block growth of breast CSCs.

Weinberg is a member of the **Whitehead Institute for Biomedical Research** and professor of biology at the **Massachusetts Institute of Technology**. He did not respond to requests for an interview.

### Moving forward

The corresponding authors on the papers told *SciBX* they have ideas

**"We may finally be able to determine what role cancer stem cells play in the initial events of tumor formation and how those cells drive tumor progression. That information could reveal periods of tumor progression when cancer stem cells are more susceptible to therapy."**

**—Mick Bhatia,  
McMaster University**

about how to use the lineage-tracing methods in both the target discovery and compound screening setting.

"We plan to purify the cancer stem cells from the mice and use deep sequencing to generate mutational and epigenetic profiles that can be compared with the profiles of noncancer stem cells from the same mice," said Parada, corresponding author on the glioma study. "Differences between the two profiles could point to pathways that are dysregulated in cancer stem cells and might be good targets."

"We are also setting up a high throughput platform that pools tumors from multiple mice used in the studies. We will then use those tumor cells to screen small molecules and

siRNA for their ability to arrest cellular metabolic activity. Hits from that screen will then be validated in primary human tumor cells, where mechanistic details can be worked out," he added.

"Because our screen is based on cancer stem cells isolated directly from the tumor in its natural environment, we believe the compounds we identify may have a better chance of therapeutic success than compounds identified using screens based on tumor transplantation or cell lines modified to have cancer stem cell-like properties," said Parada.

Simons, corresponding author on the skin cancer study, told *SciBX* his group plans to use the lineage-tracing method "to investigate the biomolecular pathways that lead to the dysregulation of the stem cell compartment."

He added that the method may provide a new way "to define the mode of tumor growth in different types of cancer and during metastasis and relapse, which may have important implications for the development of new therapeutic strategies."

Clevers, corresponding author on the intestinal cancer study, did not respond to interview requests.

### Longer-term potential

Lineage tracing and xenograft models could potentially be combined into a single screening platform for CSCs, said Wicha.

"One method will tell us how a compound acts on transplanted human cancer stem cells, while the other method tells us how a compound acts on cancer stem cells in an intact mouse tumor. Presumably a compound that is active in both scenarios would be prioritized as a strong development candidate," he said.

Even by itself, the lineage-tracing method could provide information on CSC biology not available from the xenograft studies. "It should be possible to modify the method used in the papers to include two color tracers, one expressed in cancer stem cells, the other in stromal stem cells. Tracing the interactions between the two over time could then show how the tumor niche and microenvironment influence the function of cancer stem cells," said Bhatia.

The CSCs identified by lineage tracing could also be used in target discovery, providing a more definitive gene and protein expression profile useful for identifying new targets specifically expressed in those cells, said Christopher Reyes, cofounder and CSO of **Eclipse Therapeutics Inc.**

Eclipse uses its CSC Rx Discovery platform to identify mAb therapeutics that inhibit growth of CSCs. Eclipse's lead compound is ET101, a preclinical mAb against an undisclosed CSC target on solid tumors.

The findings in all three papers are not covered by patents.

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#### COMPANIES AND INSTITUTIONS MENTIONED

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**The University of Texas Southwestern Medical Center**, Dallas, Texas  
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# Amyloids for inflammation

By Kai-Iye Lou, Staff Writer

Researchers at **Stanford University** have found that systemic treatment with  $\beta$ -amyloid peptides can reduce inflammation and reverse paralysis in mouse models of multiple sclerosis.<sup>1</sup> **Cardinal Therapeutics Inc.** has licensed the work and now is developing anti-inflammatory amyloids. The company hopes to select a specific indication and name a lead compound by year end.

$\beta$ -Amyloid ( $A\beta$ ) is the plaque-forming protein linked to Alzheimer's disease (AD) pathology. Past studies by academic groups have shown that  $\beta$ -amyloid is upregulated in multiple sclerosis (MS) lesions.<sup>2,3</sup> However, the role of  $\beta$ -amyloid in MS was not well defined, and it was unclear whether it was harmful or protective. A Stanford research group led by Lawrence Steinman published data in 2007 showing that  $\beta$ -amyloid could be the target of inflammatory processes in MS, thus suggesting it might have a deleterious role.<sup>4</sup>

Steinman is a professor of neurology and neurological sciences, pediatrics and genetics at the Beckman Center for Molecular and Genetic Medicine at the **Stanford University School of Medicine**.

To further evaluate the significance of  $\beta$ -amyloid in MS, the Stanford group opted to systemically deliver  $\beta$ -amyloid peptides to mice with experimental autoimmune encephalitis (EAE), with the expectation that doing so would exacerbate the disease phenotype.

"Based on our previous work, our prediction was that exogenous delivery of  $A\beta$  peptides would worsen the disease phenotype of the mouse EAE model," said Steinman.

Much to the group's surprise,  $\beta$ -amyloid peptides had the opposite effect. Across four different mouse EAE models, intraperitoneal injection of two disease-associated  $\beta$ -amyloid peptides delayed onset and reduced disease severity compared with vehicle. The peptides also inhibited the production of proinflammatory cytokines in lymphoid tissues.

Moreover, knocking out amyloid precursor protein (APP), the precursor to the two  $\beta$ -amyloid peptides, exacerbated the EAE disease phenotype in the mouse model.

The results were published in *Science Translational Medicine*.

"Our work represents a contrarian therapeutic opportunity, and at this stage Cardinal Therapeutics is looking for a partner to help move the science forward," said Steinman, corresponding author on the paper and a cofounder of Cardinal Therapeutics. "I think the biggest concern from a regulatory standpoint is the strong opinions and negative reputation associated with the amyloid class of molecules, but my view is that we need to move the science to where the data are going."

Although  $\beta$ -amyloid peptides are cytotoxic against immune cell populations that can drive MS, Steinman does not think that is the primary mechanism of action underlying the therapeutic effects in the mouse EAE model. Instead, he suspects the  $\beta$ -amyloid peptides are acting as binders of proinflammatory cytokines and also forming into protective amyloid fibrils that could inhibit the formation of proinflammatory amyloid fibrils.

Indeed, the cytotoxic effects of the  $\beta$ -amyloid peptides *in vitro* did not translate into the mouse EAE model. Moreover, Steinman said unpublished data from mass spectrometry studies suggest the  $\beta$ -amyloid peptides are binding to proinflammatory mediators in plasma.

Jonathan Rothbard, CSO of Cardinal Therapeutics and a senior research scientist in the Department of Medicine at the Stanford University School of Medicine, said the findings present another example suggesting amyloidogenic compounds could have therapeutic utility in inflammation-related indications.

"In collaboration with Dr. Steinman, we have shown that compounds involved in the formation of amyloid fibrils, such as crystallin  $\alpha$ B, can themselves inhibit the formation of other amyloid fibrils," he told *SciBX*.

Rothbard and Steinman also published data earlier this year showing crystallin  $\alpha$ B (CRYAB; HSPB5) can bind to proinflammatory mediators and reduce their concentration in plasma.<sup>5</sup>

## Unifying structural features

Cardinal has a program to develop therapeutic amyloidogenic compounds, and Rothbard said the new findings could provide additional insights into the structural features underlying the anti-inflammatory effects of such molecules.

