

THIS WEEK

ANALYSIS

COVER STORY

1 IRS audit for tumors

An Israeli academic-industry partnership has discovered small molecules that target insulin receptor substrates 1 and 2, which sit downstream of the cancer-associated insulin-like growth factor-1 receptor. The compounds have been licensed to NovoTyr.

TRANSLATIONAL NOTES

4 Oxford goes big (data)

University of Oxford is bringing big data to translational research. The university, the U.K. government and a philanthropist are infusing up to £90 million (\$138.3 million) to set up a new hub that will use large-scale data analysis to improve the odds of identifying clinically relevant molecular targets.

TOOLS

5 Revisiting adrenomedullin in preeclampsia

A North Carolina team has shown that fetal deficiency in adrenomedullin resulted in mouse placental abnormalities similar to those found in preeclampsia. The results point to adrenomedullin as a potential marker for the indication.

7 Finding a home for nuclear transfer

Oregon Health & Science University researchers have for the first time generated stable lines of human embryonic stem cells via somatic cell nuclear transfer. Whether the platform can carve a niche among existing stem cell-based techniques will hinge on how the cells compare with those generated through other approaches.

THE DISTILLERY

10 This week in therapeutics

Treating aromatase inhibitor-resistant breast cancer with RET inhibitors; enhancing the efficacy of antidepressant drugs with RGS4 modulators; treating Cushing's disease with TR4 inhibitors; and more...

16 This week in techniques

Postsurgical resection model for metastatic breast cancer; collagen-like, cell-penetrating peptides for drug delivery; classification system for endometrial cancers; and more...

INDEXES

18 Company and institution index

18 Target and compound index

IRS audit for tumors

By Lev Osherovich, Senior Writer

An Israeli academic-industry partnership has discovered small molecules that interfere with signaling by insulin-like growth factor-1 receptor, a cancer-associated receptor tyrosine kinase. The new compounds, licensed to **NovoTyr Therapeutics Ltd.**, could be superior to conventional approaches to hitting this target because they cause destruction of two key downstream effectors, insulin receptor substrate 1 and insulin receptor substrate 2.¹

Excessive activity of insulin-like growth factor-1 receptor (IGF1R; CD221) is a common feature in many tumor types. When activated by extracellular ligands such as insulin and insulin-like growth factor-1 (IGF-1), IGF1R recruits the intracellular proteins insulin receptor substrate 1 (IRS1) and IRS2 to relay a proliferative signal to a range of downstream pathways that drive tumor growth.²

Most compounds that target IGF1R are mAbs and have had a poor track record in the clinic. In 2010, **Pfizer Inc.**'s figitumumab (CP-751,871; CP-751871) failed a Phase III trial in advanced nonadenocarcinoma non-small cell lung cancer (NSCLC). In 2012, **Amgen Inc.** and **Takeda Pharmaceutical Co. Ltd.** terminated a Phase III trial of ganitumab (AMG 479) in pancreatic cancer owing to lack of efficacy.

Figitumumab was discontinued. Ganitumab remains in Phase II testing for a range of solid tumors, as does cixutumumab (IMC-A12) from **Eli Lilly and Co.**

The most advanced small molecule IGF1R inhibitor is **Astellas Pharma Inc.**'s linsitinib (ASP7487), which is in Phase III trials for adrenocortical carcinoma.

NovoTyr, a spinout from the laboratory of Alexander Levitzki, a professor of biochemistry at **The Hebrew University of Jerusalem**, initially set out to find selective kinase inhibitors of IGF1R but instead came across compounds that led to the hyperphosphorylation and degradation of IRS1 and IRS2.

"We were looking for inhibitors that compete for the substrate binding domain of IGF1R," said Levitzki. "We found that some of these molecules are in fact allosteric inhibitors that induce the dissociation of IRS1 and IRS2 from the receptor. This causes them to shift into the cytoplasm and be phosphorylated and then become degraded. This is a first-of-a-kind mechanism."

In principle, degradation of IRS1 and IRS2 should lead to longer-lasting and more potent IGF1R pathway inhibition than conventional kinase inhibitors or mAbs. The challenge now is to show that the compounds perform better than other therapeutic candidates and are well tolerated.

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Taxing tumors

Levitzki's team used SAR studies to identify compounds that blocked the enzymatic activity of full-length IGF1R. Surprisingly, the team found that the compounds did not block binding of ATP or inhibit the activity of a shortened version of IGF1R that contains only its kinase domain.

On the basis of this enzymological profile, the team suspected that the compounds were allosteric inhibitors that bind far from a target's active site but cause structural changes that alter the target's activity.

In a variety of cultured tumor cells, the best of the compounds inhibited tumor growth and led to hyperphosphorylation of IRS1 and IRS2 at serine residues whose phosphorylation is known to inhibit the proteins' activity. Over time, cells containing hyperphosphorylated IRS1 and IRS2 proteins underwent degradation, whereas vehicle-treated controls did not.

The group used a range of pharmacological tools to uncover the compounds' mechanism of phosphorylating and degrading IRS1 and IRS2 and found that it was mediated by the MAP kinase 1 (MAPK1; ERK-2) and MAPK3 (ERK-1) pathway.

In mouse xenograft models for melanoma, ovarian cancer and prostate cancer, the best of the compounds inhibited tumor growth and increased survival compared with no treatment.