However, he noted that the  $\beta$ -amyloid peptides used in the paper would not be good therapeutic candidates because they are neurotoxic, have poor solubility and are difficult to synthesize.

"Right now, we are trying to identify unifying structural features of peptides that could give us insights on how to develop compounds that promote the formation of protective amyloid fibrils," Rothbard told *SciBX*.

He said Cardinal's lead compound would most likely be a peptide or peptidomimetic rather than a small molecule, as the latter class is not known to possess fibril-forming properties.

"The goal at Cardinal is to develop a long-acting amyloid, run the necessary medicinal chemistry studies to optimize its properties and then identify an optimal therapeutic formulation" for the disease we want to treat, said Steinman.

Rothbard said Cardinal's initial disease focus will be in an inflammation-related indication but noted it is unlikely to be MS, as the approval of Gilenya fingolimod and recent regulatory submissions have created a competitive barrier for new entrants.

Gilenya, an oral once-daily sphingosine 1-phosphate receptor agonist from **Novartis AG**, was approved in 2010 to treat relapsing forms of MS. **Sanofi's** Aubagio teriflunomide, a dihydroorotate dehydrogenase (DHODH) inhibitor, also is under FDA and EMA review for relapsing forms of the disease. Earlier this year, **Biogen Idec Inc.** submitted regulatory applications to the FDA and EMA seeking approval for BG-12, a dimethyl fumarate that activates the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2) pathway, in relapsing-remitting MS.

**"Right now, we are trying to identify unifying structural features of peptides that could give us insights on how to develop compounds that promote the formation of protective amyloid fibrils."**

**—Jonathan Rothbard,  
Cardinal Therapeutics Inc.**

Steinman said that if the group were to settle on MS, the focus would be on populations that still have unmet needs, such as in patients who have primary progressive and secondary progressive disease.

Stanford has issued and pending patents covering amyloids and their therapeutic application to inflammatory disorders. Cardinal has exclusively licensed the IP covering amyloid-based compounds and is seeking a partner. IP covering use of  $\beta$ -amyloid peptides in MS is available for licensing from the university's Office of Technology Licensing.

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#### COMPANIES AND INSTITUTIONS MENTIONED

**Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.

**Cardinal Therapeutics Inc.**, Menlo Park, Calif.

**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France

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# Finding the perfect combination

By Tracey Baas, Senior Editor

Two independent research teams have used cell culture methods to show that high hepatocyte growth factor/scatter factor levels drive resistance to BRAF inhibitors in melanoma.<sup>1,2</sup> The findings could provide a rationale for combining hepatocyte growth factor/scatter factor or c-Met proto-oncogene inhibitors with BRAF inhibitors to overcome treatment resistance in the disease.

A team at **Genentech Inc.** focused on growth factor-driven resistance mechanisms in tumor cells, whereas a group from the **Broad Institute of MIT and Harvard** studied the contribution of the tumor microenvironment to resistance.

The Genentech team hypothesized that drug resistance in tumor cells may result from the engagement of cell signaling pathways that can compensate for the loss of activity in the inhibited pathway, thus allowing cancer cells to survive even when treated with a kinase inhibitor.

To test that idea, the group treated a panel of 41 cancer cell lines that were highly sensitive to kinase inhibition with a kinase inhibitor plus one of six different growth factors.

Indeed, most of the cell lines lost sensitivity to the kinase inhibitor in the presence of one or more of the tested growth factors, suggesting activation of alternative pathways could promote resistance.

The factors that most frequently promoted resistance to kinase inhibitors were hepatocyte growth factor/scatter factor (HGF/SF), fibroblast growth factor (FGF) and neuregulin 1 (NRG1).

The researchers next looked at the effects of these growth factors in *BRAF* mutant melanoma.

In about half of *BRAF* mutant melanoma cell lines, HGF/SF induced expression of its receptor, c-Met proto-oncogene (MET; HGFR), and triggered resistance to the BRAF kinase inhibitor Zelboraf vemurafenib. However, in those same cells, the resistance could be reversed by treating the cells with a combination of Zelboraf and the MET inhibitor Xalkori crizotinib.

The findings translated to the *in vivo* setting. Zelboraf plus a MET inhibitor blocked tumor growth better than Zelboraf alone in two xenograft mouse models of *BRAF* mutant melanoma in which MET was artificially activated. Moreover, increased plasma HGF/SF levels in patients with *BRAF* mutant melanoma correlated with poorer survival.

Zelboraf is marketed by **Daiichi Sankyo Co. Ltd.**, **Chugai Pharmaceutical Co. Ltd.** and **Roche** to treat melanoma in patients with BRAF V600E mutations.

Xalkori is marketed by **Pfizer Inc.** to treat non-small cell lung cancer (NSCLC) and is in Phase I testing to treat other solid tumors.

In the second study, the team from the Broad Institute used a coculture system to study how 23 stromal cell types influenced the drug resistance of 45 cancer cell lines. They concluded that stromal-mediated resistance was common in the cells.

Cocultures of *BRAF* mutant melanoma cell lines and stromal fibroblasts led to MET activation and resistance to BRAF inhibition in the melanoma cells. Fibroblast-conditioned growth medium also led to resistance in the *BRAF* mutant melanoma cell lines, suggesting the stromal fibroblasts were secreting a factor that caused the resistance.

An antibody array-based analysis of 567 secreted factors showed that increased BRAF resistance correlated with increased levels of HGF/SF. Moreover, HGF/SF-neutralizing antibodies or Xalkori reversed resistance in cocultures of *BRAF* mutant melanoma cells and fibroblasts.

Finally, the researchers used immunohistochemistry to examine HGF/SF expression in biopsy samples from patients with *BRAF* mutant melanoma. The team detected HGF/SF in the tumor-associated stromal cells in 68% of the patients, and HGF/SF secretion from stromal cells was associated with poorer response to BRAF inhibitors ( $p < 0.05$ ).

Both studies were published in *Nature*.

At least two HGF/SF mAb antagonists are in the clinic. **Amgen Inc.**'s rilotumumab is in Phase II testing for brain cancer and gastric cancer and Phase I/II trials for colorectal cancer. **Aveo Pharmaceuticals Inc.**'s ficlatuzumab is in Phase II testing for NSCLC and Phase I trials for head and neck cancer.

A **Novartis AG** group published a similar approach this month using a cell-based assay to screen the potential of 3,482 different secreted proteins to activate alternative kinase pathways and cause resistance to kinase inhibitors in tumor cells. A number of secreted proteins induced resistance, with ligands of epidermal growth factor receptor 1 (EGFR1; HER1; ErbB1), fibroblast growth factor receptor (FGFR) and MET families showing a broad ability to compensate for inhibition of the original targeted kinase.<sup>3</sup>

Novartis declined requests for an interview.

## Providing the relevance

"Both studies provide new information that can be quickly applied in the clinic. The immediate next step is to use stromal HGF/SF levels or tumor MET overexpression as potential predictive biomarkers of response to combined BRAF inhibition plus HGF/MET antagonists for clinical trials in *BRAF* mutant melanoma," said Roger Lo. "And in the long run, the screening strategy will help to guide strategic selection of combination therapies to treat a variety of cancers."

Lo is assistant professor of medicine at the **University of California, Los Angeles David Geffen School of Medicine** and a member of UCLA's Jonsson Comprehensive Cancer Center. He was an author on one of the papers.

Gideon Bollag, SVP of research at Daiichi's Plexxikon unit, agreed. However, he noted that "it is unclear if the elevated HGF levels occur

**"Being able to subgroup cases by overexpression of particular RTK ligands could provide an important opportunity to select appropriate combination therapies. Peripheral blood or circulating tumor cells from patients undergoing targeted anticancer therapies could be interrogated for the presence of RTK ligands and other growth factors before and during treatment."**

—Jeffrey Settleman,  
Genentech Inc.

in response to the inhibitor or rather if activation of the HGF/MET pathway predicts poor outcome independent of therapy. Nonetheless, appropriate agents should be selected—perhaps crizotinib and vemurafenib—protocols written and trials commenced.”

“More and more literature points to the protumorigenic role of stromal cells. Perhaps these cells initially attack the cancer cells, but often tumors are able to circumvent these cells and eventually hijack the cells to support tumor growth, invasion and metastasis,” Bollag said. “We predict that future treatment decisions will include characterization of the stromal cells in tumor biopsies or using direct imaging techniques, so that appropriate agents can be selected on a case-by-case basis.”

Both teams also plan to expand their screening studies to find the most clinically relevant mechanisms of acquired drug resistance in cancer cells.

“Our study has already provided a number of leads regarding mechanisms of resistance and secreted factors that induce that resistance,” said Todd Golub, leader of the Broad Institute team. “We are going to further pursue these leads in *BRAF* mutant melanoma and also in non-*BRAF*, nonmelanoma cancers.”

Golub is professor of pediatrics at **Harvard Medical School**, an investigator at **Dana-Farber Cancer Institute** and director of the cancer program at the Broad Institute.

“The Genentech team is currently investigating several hundred growth factors on larger panels of patient-derived tumor cell lines. In order to predict which RTK [receptor tyrosine kinase] ligand-dependent mechanisms of resistance are potentially clinically relevant, the prevalence of the various growth factors that can drive RTK-mediated drug resistance will have to be assessed; therefore, the more patient-derived cancer cell lines and tumor samples we can examine, the better,” said team leader Jeffrey Settleman, who is also senior director of discovery oncology at Genentech.

Once the company identifies the most clinically relevant mechanisms of acquired resistance, the next steps will be selecting the most appropriate patient subgroups for clinical trials and using the best combination of therapies for each subgroup.

“Being able to subgroup cases by overexpression of particular RTK ligands could provide an important opportunity to select appropriate combination therapies,” Settleman said. “Peripheral blood or circulating tumor cells from patients undergoing targeted anticancer therapies could be interrogated for the presence of RTK ligands and other growth factors before and during treatment.”

“Resistance to single therapy is common, and when it does occur in the clinic, it’s really too late to start thinking about rational combinations,” Golub added. “We want to use our coculture system to identify the important mechanisms underlying drug resistance with the ultimate goal of providing rational combination therapies.”

“The tumor most likely uses multiple mechanisms to induce resistance and escape drug efficacy,” continued Golub. “My gut feeling

is that a therapeutic cocktail—like those for HIV—might be more effective at treating an individual’s cancer than sequential therapeutic delivery.”

### A different kind of animal

The findings of the two papers also will change how researchers use animal studies to model *in vivo* relevance.

“The important take-home message is that the tumor microenvironment may be just as important as the tumor cells themselves,” said Settleman. “This means we’re going to have to be creative with our animal models. Simple xenografts may not be sufficient. For example, murine stromal factors may not affect human cancer cells, and consequently we might miss that important interaction between stromal and cancer cells.”

“In order to make the best possible use of these new insights to help drive drug development and provide strategic combination therapies, we will undoubtedly need to explore such mechanisms more deeply,” he said.

Genentech did not disclose the patent or licensing status of its findings.

The Broad Institute also did not disclose patenting or licensing status. The general screening approach is not patented.

Baas, T. *SciBX* 5(32); doi:10.1038/scibx.2012.832  
Published online Aug. 16, 2012

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2. Straussman, R. *et al. Nature*; published online July 4, 2012; doi:10.1038/nature11183  
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3. Harbinski, F. *et al. Cancer Discov.*; published online Aug. 8, 2012; doi:10.1158/2159-8290.CD-12-0237  
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### COMPANIES AND INSTITUTIONS MENTIONED

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.  
**Aveo Pharmaceuticals Inc.** (NASDAQ:AVEO), Cambridge, Mass.  
**Broad Institute of MIT and Harvard**, Cambridge, Mass.  
**Chugai Pharmaceutical Co. Ltd.** (Tokyo:4519), Tokyo, Japan  
**Daiichi Sankyo Co. Ltd.** (Tokyo:4568; Osaka:4568), Tokyo, Japan  
**Dana-Farber Cancer Institute**, Boston, Mass.  
**Genentech Inc.**, South San Francisco, Calif.  
**Harvard Medical School**, Boston, Mass.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**University of California, Los Angeles David Geffen School of Medicine**, Los Angeles, Calif.

# CIRM: get a little closer

By Michael J. Haas, Senior Writer

In its latest batch of grants the **California Institute for Regenerative Medicine** divided a smaller pool of funding among fewer research teams than it did in 2009, reflecting the institute's interest in funding projects that are close to entering the clinic.

Last month, CIRM announced awards totaling \$151 million to teams from 7 academic institutions and 1 company—**StemCells Inc.**—that are expected to submit INDs or complete Phase I or Phase II testing when work on the 4-year grants is complete (see **Table 1, “2012 CIRM grants”**).

StemCells will use its \$20 million grant to develop HuCNS-SC, purified human neural stem cells, to treat spinal cord injury (SCI) in the neck. The company already has the technology in Phase I/II testing to treat SCI in the back.

Two of CIRM's partners will contribute additional funding to specific projects. The **Andalusian Initiative for Advanced Therapies** will provide \$1.6 million to the Spanish collaborators of a team at the **University of California, Davis** that is developing an intramuscular injection of VEGF-producing mesenchymal stem cells (MSCs) to treat critical limb ischemia.

The U.S. **NIH** will provide undisclosed funds and resources to a team at **University of California, Los Angeles** that is developing stem cells engineered to express melanoma-specific T cell receptors (TCRs) to treat melanoma.

“NIH's dollar commitment is difficult to quantify because the project will involve the time of staff scientists already on the NIH payroll, along with the use of existing equipment” at the agency, said CIRM spokesperson Don Gibbons.

Gibbons said CIRM selected the 8 projects from a total of 21 applications,

including 6 from industry. Of the 13 projects that did not receive grants, 2—including 1 from **OncoMed Pharmaceuticals Inc.**—have been sent back to CIRM's panel for re-review in light of new data submitted by the applicants. Those data address the reasons the review panel originally decided those projects did not meet CIRM's criteria, he said.

Gibbons noted that, compared with in 2009, the pool of applicants and number of awards were smaller this year because “the call for applications was more specific about how close to clinical trials the teams needed to be for funding.”