The team did not report a head-to-head comparison of its compounds with other IGF1R inhibitors. Results were published in *Cancer Research*. The compounds are covered by pending patents that have been licensed to NovoTyr.

Mixed signals

Levitzki and Hadas Reuveni, study coauthor and NovoTyr's CEO, said that the principal advantage of the new compounds over conventional IGF1R inhibitors is higher potency *in vivo*.

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“Compared to conventional IGF1R kinase inhibitors, which are given at a high frequency of one to two times a day, only a short exposure to the NovoTyr compounds is required to gain a long-lasting effect on IRS1 and IRS2,” said Reuveni.

“You don’t just block the signaling; you actually eliminate the downstream signaling factor,” said Levitzki. “You could have more time between doses.”

Another selling point is the potential of the compounds to overcome resistance to other IGF1R-targeting compounds, including IGF1R-targeting mAbs.

Reuveni said that tumors treated with anti-IGF1R mAbs can develop resistance by upregulating a range of related receptors, including insulin receptor (INSR) and Src. The catch is that all of those receptors rely on IRS1 or IRS2 to send a downstream signal. Thus, destroying those proteins with the NovoTyr compounds could reduce the emergence of IGF1R inhibitor resistance.

“We think of IRS1 as an adaptor protein. IRS1 participates in a lot of signaling pathways, so it could interact with other kinases,” said Douglas Yee, a professor of medicine and pharmacology at the **University of Minnesota Medical School** and director of the **University of Minnesota Masonic Cancer Center**.

“Conventional approaches to targeting IGF1R downregulate the receptor activity but don’t have much of an effect on IRS1,” added Yee. “To really shut off IGF-1 signaling, you really have to shut off both the IGF1R and INSR. Hitting the downstream adaptor proteins may be the way to do this.”

Reuveni noted that several other cancer-associated signaling pathways use IRS1 and IRS2 to relay tumor growth signals, so the compounds could be useful beyond IGF1R-overexpressing tumors.

Along these lines, the team found the compounds prevented growth of cultured tumors resistant to Zelboraf vemurafenib (PLX4032), a small molecule inhibitor of mutant BRAF that is marketed by **Roche** and **Daiichi Sankyo Co. Ltd.** to treat metastatic melanoma. The team showed that those tumors had high expression of IRS1 and IRS2 compared with Zelboraf-sensitive cells.

Cancer and metabolism

The next step for NovoTyr is to continue preclinical toxicology studies. One potential concern is whether the molecules will show an unwanted

effect on normal insulin and IGF-1 signaling in metabolism.

“Theoretically, you might expect that comprehensive blockade of the entire receptor family would have broad metabolic effects,” said Michael Pollak, a professor of oncology and medicine at **McGill University**. “The authors’ to-do list should be to rule out toxicity and, if there

isn’t, they should understand why, since you would expect that this would cause diabetes-like effects.”

“Metabolic effects are always a concern. If this affects the function of adaptor proteins, there could be a profound effect on glucose homeostasis,” said Yee. Another concern is whether there would be

knock-on effects on other signaling pathways that use IRS1 and IRS2. Pollak said that tinkering with other proliferative pathways such as mammalian target of rapamycin (mTOR; FRAP; RAFT1) and protein kinase B (PKB; PKBA; AKT; AKT1) signaling can affect IRS1 and IRS2 activity, so NovoTyr’s compounds might affect those pathways differently than do direct IGF1R inhibitors.

“Eliminating the IRS proteins is a very interesting but hard-to-predict intervention because of all of the feedback loops that converge” on IRS1 and IRS2, said Pollak.

Despite these concerns, Pollak said that the Israeli team’s approach is fundamentally different from what has been tried before. “It’s not just another incremental advance,” he said. “This belongs on the desk of a venture capitalist. It really is novel, and it just might work.”

The team already has shown the compounds are well tolerated by mice in the short term and now plan to do long-term toxicology studies.

NovoTyr was founded in 2005, and Reuveni said that the company “has raised an overall amount of \$3.5 million from several parties, mainly the **Office of the Chief Scientist in the Ministry of Economy** in Israel and from **Teva Pharmaceutical Industries Ltd.**”

She said that the Israeli government investment was provided through the **Meytav Technological Incubator**, which holds more than 60% of NovoTyr’s equity. The other shareholders are Teva, Hebrew University, cofounders Levitzki and Reuveni and some of NovoTyr’s directors.

“At the moment the company is eager to raise venture capital investment,” added Levitzki.

Reuveni said that Teva declined to exercise an exclusive option to acquire NovoTyr’s compounds and that the molecules are available for licensing or partnering. Reuveni declined to say why Teva had passed on the compounds.

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“It’s not just another incremental advance. This belongs on the desk of a venture capitalist. It really is novel, and it just might work.”

**—Michael Pollak,
McGill University**

Oxford goes big (data)

By C. Simone Fishburn, Senior Editor

The **University of Oxford** is bringing big data to translational research. The university, the U.K. government and a philanthropist are infusing up to £90 million (\$138.3 million) to set up a new hub that will use large-scale data analysis to improve the odds of identifying clinically relevant molecular targets.