In 2009, CIRM awarded a total of \$229.8 million to 14 projects that were expected to result in IND submissions during the 4-year grant period.<sup>1</sup> CIRM has reviewed the progress of each of those projects annually in conjunction with the Clinical Development Advisory Panel (CDAP), which is composed of industry and other experts outside CIRM, Gibbons said.

According to a CDAP report issued by CIRM in March, 12 of the projects from 2009 are on track to meet their original goals with no changes in funding levels (see **Table 2, “Update on 2009 CIRM grants”**). Moreover, 2 of those 12 projects have spawned new companies: in 2011 the **City of Hope** brain cancer project leader founded **TheraBiologics Inc.**, and also in 2011 the **University of Southern California (USC)** age-related macular degeneration (AMD) project team spun out **Regenerative Patch Technologies Inc.**

Also according to the CDAP report, CIRM recommended that the **University of California, San Diego**–led leukemia project team focus its efforts on developing two potential antibody therapeutics targeting leukemia stem cells to treat acute myelogenous leukemia (AML) and chronic lymphocytic leukemia (CLL). The team's project originally aimed to identify up to three antibodies and three small molecules to treat AML, CLL and three other hematological malignancies.

The CDAP report also noted that CIRM discontinued the grant to a **University of California, San Francisco**–led brain tumor project because it failed to reach an undisclosed milestone.

**Table 1. 2012 CIRM grants.** Research grants awarded by the California Institute for Regenerative Medicine (CIRM) to develop stem cell-based therapies.

Source: CIRM

Lead Institution	Lead principal investigator	CIRM funding (\$M)	Proposal summary
Cedars-Sinai Medical Center	Clive Svendsen	17.8	Treat amyotrophic lateral sclerosis (ALS) using progenitor cells secreting glial cell–derived neurotrophic factor (GDNF)
Stanford University	Robert Robbins	20.0	Treat end-stage heart failure using embryonic stem cell (ESC)-derived cardiomyocytes
Stanford University	Judith Shizuru	20.0	Develop a method for chemotherapy-free bone marrow transplants (BMTs) in severe combined immunodeficient (SCID) patients using an antibody that targets blood cell–forming stem cells
StemCells Inc.	Nobuko Uchida	20.0	Treat cervical spinal cord injury (SCI) using neural stem cells
University of California, Davis	John Laird	14.2	Treat critical limb ischemia using intramuscular injection of VEGF-producing mesenchymal stem cells (MSCs)
UC Davis	Nancy Lane	20.0	Treat osteoporosis using endogenous MSCs
UC Davis	Vicki Wheelock	19.0	Treat Huntington's disease (HD) using bone marrow–derived MSCs engineered to produce brain-derived neurotrophic factor (BDNF)
University of California, Los Angeles	Antoni Ribas	20.0	Treat melanoma using stem cells engineered to express melanoma-specific T cell receptors (TCRs)
<b>Total</b>		<b>151.0</b>	

**Table 2. Update on 2009 CIRM grants.** Status of research grants awarded in 2009 by the California Institute for Regenerative Medicine (CIRM) to develop stem cell-based therapies.

Source: CIRM

Lead institution	Lead principal investigator	CIRM funding (\$M)	Proposal summary	Status
Cedars-Sinai Medical Center	Eduardo Marbán	5.6	Treat advanced heart failure using autologous cardiac-derived cardiospheres or cardiosphere-derived cells	Team is developing allogeneic cardiac-derived cells and on track to submit an IND within four-year award period
City of Hope	Karen Aboody	18.0	Treat recurrent glioblastoma using neural stem cells modified to carry a tumor-killing drug	Team is on track to complete preclinical proof of concept by end of 2012
City of Hope	John Zaia	14.6	Treat HIV using genetically modified autologous hematopoietic stem cells that give rise to HIV-resistant T cells	Team is progressing toward IND-enabling studies
Stanford University	Alfred Lane	11.7	Treat epidermolysis bullosa using genetically modified induced pluripotent stem (iPS) cells derived from patient's skin cells	Team has generated iPS cell lines from several patients
Stanford University	Gary Steinberg	20.0	Treat stroke using implanted neural stem cells derived from human embryonic stem cells (hESCs)	Team has shown functional recovery in three preclinical models of stroke
Stanford University	Irving Weissman	20.0	Develop a mAb that targets leukemia stem cells	Team is conducting preclinical studies of a humanized anti-CD47 mAb
University of California, Los Angeles	Irvin Chen <sup>A</sup>	20.0	Treat HIV using RNAi-modified autologous hematopoietic stem cells that give rise to HIV-resistant T cells	Team has identified small hairpin RNAs that prevent HIV cell entry and replication
UCLA	Donald Kohn	9.2	Treat sickle cell disease using genetically modified hematopoietic stem cells that become normal red blood cells	Team has identified a lead therapeutic and had a pre-IND meeting with FDA
UCLA	Dennis Slamon	20.0	Develop compounds that target cancer stem cells in glioma, colon and ovarian tumors	Team is conducting IND-enabling studies of a lead inhibitor targeting an undisclosed kinase
University of California, San Diego	Dennis Carson	20.0	Develop mAbs and small molecules that destroy leukemia stem cells to treat acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and three other hematological malignancies	Grant revised in 2012 to focus on two mAbs to treat AML and CLL; budgets and timelines being reassessed
UCSD	Larry Goldstein <sup>B</sup>	15.6	Treat amyotrophic lateral sclerosis (ALS) by implanting precursor astrocyte cells derived from hESCs	Team anticipates selecting a single cell line by mid-2012
University of California, San Francisco	Mitchel Berger	19.2	Treat brain tumors using neural stem cells modified to carry a tumor-killing drug	Grant discontinued in March 2012 for failure to meet an undisclosed milestone
University of Southern California	Mark Humayun	15.9	Treat age-related macular degeneration (AMD) using transplanted retinal pigment epithelium (RPE) cells derived from hESCs	Team on track to file IND within four-year award period
ViaCyte Inc. <sup>C</sup>	Allan Robins <sup>D</sup>	20.0	Treat type 1 diabetes by implanting islet stem cells generated from hESCs	Team is preparing for IND-enabling studies
<b>Total</b>		<b>229.8</b>		

<sup>A</sup>Geoff Symonds at biotech company **Calimmune Inc.** is also a principal investigator. <sup>B</sup>The original principal investigator was Samuel Pfaff of the **Salk Institute for Biological Studies**. <sup>C</sup>Formerly Novocell Inc.; the company changed its name to ViaCyte in 2010. <sup>D</sup>The original principal investigator was Emmanuel Baetge of Novocell (now ViaCyte).

Gibbons declined to say which of the 2009 projects might reach the clinic first but added that CIRM president Alan Trounson “has indicated he thinks the HIV team at City of Hope and the macular degeneration team of USC are pretty close.”

Haas, M.J. *SciBX* 5(32); doi:10.1038/scibx.2012.833  
Published online Aug. 16, 2012

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Andalusian Initiative for Advanced Therapies, Seville, Spain

California Institute for Regenerative Medicine, San Francisco, Calif.

City of Hope, Duarte, Calif.