The center comprises a Big Data Institute (BDI) that will develop systems for gathering and analyzing large sets of data and a Target Discovery Institute (TDI) that will use genomic and chemical screens to identify new drug targets. In addition, the TDI will house some of the **SGC Oxford** branch of the **Structural Genomics Consortium** (SGC), a public-private partnership that performs large-scale 3D structural analysis of biomedically relevant proteins.¹

The impetus for the new hub is the high failure rate of compounds that enter clinical trials. This led a group of Oxford professors to design an approach that would increase the probability of potential disease targets translating into strategies for efficacious therapeutics.

Peter Ratchliffe, a professor of clinical medicine at the University of Oxford who is leading the TDI branch of the center, said that the accurate selection of drug targets is the “most important missing link between academic research and drug development.”

The new translational center is designed to work bi-directionally. In one direction, TDI and SGC will feed molecular target hypotheses to BDI. BDI will mine its banks of data from human genomic, imaging and population health studies to determine how strong the correlation is between a specific biological factor and a given disease.

In the other direction, BDI will search for associations based on epidemiological analyses and will provide the laboratory researchers at TDI with potential new targets and mechanisms to investigate. In the U.K., large cohorts of subjects have participated in Oxford-led initiatives such as [The Million Women Study](#) and the **UK Biobank**. Those studies have provided comprehensive source data from tens of thousands of individuals that will be available to BDI.

For example, “digital images and X-rays have been around for a long while, but we haven’t maximized the information that we’ve gleaned from them,” noted John Bell, Regius Professor of Medicine at the University of Oxford and a cofounder of the new BDI. Thus, he said, one function of BDI will be to find automated ways to extract measurements from images and then transform the data into information that can be analyzed.

“We need new approaches for turning data into information,” added Rory Collins, a professor of medicine and epidemiology at the University of Oxford and CEO and principal investigator of UK Biobank. Collins,

who will head the population health and epidemiology division of BDI, said developing tools to enable data analysis will be a principal function of BDI.

BDI already has geneticists and epidemiologists to design the studies and analyze the data. Collins told *SciBX*, “The glue will be the bioinformatics and computer people” that BDI plans to recruit who can create algorithms for extracting usable information from the large banks of data rendered anonymous from clinical trials, imaging studies and routine medical health records.

The new systems developed by BDI will be publicly available, as will all new structures and reagents developed by SGC. In contrast, TDI will patent and publish its work. Licensing or partnering will be necessary to take its molecules forward as TDI is not set up to perform IND-enabling or clinical studies. Instead, its focus is generating preoptimized scaffolds or probe compounds suitable for early stage animal studies.

A new gift of £20 million (\$30.7 million) from the philanthropic **Li Ka Shing Foundation** will help fund BDI research, adding to £20 million (\$30.7 million) from the U.K. government and £50 million (\$76.8 million) from the University of Oxford to construct new buildings and recruit staff for TDI and BDI.

Although the translational hub has backing from industry, there are no specific deliverables required of TDI or BDI by the corporate investors.

“This is not just about funds,” said Chas Bountra, a professor of translational medicine at the University of Oxford and chief scientist at SGC Oxford. It is also about contributing expertise, medicinal chemistry and compound libraries and receiving access to the output.

Ultimately, the new big data approach being taken by the Oxford hub will be measured by an improved success rate in translating preclinical findings to clinical efficacy. “There are real signals to be found” in the databases, said Collins.

Bountra said the new center will be considered a success when its products get picked up by biotech or pharma companies and taken into clinical development.

“We need new approaches for turning data into information.”

—Rory Collins,
University of Oxford

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Revisiting adrenomedullin in preeclampsia

By Michael J. Haas, Senior Writer

A North Carolina team has shown that fetal deficiency in adrenomedullin resulted in mouse placental abnormalities similar to those found in preeclampsia, thereby underscoring adrenomedullin's potential as a marker for the indication.¹ Future studies will need to replicate the findings in other animal models and determine whether low adrenomedullin levels are found in all preeclampsia cases or just a subset.

Preeclampsia involves hypertension and proteinuria and occurs in about 5% of pregnant women. The condition can lead to life-threatening seizures (eclampsia). Preeclampsia is thought to involve insufficient remodeling of maternal uterine spiral arteries, which are part of the uteroplacental vasculature that changes to accommodate the need for low-resistance, high-capacity blood flow to the fetus.

The condition is usually not diagnosed until the second or third trimester of pregnancy—long after key steps in placental development have occurred.

The standard of care for managing the condition includes antihypertensive drugs, magnesium sulfate (to prevent seizures) and steroids to promote fetal lung development before delivery. The only effective treatment is delivery of the baby by induced labor or Caesarean section.

The precise pathogenic mechanisms of preeclampsia are not well understood, although prior studies have shown that signaling between the vasodilatory peptide adrenomedullin (ADM; AM) and its receptor, calcitonin receptor-like (CRLR; CALCRL), has a role in placental development^{2,3} and have suggested an association between low maternal serum levels of ADM and preeclampsia.⁴

Data linking serum ADM levels to preeclampsia have been inconclusive because of technical limitations in handling and measuring the peptide.

“Adrenomedullin is very sticky and adheres readily to plastic, glass and other lab equipment, and it has a very short half-life,” Kathleen Caron told *SciBX*.

Caron is an associate professor of cell biology and physiology and assistant dean for research at **The University of North Carolina at Chapel Hill School of Medicine**.