National Institutes of Health, Bethesda, Md.

OncoMed Pharmaceuticals Inc., Redwood City, Calif.

Regenerative Patch Technologies Inc., Glendale, Calif.

StemCells Inc. (NASDAQ:STEM), Newark, Calif.

TheraBiologics Inc., Los Angeles, Calif.

University of California, Davis, Calif.

University of California, Los Angeles, Calif.

University of California, San Diego, La Jolla, Calif.

University of California, San Francisco, Calif.

University of Southern California, Los Angeles, Calif.

## This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Cancer</b>				
Cancer	5-Methoxytryptophan (5-MTP)	<p>Mouse and cell culture studies suggest 5-MTP could help treat cancer. In a human lung cancer cell line, 5-MTP decreased proliferation and invasiveness compared with no treatment. In a mouse xenograft model of human lung cancer, intraperitoneal injection of 5-MTP decreased tumor growth and metastasis compared with vehicle injection. Next steps include understanding the underlying mechanisms by which 5-MTP suppresses tumorigenesis.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.834</b>  <b>Published online Aug. 16, 2012</b></p>	Extracts patented; unlicensed	<p>Cheng, H.-H. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 31, 2012;  doi:10.1073/pnas.1209919109  <b>Contact:</b> Kenneth K. Wu, National Health Research Institutes, Zhunan, Taiwan  e-mail:  <a href="mailto:kkgo@nhri.org.tw">kkgo@nhri.org.tw</a>  <b>Contact:</b> George Klein, Karolinska Institute, Stockholm, Sweden  e-mail:  <a href="mailto:georg.klein@ki.se">georg.klein@ki.se</a></p>
Cancer	Cyclin dependent kinase 8 (CDK8); CDK19 (CDC2L6); cyclin-dependent kinase inhibitor 1A (p21, Cip1; CDKN1A; CIP1)	<p><i>In vitro</i> and mouse studies suggest dual CDK8 and CDK19 inhibitors could help improve chemotherapy efficacy. DNA-damaging chemotherapies can induce p21-regulated expression of tumor-promoting factors in tumors and host cells. Library screening, hit optimization and testing in human cancer cell lines identified Senexin A, an inhibitor of CDK8 and CDK19 that blocked p21-induced expression of multiple tumor-supporting proteins. In a mouse model of lung cancer, Senexin A plus doxorubicin decreased tumor growth compared with doxorubicin alone. Ongoing work by Senex Biotechnology Inc. includes testing an optimized form of Senexin A in animal models of lung, breast, colon and prostate cancer.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.835</b>  <b>Published online Aug. 16, 2012</b></p>	Patented by Senex Biotechnology; available for licensing	<p>Porter, D.C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 6, 2012;  doi:10.1073/pnas.1206906109  <b>Contact:</b> Igor B. Roninson, Senex Biotechnology Inc., Columbia, S.C.  e-mail:  <a href="mailto:roninsoni@sccp.sc.edu">roninsoni@sccp.sc.edu</a></p>
Cancer	Smoothed (SMO)	<p><i>In vitro</i> studies identified inhibitors of SMO ciliary localization and cilia assembly that could help treat Hedgehog pathway-driven cancers. A high throughput, fluorescence, cell-based screen identified 10 small molecules that inhibited SMO ciliary localization and cilia assembly. Nine of the compounds showed direct binding to the receptor. In a Hedgehog-driven basal cell carcinoma-like cell line, all 10 compounds inhibited proliferation. Next steps could include testing the compounds in additional models of Hedgehog-driven cancers.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.836</b>  <b>Published online Aug. 16, 2012</b></p>	Patent and licensing status unavailable	<p>Wu, V.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 3, 2012;  doi:10.1073/pnas.1207170109  <b>Contact:</b> Jeremy F. Reiter, University of California, San Francisco, Calif.  e-mail:  <a href="mailto:jeremy.reiter@ucsf.edu">jeremy.reiter@ucsf.edu</a>  <b>Contact:</b> Michelle Arkin, same affiliation as above  e-mail:  <a href="mailto:michelle.arkin@ucsf.edu">michelle.arkin@ucsf.edu</a></p>
Lymphoma	c-Myc (MYC); zinc finger protein 36 C3H type homolog (ZFP36; TTP)	<p>Mouse and cell culture studies suggest increasing TTP signaling could help treat and prevent MYC-driven lymphomas. In a mouse model of Myc-driven lymphoma, <i>Ttp</i> overexpression in B cells increased median survival compared with no overexpression. In isolated mouse B cells, <i>Ttp</i> prevented malignancy by blocking Myc's proliferative response. Next steps include running small molecule screens for compounds that restore TTP expression and identifying targets of TTP itself that could have potential for use in cancer diagnostics and therapy.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.837</b>  <b>Published online Aug. 16, 2012</b></p>	Unpatented; licensing status not applicable	<p>Rounbehler, R.J. <i>et al. Cell</i>; published online Aug. 3, 2012;  doi:10.1016/j.cell.2012.06.033  <b>Contact:</b> John L. Cleveland, Scripps Florida, Jupiter, Fla.  e-mail:  <a href="mailto:jcleve@scripps.edu">jcleve@scripps.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cardiovascular disease</b>				
Organ damage	Transforming growth factor- $\beta$ receptor II (TGF $\beta$ -RII; TGFBR2)	<i>In vitro</i> studies suggest a TGFBR2 inhibitor could help regenerate damaged cardiac tissue. A screen of small molecules in a mouse embryonic stem cell (ESC) differentiation assay identified a TGFBR2 inhibitor that induced differentiation of mesoderm to cardiomyocytes. In human ESCs, adding the inhibitor to an established differentiation protocol for generating cardiomyocytes increased yield to 60% from 30% for vehicle. Ongoing work includes optimizing the inhibitor for testing in animal models of cardiac injury.  <b>SciBX 5(32); doi:10.1038/scibx.2012.838</b> <b>Published online Aug. 16, 2012</b>	Patented by the Sanford-Burnham Medical Research Institute, the Human BioMolecular Research Institute and ChemRegen Inc.; available for licensing or partnering	Willems, E. <i>et al. Cell Stem Cell</i> ; published online Aug. 3, 2012; doi:10.1016/j.stem.2012.04.025 <b>Contact:</b> Mark Mercola, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: <a href="mailto:mmercola@sanfordburnham.org">mmercola@sanfordburnham.org</a> <b>Contact:</b> Erik Willems, same affiliation as above e-mail: <a href="mailto:ewillems@sanfordburnham.org">ewillems@sanfordburnham.org</a>