Caron has long postulated that ADM has an important role in preeclampsia. In 2006 and 2008, she led teams that reported that pregnant, *Adm* heterozygous knockout mice showed abnormal implantation of fertilized eggs, abnormal placental development and restrictions to fetal growth that were eventually lethal.^{5,6}

However, the phenotypes observed in those studies confirmed a role for maternal *Adm* in pregnancy but “were not quite what I would consider pre-eclamptic,” she said.

Thus, for the new study, Caron's team speculated that complete *Adm* deficiency in the mouse fetus might contribute to a preeclamptic phenotype in the placenta and thus identify the peptide as a potential marker or therapeutic target in the indication.

The team first crossed *Adm* heterozygous knockout mice to generate offspring that included *Adm* homozygous knockout fetuses. Compared with their wild-type littermates, homozygous knockout fetuses showed two key features of human preeclampsia: decreased remodeling of placental vasculature and decreased placental recruitment of the maternal uterine NK cells required for that remodeling.

The team saw similar reductions in vascular remodeling and maternal uterine NK cell recruitment in *Calcr1* homozygous knockout fetuses.

Placentas of mouse fetuses that overexpressed *Adm* showed normal vascular remodeling and a 30% increase in recruitment of maternal uterine NK cells compared with those of wild-type littermates.

Finally, maternal uterine NK cells from wild-type mice treated with *Adm* showed increased secretion of cytokines, chemokines and matrix metalloproteases involved in remodeling of placental vasculature compared with untreated cells.

Taken together, the results highlighted a pathogenic role for ADM in preeclampsia and the need to re-evaluate the target as a marker for the condition, the team wrote in its report in *The Journal of Clinical Investigation*.

“Preeclampsia is not a single condition with a single etiology. It is unlikely that adrenomedullin or any other single factor is responsible for preeclampsia.”

—C. David Adair,
Glenveigh Medical LLC

Caron added, “The importance of the baby and fetal tissue to preeclampsia has been widely assumed, but few—if any—fetal-derived factors have been identified with such a clear correlation to the pathophysiological manifestation of preeclampsia as adrenomedullin.”

Caron's team also included researchers from **The University of North Carolina at Chapel Hill** and **Duke University Medical Center (DUMC)**.

“This study broadens understanding of the early development of the fetus and placenta and, by explaining some placental features of the disease, confirms that adrenomedullin seems to play a role in preeclampsia,” said C. David Adair. “It also raises new questions to investigate.”

Adair is founder, chairman and CSO of **Glenveigh Medical LLC** and vice chair of obstetrics and gynecology at **The University of Tennessee College of Medicine Chattanooga**.

One of those new questions, he said, is whether the findings in mice are relevant to human preeclampsia. He noted that in the team's experiments, “none of the pregnant females developed the hypertension and proteinuria associated with preeclampsia.”

In the *JCI* paper, the team wrote that because only one-quarter of the fetuses in a pregnant female were *Adm* homozygous knockouts—all of which died and were reabsorbed at mid-gestation—it was “unlikely that a minority of placentas could induce the presentation of overt maternal preeclampsia early in gestation.”

Adair said that the explanation is plausible, but he still thinks mice might not make the best models for preeclampsia because they have a different type of placenta from that of humans.

Instead, he wanted to see the findings replicated in guinea pigs, whose placental type is more similar to that of humans. However, he acknowledged that pregnant guinea pigs would also carry a minority of *Adm* homozygous knockout fetuses in each litter and so might not develop overt preeclampsia.

“The only animals that have single offspring and a placenta comparable to humans are primates, but these are challenging and expensive to use as models for any disease,” he said. “There is just not a good animal model for preeclampsia.”

Caron agreed that studying the *Adm* homozygous knockout phenotype in guinea pigs, nonhuman primates and other species could be useful. “But the drawback is that we do not yet have sophisticated and robust genetic engineering capabilities in these species,” she said. “The process of spiral artery remodeling is actually well conserved between all of these species. So there is just as much to learn from studying a mouse as there is from studying any other animal—except maybe humans.”

Going pro

If the *JCI* findings do translate into humans, Adair said that the results would be more likely to help diagnose a subset of preeclampsia cases rather than all of them.

“Preeclampsia is not a single condition with a single etiology,” he said. “It is unlikely that adrenomedullin or any other single factor is responsible for preeclampsia.”

To establish the subset of patients in which ADM might be a marker, the team “could test adrenomedullin in samples from a serum bank and look for correlations between it and abnormalities in placental samples,” Adair said. “Or they could run an open-enrollment study in women who are 12–16 weeks pregnant—when we think preeclampsia begins—measure their adrenomedullin levels, then follow them over time to see which women develop preeclampsia.”

Indeed, Caron said, the team now plans to study serum ADM as a marker of preeclampsia in pregnant women.

The group plans to use an antibody-based assay for pro-adrenomedullin (pro-AM) marketed by the Brahms GmbH subsidiary of **Thermo Fisher Scientific Inc.** as a research tool to diagnose acute myocardial infarction (MI), acute destabilized heart failure and lower respiratory tract infections. Pro-AM is a stable precursor of ADM, and its serum levels correlate closely with those of the peptide, Caron said.

The assay measures serum pro-AM more accurately and reliably than is possible for serum ADM, thereby allowing the team to determine how closely ADM correlates with preeclampsia and whether the peptide could be a prognostic or diagnostic marker of the condition in early pregnancy, she said.

She added, “I think that a reliable assay might allow detection of abnormally low levels of ADM as early as the first trimester.”