<b>Dermatology</b>				
Dermal ulcers	Acid-sensing ion channel-3 (ASIC3; ACCN3)	Rodent studies suggest increasing ASIC3 channel activity could help prevent dermal ulcers. An impaired pressure-induced vasodilation response is associated with the formation of dermal ulcers. In <i>Asic3</i> <sup>-/-</sup> mice, local pressure application failed to induce vasodilation responses, and prolonged pressure application increased the formation of ischemic lesions compared with that seen in wild-type controls. In rats, subcutaneous or topical treatment with ASIC3 inhibitors abolished pressure-induced vasodilation, whereas saline treatment did not. Next steps could include testing the effects of increasing ASIC3 channel activity.  <b>SciBX 5(32); doi:10.1038/scibx.2012.839</b> <b>Published online Aug. 16, 2012</b>	Patent and licensing status unavailable	Fromy, B. <i>et al. Nat. Med.</i> ; published online July 29, 2012; doi:10.1038/nm.2844 <b>Contact:</b> Michel Lazdunski, Institute of Molecular and Cellular Pharmacology, Centre National de la Recherche Scientifique (CNRS), Valbonne, France e-mail: <a href="mailto:lazdunski@ipmc.cnrs.fr">lazdunski@ipmc.cnrs.fr</a> <b>Contact:</b> Jean Louis Saumet, University Claude Bernard Lyon 1, Lyon, France e-mail: <a href="mailto:jean-louis.saumet@univ-lyon1.fr">jean-louis.saumet@univ-lyon1.fr</a>
Scars/wrinkles	ADAM metallopeptidase domain 12 (ADAM12)	Mouse studies suggest inhibiting ADAM12 could help prevent tissue fibrosis and scarring. In mice, Adam12-expressing perivascular cells gave rise to profibrotic myofibroblasts in response to injury. Also in mice, injection of Adam12-targeted small interfering RNA into injured muscle tissue decreased markers of fibrosis compared with injection of control siRNA. Next steps could include <i>in vivo</i> studies to determine the role of ADAM12-expressing cells in scleroderma and other chronic fibrotic diseases.  <b>SciBX 5(32); doi:10.1038/scibx.2012.840</b> <b>Published online Aug. 16, 2012</b>	Patented; available for licensing from the Pasteur Institute Office of Technology Transfer and Entrepreneurship <b>Contact:</b> Mai Ban, Pasteur Institute, Paris, France e-mail: <a href="mailto:mai.ban@pasteur.fr">mai.ban@pasteur.fr</a>	Dulauroy, S. <i>et al. Nat. Med.</i> ; published online July 29, 2012; doi:10.1038/nm.2848 <b>Contact:</b> Lucie Peduto, Pasteur Institute, Paris, France e-mail: <a href="mailto:lucie.peduto@pasteur.fr">lucie.peduto@pasteur.fr</a>
<b>Endocrine/metabolic disease</b>				
Diabetes	BR serine/threonine kinase 2 (BRSK2)	Human tissue and mouse studies suggest antagonizing BRSK2 could help treat type 2 diabetes. In human and mouse tissue samples, BRSK2 was expressed in pancreatic islets. In mice, small interfering RNA against <i>Brsk2</i> increased both glucose tolerance and serum insulin levels compared with control siRNA. Next steps could include developing selective inhibitors of BRSK2.  <b>SciBX 5(32); doi:10.1038/scibx.2012.841</b> <b>Published online Aug. 16, 2012</b>	Patent and licensing status unavailable	Chen, X.-Y. <i>et al. J. Biol. Chem.</i> ; published online July 13, 2012; doi:10.1074/jbc.M112.375618 <b>Contact:</b> Long Yu, Fudan University, Shanghai, China e-mail: <a href="mailto:longyu@fudan.edu.cn">longyu@fudan.edu.cn</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Infectious disease</b>				
Anthrax	<i>Bacillus anthracis</i> lethal factor	<i>In vitro</i> studies suggest depsidones could help treat anthrax exposure. A high throughput screen for compounds that inhibit the cleavage of mitogen-activated protein kinase kinases (MKKs) by <i>B. anthracis</i> lethal factor identified 13 compounds. One of the compounds, the depsidone stictic acid, inhibited the enzyme by binding at a site other than the active site. In human macrophages, pretreatment with stictic acid or other depsidone analogs decreased anthrax toxin-induced cell death compared with no pretreatment. Next steps could include testing the effects of the compounds after anthrax exposure. IQ Therapeutics B.V.'s IQ-DAA, a dual antibody targeting <i>B. anthracis</i> lethal factor and protective antigen, is in Phase I testing to treat anthrax.  <b>SciBX 5(32); doi:10.1038/scibx.2012.842</b> <b>Published online Aug. 16, 2012</b>	Patent and licensing status unavailable	Bannwarth, L. <i>et al. J. Chem. Biol.</i> ; published online July 27, 2012; doi:10.1016/j.chembiol.2012.05.013 <b>Contact:</b> Benjamin E. Turk, Yale School of Medicine, New Haven, Conn. e-mail: <a href="mailto:ben.turk@yale.edu">ben.turk@yale.edu</a>
Bacterial infection; viral infection	Transforming growth factor- $\beta$ (TGFB); TGF $\beta$ )	Mouse and cell culture studies suggest inhibiting TGF $\beta$ signaling could help protect newborns from infection. In culture, TGF $\beta$ prevented maturation of mouse NK cells. Infant mice with Tgf $\beta$ -resistant NK cells showed a greater ability to resist and control infection with murine cytomegalovirus than wild-type littermates. Next steps could include developing a strategy to selectively inhibit TGF $\beta$ in NK cells.  <b>SciBX 5(32); doi:10.1038/scibx.2012.843</b> <b>Published online Aug. 16, 2012</b>	Unpatented; licensing status not applicable; available for partnering and collaboration	Marcoc, J.P. <i>et al. Nat. Immunol.</i> ; published online Aug. 5, 2012; doi:10.1038/ni.2388 <b>Contact:</b> Yasmina Laouar, University of Michigan, Ann Arbor, Mich. e-mail: <a href="mailto:ylaouar@umich.edu">ylaouar@umich.edu</a>
<b>Neurology</b>				
Alzheimer's disease (AD)	Not applicable	Mouse studies suggest reducing proinflammatory cytokine levels could help treat AD. In a mouse model of AD, chronic treatment with a small molecule anti-inflammatory compound before symptom onset decreased proinflammatory cytokine levels compared with saline control treatment and prevented loss of synaptic proteins. In brain slices from the mice, the anti-inflammatory compound increased synaptic plasticity required for learning and memory compared with vehicle control. Next steps include testing the compound in clinical trials. Transition Therapeutics Inc.'s TT-301, a small molecule that inhibits the overproduction of inflammatory cytokines, is in Phase I testing to treat brain injury and is in preclinical development for AD.  <b>SciBX 5(32); doi:10.1038/scibx.2012.844</b> <b>Published online Aug. 16, 2012</b>	Patent applications filed; licensed to Transition Therapeutics; available for partnering	Bachstetter, A.D. <i>et al. J. Neurosci.</i> ; published online July 25, 2012; doi:10.1523/JNEUROSCI.1496-12.2012 <b>Contact:</b> Linda J. Van Eldik, University of Kentucky, Lexington, Ky. e-mail: <a href="mailto:linda.vaneldik@uky.edu">linda.vaneldik@uky.edu</a>
Multiple sclerosis (MS)	$\beta$ -Amyloid 40; $\beta$ -amyloid 42	Mouse studies suggest amyloid peptides could help treat MS. In four different mouse models of experimental autoimmune encephalitis (EAE), intraperitoneal injection of $\beta$ -amyloid 40 or 42 peptide delayed disease onset and decreased disease severity compared with vehicle control injection. Next steps include developing a long-acting, amyloid-based compound and evaluating its effects in models of progressive MS. Cardinal Therapeutics Inc. is developing amyloid-based therapeutics for multiple human diseases ( <i>see Amyloids for inflammation, page 5</i> ).  <b>SciBX 5(32); doi:10.1038/scibx.2012.845</b> <b>Published online Aug. 16, 2012</b>	Covered by issued and pending patents; licensed to Cardinal Therapeutics; available for licensing and partnering	Grant, J.L. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 1, 2012; doi:10.1126/scitranslmed.3004145 <b>Contact:</b> Lawrence Steinman, Stanford University, Stanford, Calif. e-mail: <a href="mailto:steinman@stanford.edu">steinman@stanford.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Parkinson's disease (PD)	Liver X receptor- $\beta$ (NR1H2; LXR- $\beta$ ); LXR	<p>Mouse studies suggest LXR agonists could help treat PD. In a mouse model of chemically induced PD, <i>Lxr</i>-<math>\beta</math>-deficient mice had greater dopaminergic neurotoxicity and fewer dopamine-producing neurons than wild-type controls. In the same model, an LXR agonist protected wild-type mice from loss of dopaminergic neurons and fibers. Next steps include evaluating the agonist in additional PD models and also in models of Alzheimer's disease (AD).</p> <p>Exelixis Inc.'s LXR agonist, XL652, is in Phase I testing to treat metabolic syndrome.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.846</b> Published online Aug. 16, 2012</p>	Unpatented; licensing status not applicable	<p>Dai, Y.-b. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 23, 2012; doi:10.1073/pnas.1210833109</p> <p>Contact: Jan-Åke Gustafsson, University of Houston, Houston, Texas e-mail: <a href="mailto:jgustafsson@uh.edu">jgustafsson@uh.edu</a></p>
Neurology	Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2); glial fibrillary acidic protein (GFAP)	<p>Mouse studies suggest increasing NRF2 activity could help treat Alexander disease, a neurodegenerative condition caused by a <i>GFAP</i> mutation. In a mouse model of Alexander disease, overexpression of the Nrf2 transcription factor restored body weight and decreased <i>Gfap</i> levels and <i>Gfap</i> protein inclusions in the brain compared with normal Nrf2 expression. Next steps include identifying a compound that can increase Nrf2 activity in the brain.</p> <p>At least four companies have NRF2 activators in clinical and preclinical testing for various diseases.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.847</b> Published online Aug. 16, 2012</p>	Unpatented; genetic mouse model available for licensing	<p>LaPash Daniels, C.M. <i>et al. J. Neurosci.</i>; published online Aug. 1, 2012; doi:10.1523/JNEUROSCI.1494-12.2012</p> <p>Contact: Christine M. LaPash Daniels, University of Wisconsin-Madison, Madison, Wis. e-mail: <a href="mailto:lapashdaniel@waisman.wisc.edu">lapashdaniel@waisman.wisc.edu</a></p>
<b>Other</b>				
Hearing loss	Solute carrier family 17 sodium-dependent inorganic phosphate cotransporter member 8 (SLC17A8; VGLUT3)	<p>Mouse studies suggest gene therapy could help treat congenital deafness caused by mutations in <i>VGLUT3</i>. In <i>Vglut3</i> knockout mice, an adeno-associated viral (AAV) vector encoding wild-type <i>Vglut3</i> engineered to be expressed in the inner ear increased hearing compared with no treatment. Next steps include constructing and testing AAV vectors bearing other genes mutated in congenital deafness.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.848</b> Published online Aug. 16, 2012</p>	Unpatented; licensing status not applicable	<p>Akil, O. <i>et al. Neuron</i>; published online July 26, 2012; doi:10.1016/j.neuron.2012.05.019</p> <p>Contact: Lawrence R. Lustig, University of California San Francisco, Calif. e-mail: <a href="mailto:llustig@ohns.ucsf.edu">llustig@ohns.ucsf.edu</a></p>