Caron acknowledged that ADM might be a useful marker only for a subset of pre-eclampsia cases. “But the answer will depend on just how broadly adrenomedullin signaling is interconnected with other genetic factors and pathways in preeclampsia,” she said. “We—and others—need to test these ideas in large trials.”

She also said that her team and collaborators at DUMC have developed screening assays to identify small molecule CRLR agonists as potential therapies for preeclampsia.

The findings reported in *JCI* are unpatented and unlicensed. The *Adm* homozygous knockout mouse models are available for licensing, Caron said.

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Finding a home for nuclear transfer

By Kai-Jye Lou, Senior Writer

Oregon Health & Science University researchers have for the first time generated stable lines of human embryonic stem cells via somatic cell nuclear transfer.¹ Whether the platform can carve a niche among existing stem cell–based techniques will hinge on how the cells compare with those generated through other approaches.

Generating embryonic stem cells (ESCs) via somatic cell nuclear transfer (SCNT) involves taking an unfertilized oocyte, removing its nucleus and then transplanting the nucleus of a somatic cell into the enucleated oocyte. The resulting cell is then activated and allowed to divide until a blastocyst is formed. ESCs are collected from this blastocyst and used to establish cell lines.

Researchers in the stem cell space have previously reported on the use of SCNT to generate ESC lines from a range of lab animals,² including nonhuman primates in a study led by Shoukhrat Mitalipov and published in *Nature* in 2007.³

Mitalipov is an associate scientist in the Division of Reproductive and Developmental Sciences in the **Oregon National Primate Research Center** at OHSU.

The next hurdle was to use SCNT to generate ESC lines from human cells. However, early attempts to do so were not successful because human cells generated through SCNT typically stopped dividing after only a few rounds—a phenomenon called early embryonic arrest.^{4,5}

SCNT had been further sidelined owing to the limited supply of donor oocytes and the advent of induced pluripotent stem (iPS) cell technologies.⁶ The latter are easier to use, more scalable and subject to fewer funding restrictions and ethical considerations than SCNT.

Now, Mitalipov's group at OHSU has reported a protocol that enables the generation of stable human ESC (hESC) lines from cells obtained via SCNT. The researchers used SCNT to fuse fibroblasts from a human cell line with enucleated donor oocytes and then activated the resulting cells.

In culture medium containing caffeine, a subset of the activated cells continued to divide past the early embryonic stage and formed blastocysts. The researchers were able to derive stable ESC lines from these blastocysts. The OHSU group reported in 2007 that adding caffeine to culture medium improved the development of SCNT-generated nonhuman primate cells into blastocysts.⁷

In the current study, the resulting ESCs expressed known pluripotency markers, formed teratomas when injected into mice and inherited the genome of the donor fibroblast.

Importantly, and contrary to earlier assumptions that deriving an hESC line by SCNT would require unfeasible quantities of donor oocytes,⁸ the researchers were able to derive at least one ESC line per round of oocyte donation. The result suggests that the SCNT approach could be scalable.

The team's results were published in *Cell*.

Comparative metrics

The key question is what role SCNT-derived ESCs might have among existing stem cell–based techniques (see Table 1, “Stem cell types and methods for stem cell generation”). It is probable that the SCNT approach will need to play catch-up with its peers.

iPS cells have already begun to take root in disease modeling and drug screening. For example, **Cellular Dynamics International Inc.** markets a suite of human iPS cell–derived cell lines and related services for such applications, and **iPierian Inc.** is using its in-house iPS cell technology platforms to aid the discovery of new therapies.

Researchers will generally want to see whether SCNT-derived hESCs have properties that would make them superior to iPS cells, other hESC lines or tissue-specific stem cells in a particular therapeutic or nontherapeutic setting.

To sort this out, researchers need to first comprehensively characterize SCNT-derived hESCs and compare them with stem cells generated by other approaches.

The New York Stem Cell Foundation CEO Susan Solomon told *SciBX* that the foundation and its collaborators are doing just that.

“We’re already conducting comparative cell studies on SCNT-derived ESCs, iPS cells and other ESCs to characterize their similarities and differences.”

**—Susan Solomon,
The New York Stem Cell Foundation**

“We’re already conducting comparative cell studies on SCNT-derived ESCs, iPS cells and other ESCs to characterize their similarities and differences,” she said. Solomon declined to disclose details about the origin of the SCNT-derived ESCs.

One area in which SCNT-derived hESCs could potentially shine is in the generation of genetically matched tissues for transplantation. Cells derived from current ESC lines are not genetically matched to the

patient, which decreases their suitability for use in long-term grafts, in which transplanted cells need to persist and remain functional.

Indeed, Solomon thinks that hematopoietic stem cell transplantation might be an area in which SCNT-derived hESCs could have utility given the high cost and difficulty of finding a genetic match.

“If researchers were able to develop a way to safely derive hematopoietic stem cells from patient-matched ESCs, it would likely result in a less costly and more efficient approach than trying to find a match through a registry,” she told *SciBX*.

Another niche area to consider—and one in which SCNT-derived hESCs could have a potential advantage over iPS cells—would be in patients who have diseases caused by mutations in mitochondrial DNA, said Natalie DeWitt, special projects officer at the **California Institute for Regenerative Medicine**.