## This week in techniques

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

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
Statistical genomic analysis approach to determine driver mutations in melanoma	A statistical genomic analysis approach to determine driver mutations in melanoma could help identify new targets to treat the disease. Driver mutations in melanoma are difficult to identify due to the large number of random mutations induced by UV damage. Using genomic sequence data from paired tumor and normal tissues of patients with melanoma, a baseline mutation rate was defined and used to help identify five new candidate genes that could drive the disease: <i>protein phosphatase 6 catalytic subunit (PPP6C)</i> , <i>ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1; RAC1)</i> , <i>sorting nexin 31 (SNX31)</i> , <i>transforming acidic coiled-coil containing protein 1 (TACC1)</i> and <i>serine/threonine kinase 19 (STK19)</i> . Next steps include applying the strategy to a larger cohort of patients with melanoma as well as to patients with lung cancer.	Patent application filed; available for licensing	Hodis, E. <i>et al. Cell</i> ; published online July 20, 2012; doi:10.1016/j.cell.2012.06.024 Contact: Lynda Chin, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:lchin@mdanderson.org">lchin@mdanderson.org</a> Contact: Levi A. Garraway, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:levi_garraway@dfci.harvard.edu">levi_garraway@dfci.harvard.edu</a>
<b>Disease models</b>			
Guinea pig models for assessing safety of human embryonic stem cell (hESC)-derived cardiomyocyte transplants	Guinea pigs could help assess the safety and efficacy of hESC-derived cardiomyocyte transplants. In guinea pig models of cardiac injury, hESC-derived cardiomyocyte grafts integrated with host cardiac tissue and beat synchronously with host cardiomyocytes. The cardiomyocyte grafts also decreased left ventricular dilation and deterioration and the incidence of ventricular tachycardia compared with noncardiomyocyte grafts. Ongoing work includes testing methods for improving the performance of hESC-derived cardiomyocyte transplants in the guinea pig models.	Unpatented; available for partnering	Shiba, Y. <i>et al. Nature</i> ; published online Aug. 5, 2012; doi:10.1038/nature11317 Contact: Michael A. Laflamme, University of Washington, Seattle, Wash. e-mail: <a href="mailto:laflamme@u.washington.edu">laflamme@u.washington.edu</a> Contact: Charles E. Murry, same affiliation as above e-mail: <a href="mailto:murry@uw.edu">murry@uw.edu</a>
Induced pluripotent stem (iPS) cell-derived neurons from patients with familial Parkinson's disease (PD)	iPS cell-derived neurons from patients with PD may help characterize disease phenotypes and aid in the identification of therapeutics that correct the phenotypes. iPS cell-derived neurons from patients with <i>leucine-rich repeat kinase 2 (LRRK2)</i> and <i>PTEN induced putative kinase 1 (PINK1)</i> mutations were more sensitive to PD-associated chemical toxins and stressors than neurons derived from healthy controls. Neurons from patients with <i>LRRK2</i> mutations had greater mitochondrial mobility than neurons from patients with <i>PINK1</i> mutations or healthy controls. Next steps include generating iPS cell-derived neurons from other patients with familial PD.	Patent application filed; available for licensing	Cooper, O. <i>et al. Sci. Transl. Med.</i> ; published online July 4, 2012; doi:10.1126/scitranslmed.3003985 Contact: Ole Isacson, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:isacson@hms.harvard.edu">isacson@hms.harvard.edu</a>
Mouse models of human CC chemokine receptor 9 (CCR9; CDw199)-expressing colorectal cancer	Mouse models based on CCR9-expressing human colorectal cancer cell lines could help identify new therapies to treat the disease. In colorectal cancer tumors from patients, CCR9 levels were upregulated in primary tumors and downregulated in metastatic tumors. In mice, cell lines derived from the CCR9-expressing primary colorectal cancer tumors produced a larger number of gastrointestinal tumors than cell lines derived from the metastatic tumors. In mice receiving the CCR9-expressing cells, small hairpin RNA against <i>CCR9</i> decreased tumor formation in the gastrointestinal tract but also increased tumor formation outside of it compared with scrambled control shRNA. Ongoing work includes using multiple CCR9-expressing colorectal cancer cell lines in xenograft mouse models to identify inhibitors of colorectal cancer metastasis.	Patent application filed covering the CCR9-expressing colorectal cancer cell lines; available for licensing	Chen, H.J. <i>et al. J. Clin. Invest.</i> ; published online Aug. 6, 2012; doi:10.1172/JCI62110 Contact: Steven Lipkin, Weill Cornell Medical College, New York, N.Y. e-mail: <a href="mailto:stl2012@med.cornell.edu">stl2012@med.cornell.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug platforms</b>			
Crystal structures of HCV NS3/4A protease complex with HCV protease inhibitors	<p>Crystal structures of HCV NS3/4A proteases complexed with HCV protease inhibitors could aid the development of new therapeutics against drug-resistant HCV strains. Researchers generated crystal structures of wild-type HCV NS3/4A protease and three common drug-resistant variants in complex with four small molecule protease inhibitors. The structures showed that Incivek telaprevir, danoprevir, vaniprevir and MK-5172 interact at sites on the wild-type protease that are mutated in drug-resistant variants, such as R155, A156 and D168. Next steps include characterizing additional drug-resistant variants of the HCV NS3/4A protease complex and conducting studies to better understand the role of the protease's helicase domain.</p> <p>Vertex Pharmaceuticals Inc., Johnson &amp; Johnson and Mitsubishi Tanabe Pharma Corp. market Incivek to treat HCV.</p> <p>Merck &amp; Co. Inc.'s vaniprevir is in Phase III testing and MK-5172 is in Phase II testing for HCV.</p> <p>Roche's danoprevir is in Phase II testing to treat HCV.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.853</b> Published online Aug. 16, 2012</p>	Unpatented; licensing status not applicable; available for partnering and collaborations	Romano, K.P. <i>et al. PLoS Pathog.</i> ; published online July 26, 2012; doi:10.1371/journal.ppat.1002832 <b>Contact:</b> Celia A. Schiffer, University of Massachusetts Medical School, Worcester, Mass. e-mail: <a href="mailto:celia.schiffer@umassmed.edu">celia.schiffer@umassmed.edu</a>
Genetic lineage markers for identifying glioma cancer stem cells	<p>Mouse studies suggest cell-specific expression of GFP-based genetic elements could be useful for identifying compounds that target glioma stem cells. Transgenic mice were engineered to develop gliomas that consist of a large population of highly proliferative GFP-negative cells and a small population of quiescent GFP-positive cells. Chemotherapy eradicated GFP-negative tumor cells but not GFP-positive tumor cells. When chemotherapy was discontinued in these mice, the quiescent GFP-positive tumor cells gradually gave rise to a large population of highly proliferative and differentiated GFP-negative tumor cells. In this model, selective ablation of the GFP-positive cells, even in the absence of chemotherapy, blocked tumor growth and significantly increased survival compared with no ablation (<math>p=0.001</math>). Next steps include pooling gliomas from multiple mice and using them in a high throughput small molecule screen (<i>see Tracing cancer stem cells, page 1</i>).</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.854</b> Published online Aug. 16, 2012</p>	Unpatented; licensing status not applicable	Chen, J. <i>et al. Nature</i> ; published online Aug. 1, 2012; doi:10.1038/nature11287 <b>Contact:</b> Luis F. Parada, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: <a href="mailto:luis.parada@utsouthwestern.edu">luis.parada@utsouthwestern.edu</a>
Genetic lineage markers for identifying intestinal cancer stem cells	<p>Mouse studies suggest genetic lineage markers may be useful for identifying compounds that target intestinal cancer stem cells. A mouse model of <i>adenomatous polyposis coli (Apc)</i>-mutant intestinal adenoma was crossed with mice expressing <i>R26-Confetti</i>, a gene that marks leucine-rich repeat-containing G protein-coupled receptor 5 (<i>Lgr5</i>; <i>Gpr49</i>) in one of four different fluorescent colors. In the resulting mouse strain, the color-indicating <i>Lgr5</i>, an intestinal crypt stem cell marker, was enriched in a subpopulation of adenoma cells, suggesting the latter were cancer stem cells. Fluorescent tracking of the <i>Lgr5</i>-enriched adenoma cells confirmed they were multipotent and gave rise to the other cell types in the adenoma. Next steps could include isolating and further characterizing the stem cell properties of the <i>Lgr5</i>-enriched adenoma cells (<i>see Tracing cancer stem cells, page 1</i>).</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.855</b> Published online Aug. 16, 2012</p>	Patent and licensing status undisclosed	Schepers, A.G. <i>et al. Science</i> ; published online Aug. 1, 2012; doi:10.1126/science.1224676 <b>Contact:</b> Hans Clevers, Hubrecht Institute, Utrecht, the Netherlands e-mail: <a href="mailto:h.clevers@hubrecht.eu">h.clevers@hubrecht.eu</a>
Genetic lineage markers for identifying skin cancer stem cells	<p>Mouse studies suggest genetic lineage markers could be useful for identifying compounds that target skin cancer stem cells. A standard mouse model of chemical-induced skin cancer was engineered to express yellow fluorescent protein (YFP) in skin papillomas. Tracking the YFP signal over time revealed two subpopulations of tumor cells in the papilloma, one with stem cell-like features and the other with proliferative features. Further quantitative analysis of the papillomas led to a model of tumor growth that suggests a minority population of stem cell-like tumor cells gives rise to a pool of proliferative progenitor cells that lead to terminally differentiated tumor cells. Next steps include using the lineage-tracing assay to identify cellular pathways that contribute to dysregulation of cancer stem cells (<i>see Tracing cancer stem cells, page 1</i>).</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.856</b> Published online Aug. 16, 2012</p>	Unpatented; licensing status not applicable	Driessens, G. <i>et al. Nature</i> ; published online Aug. 1, 2012; doi:10.1038/nature11344 <b>Contact:</b> Benjamin Simons, University of Cambridge, Cambridge, U.K. e-mail: <a href="mailto:bds10@cam.ac.uk">bds10@cam.ac.uk</a> <b>Contact:</b> Cédric Blanpain, Free University of Brussels, Brussels, Belgium e-mail: <a href="mailto:cedric.blanpain@ulb.ac.be">cedric.blanpain@ulb.ac.be</a>

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