She noted that SCNT-derived ESCs generated from such patients should remain genetically matched but have the oocyte donor's mitochondrial DNA, which would presumably be free of disease-causing mutations. In contrast, iPS cells generated from such patients would retain their mutant mitochondrial DNA.

DeWitt said that she wanted to see studies that involve generating SCNT-derived ESC lines and iPS cell lines from the same individual followed by detailed characterization studies of the cells. She noted that such studies will help the field to better understand the pathways and mechanisms that mediate the reprogramming of cells to a

Table 1. Stem cell types and methods for stem cell generation. There are three major classes of stem cells: embryonic stem cells (ESCs), induced pluripotent stem (iPS) cells and tissue-specific stem cells. Each class has distinct advantages and drawbacks, including how the cells are generated or extracted.

Source: Refs. 1, 8–12; BCIQ: BioCentury Online Intelligence; California Institute of Regenerative Medicine; EuroStemCell

	Advantages	Drawbacks
ESCs	<ul style="list-style-type: none"> - Can differentiate into any cell type - Can self-renew indefinitely 	<ul style="list-style-type: none"> - Number of lines available is limited - Derivation requires the use of donor oocytes - Many older lines are unsuitable for therapeutic use owing to contamination - Use carries risk of teratoma - Cells derived from ESCs may not recapitulate adult cell phenotype - Use faces major ethical, regulatory and funding obstacles
Methods for generating ESCs		
Derivation from <i>in vitro</i> fertilized embryos	<ul style="list-style-type: none"> - Easier to apply than nuclear transfer - Protocols are well established - Therapeutic candidates have entered clinical trials 	<ul style="list-style-type: none"> - Donor and recipient cells are genetically distinct
Somatic cell nuclear transfer	<ul style="list-style-type: none"> - Genetically matched to somatic cell donor, except for mitochondrial DNA - Uses unfertilized oocytes 	<ul style="list-style-type: none"> - Methods are technically cumbersome - Protocols need further optimization - Scalability and efficiency of approach still need to be determined
iPS cells	<ul style="list-style-type: none"> - Can differentiate into any cell type - Can self-renew indefinitely - Donor and recipient cells can be genetically matched - Source cells are plentiful and easy to obtain - Reprogramming protocols are highly scalable - Use faces fewer ethical and funding obstacles than with ESCs 	<ul style="list-style-type: none"> - Use carries risk of teratoma - Cells derived from iPS cells may not recapitulate adult cell phenotype - Immunogenicity is possible even if cells are genetically matched - iPS cell–derived cell therapies have not yet entered clinical trials - Therapeutic development assumed to carry higher risk than ESCs
Methods for generating iPS cells		
Generated with integrating, nonexcisable DNA–based vectors	<ul style="list-style-type: none"> - Reprogramming efficiency is average to high, depending on vector - Reprogramming factor transgenes are silenced after reprogramming step - Some vectors (such as inducible lentivirus) use inducible transgene expression systems to provide fine control of reprogramming factor expression 	<ul style="list-style-type: none"> - Genomic integration raises additional safety concerns - Transgene silencing may be incomplete
Generated with integrating, excisable DNA–based vectors	<ul style="list-style-type: none"> - Reprogramming efficiency is average - Transgenes are removed from host cell genome after reprogramming step 	<ul style="list-style-type: none"> - Additional steps are needed to confirm transgene removal in cells - Some vectors (such as lentivirus with floxed transgenes) still leave sequences in host cell genome
Generated with nonintegrating DNA–based vectors	<ul style="list-style-type: none"> - Genomic integration does not occur under normal circumstances 	<ul style="list-style-type: none"> - Reprogramming efficiency is low - Vector DNA still has a low potential to integrate with host cell genome - Additional steps are needed to check for possible genomic integration
Generated with nonintegrating RNA–based vectors	<ul style="list-style-type: none"> - Reprogramming efficiency is high - Genomic integration does not occur - Some vectors (such as Sendai virus) can stimulate very high levels of reprogramming factor production - Some vectors (such as microRNAs) might be able to reprogram somatic cells refractory to other reprogramming approaches 	<ul style="list-style-type: none"> - Replicating viral vector must be removed after reprogramming step - Reprogramming with nonviral vectors may require multiple rounds of transfection
Generated with proteins and/or small molecule cocktails	<ul style="list-style-type: none"> - Genomic integration does not occur 	<ul style="list-style-type: none"> - Reprogramming efficiency is low - Need for constant supply of reprogramming factors can be expensive
Tissue-specific stem cells	<ul style="list-style-type: none"> - Marketed therapies have been shown not to cause tumors - Approved therapies that contain tissue-specific stem cells already exist - Cells usually recapitulate adult cell phenotype - Certain types (such as umbilical) can be frozen and stored - Use faces few ethical and funding obstacles compared with ESCs 	<ul style="list-style-type: none"> - Cells can differentiate into a limited number of cell types - Capacity for self-renewal is limited - Cells are present in small quantities in source tissues - Cells are less scalable than iPS cells
Methods for generating tissue-specific stem cells		
Extraction from autologous tissues	<ul style="list-style-type: none"> - Cells are genetically matched to the patient - Protocols are well established 	<ul style="list-style-type: none"> - Autologous source tissues are limited in supply
Extraction from allogeneic tissues	<ul style="list-style-type: none"> - Allogeneic source tissues may be more plentiful than autologous tissues - Method could enable the development of off-the-shelf therapies - Protocols are well established 	<ul style="list-style-type: none"> - Donor and recipient cells are genetically distinct

pluripotent state and also provide insights on how to improve iPS cell reprogramming.

She also wanted to see comparisons between the genomic integrity of SCNT-derived ESCs and that of iPS cells.

DeWitt thinks that one of the major barriers to the development of a commercially viable platform for generating SCNT-derived hESCs is the need for large quantities of human donor oocytes.

“Unless a way to create large quantities of human oocytes *in vitro* is also developed, I think it would be tough to build a commercially viable platform based on nuclear transfer,” she told *SciBX*.

Solomon added that the efficiency of the SCNT approach will also be a key determinant of whether others in this space will want to pick up the technology.

OHSU has pending patents covering the use of SCNT to generate stem cells for therapeutic application. The technology is available for licensing.

Lou, K.-J. *SciBX* 6(20); doi:10.1038/scibx.2013.481

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COMPANIES AND INSTITUTIONS MENTIONED

California Institute for Regenerative Medicine, San Francisco, Calif.
Cellular Dynamics International Inc., Madison, Wis.
iPierian Inc., South San Francisco, Calif.
The New York Stem Cell Foundation, New York, N.Y.
Oregon Health & Science University, Portland, Ore.
Oregon National Primate Research Center, Portland, Ore.



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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				
Acute myelogenous leukemia (AML)	AML1-ETO oncogenic fusion protein; cyclooxygenase-2 (COX-2)	<p><i>In vitro</i> and mouse studies suggest COX-2 inhibitors could help treat AML1-ETO⁺ AML. In normal mouse bone marrow cells, AML1-ETO overexpression increased both levels of Cox-2 and the self-renewing capacity of hematopoietic stem cells compared with no overexpression. In xenograft and orthotopic mouse models for AML1-ETO⁺ AML, a COX-2 inhibitor decreased the number and size of tumors compared with vehicle. Planned work includes a Phase II trial of an undisclosed NSAID to prevent relapse in AML.</p> <p>At least five companies have COX-2 inhibitors approved to treat pain, rheumatoid arthritis (RA), osteoarthritis and other indications.</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.482 Published online May 23, 2013</p>	Unpatented; available for partnering	<p>Zhang, Y. <i>et al. Blood</i>; published online May 3, 2013; doi:10.1182/blood-2012-08-447763 Contact: Jing-Ruey Joanna Yeh, Harvard Medical School, Boston, Mass. e-mail: jyeh1@partners.org</p>
B cell lymphoma	Histone deacetylase (HDAC); proteasome	<p>Cell culture and mouse studies suggest a combination of proteasome and HDAC inhibitors could help treat primary effusion lymphoma (PEL). In cultured PEL cells, a combination of the HDAC inhibitor Zolinza vorinostat and the proteasome inhibitor Velcade bortezomib decreased proliferation and increased apoptosis compared with either drug alone. In a mouse xenograft model for human PEL, the combination caused tumor regression and increased survival compared with either drug alone. Next steps could include evaluating the combination in a clinical trial.</p> <p>Takeda Pharmaceutical Co. Ltd. and Johnson & Johnson market Velcade to treat multiple myeloma (MM) and mantle cell lymphoma (MCL).</p> <p>Merck & Co. Inc. and Taiho Pharmaceutical Co. Ltd. market Zolinza to treat cutaneous T cell lymphoma (CTCL).</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.483 Published online May 23, 2013</p>	Patent and licensing status unavailable	<p>Bhatt, S. <i>et al. J. Clin. Invest.</i>; published online May 1, 2013; doi:10.1172/JCI64503 Contact: Juan Carlos Ramos, University of Miami, Miami, Fla. e-mail: jramos2@med.miami.edu Contact: Izidore S. Lossos, same affiliation as above e-mail: ilossos@med.miami.edu Contact: Enrique A. Mesri, same affiliation as above e-mail: emesri@med.miami.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Brain cancer	Integrin β_1 (CD29)	<i>In vitro</i> and mouse studies suggest CD29 inhibitors could help treat Avastin bevacizumab-resistant glioblastoma multiforme (GBM). In cultures of Avastin-treated or Avastin-resistant primary GBM cells, CD29 expression was greater than that in untreated or bevacizumab-sensitive cells. In mice with Avastin-resistant orthotopic xenograft GBM tumors, an anti-CD29 antibody (OS2966) decreased tumor growth compared with an inactive control IgG. In mice with Avastin-sensitive xenograft GBM tumors, OS2966 plus low-dose Avastin decreased tumor growth compared with low-dose Avastin plus control IgG. Ongoing work by OncoSynergy Inc. includes testing OS2966 in models of recurrent GBM and pancreatic cancer. Roche and its Genentech Inc. and Chugai Pharmaceutical Co. Ltd. units market Avastin, a humanized mAb against VEGF, to treat brain, breast and colorectal cancers. SciBX 6(20); doi:10.1038/scibx.2013.484 Published online May 23, 2013	Patented by The Regents of the University of California; licensed to OncoSynergy; available for partnering	Carbonell, W.S. <i>et al. Cancer Res.</i> ; published online May 3, 2013; doi:10.1158/0008-5472.CAN-13-0011 Contact: W. Shawn Carbonell, University of California, San Francisco, Calif. e-mail: shawn@oncosynergy.com
Breast cancer	Ret proto-oncogene (RET)	Studies in cell culture suggest inhibiting RET could be useful for treating aromatase inhibitor-resistant breast cancer. In cell culture and in human primary tumor samples, estrogen receptor-positive breast cancer cells treated with aromatase inhibitors had higher RET expression than estrogen receptor-negative controls. In cell culture models, a small molecule inhibitor of RET signaling decreased colony formation compared with growth factor- or hormone-treated controls. Next steps include testing combinations of RET inhibitors and aromatase inhibitors in xenograft models for breast cancer and developing more selective RET inhibitors. SciBX 6(20); doi:10.1038/scibx.2013.485 Published online May 23, 2013	Unpatented; licensing status not applicable	Morandi, A. <i>et al. Cancer Res.</i> ; published online May 6, 2013; doi:10.1158/0008-5472.CAN-12-4265 Contact: Clare M. Isacke, The Institute of Cancer Research, London, U.K. e-mail: clare.isacke@icr.ac.uk
Breast cancer	Ribosomal protein S6 kinase 90 kDa polypeptide 2 (RPS6KA2; RSK3); RPS6KA6 (RSK4); phosphoinositide-3 kinase (PI3K)	Cell culture and mouse studies suggest inhibiting RSK3 and RSK4 could be useful for treating breast cancers resistant to PI3K inhibitors. In cultured breast cancer cells, vector-mediated overexpression of RSK3 or RSK4 increased cell survival in the presence of PI3K pathway inhibitors compared with a control vector. In mouse xenograft models for human breast cancer, vector-mediated overexpression of RSK3 or RSK4 decreased tumor sensitivity to PI3K inhibitors compared with no overexpression. Next steps include identifying selective inhibitors of RSK3 and RSK4 and evaluating them in PI3K inhibitor-resistant tumors. SciBX 6(20); doi:10.1038/scibx.2013.486 Published online May 23, 2013	Unpatented; licensing status not applicable	Serra, V. <i>et al. J. Clin. Invest.</i> ; published online May 1, 2013; doi:10.1172/JCI66343 Contact: So Young Kim, Duke University, Durham, N.C. e-mail: soyoung.kim@duke.edu Contact: José Baselga, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: baselgaj@mskcc.org

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Fibroblast activation protein (FAP)	<i>In vitro</i> studies identified a boronic acid-based inhibitor of FAP that could be useful for treating cancer. Increased FAP activity is associated with various cancers. In cellular and enzymatic assays, the boronic acid-based molecule ARI-3009 inhibited FAP endopeptidase activity with low nanomolar potency and showed selectivity for the enzyme over dipeptidyl peptidases (DPPs) and prolyl endopeptidase (PREP). Next steps include testing the inhibitor in animal disease models. Vantia Therapeutics Ltd. has the FAP inhibitor VA999260 in preclinical testing to treat cancer. SciBX 6(20); doi:10.1038/scibx.2013.487 Published online May 23, 2013	Covered by issued and filed patents; licensed to Arisaph Pharmaceuticals Inc.; available for partnering	Poplawski, S.E. <i>et al. J. Med. Chem.</i> ; published online April 17, 2013; doi:10.1021/jm400351a Contact: William W. Bachovchin, Tufts University Sackler School of Biomedical Sciences, Boston, Mass. e-mail: william.bachovchin@tufts.edu
Cancer	Heat shock protein 90 (Hsp90); lysine-specific demethylase 4B (KDM4B; JMJD2B)	Cell culture studies suggest KDM4B activity could be reduced by blocking Hsp90. High KDM4B activity has been associated with tumorigenesis. In cell culture, Hsp90 interacted with KDM4B, and proteasome-mediated degradation of KDM4B was higher after pharmacological inhibition of Hsp90 than after no inhibition. Next steps include assessing the effect of Hsp90 inhibition on the stability of other histone demethylases. SciBX 6(20); doi:10.1038/scibx.2013.488 Published online May 23, 2013	Unpatented; licensing status not applicable	Ipenberg, I. <i>et al. J. Biol. Chem.</i> ; published online April 15, 2013; doi:10.1074/jbc.C113.462770 Contact: Nabieh Ayoub, Technion-Israel Institute of Technology, Haifa, Israel e-mail: ayoubn@technion.ac.il
Cancer	HER2 (EGFR2; ErbB2; neu)	Mouse and cell culture studies have identified a HER2-specific aptamer that could help treat HER2 ⁺ cancers. In a human gastric cancer cell line, a trimeric version of a HER2-specific aptamer increased lysosome-mediated degradation of HER2 compared with an inactive control oligonucleotide. In a mouse xenograft model for human gastric cancer, the trimeric, HER2-specific aptamer inhibited tumor growth more than an anti-HER2 mAb or an inactive control oligonucleotide. Next steps include testing the trimeric aptamer in combination with approved, HER2-targeting drugs. SciBX 6(20); doi:10.1038/scibx.2013.489 Published online May 23, 2013	Patent application filed; available for licensing from Yeda Research and Development Co. Ltd., the technology transfer company of the Weizmann Institute of Science Contact: Amir Naiberg, Weizmann Institute of Science, Rehovot, Israel e-mail: amir.naiberg@weizmann.ac.il	Mahlknecht, G. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 29, 2013; doi:10.1073/pnas.1302594110 Contact: Yosef Yarden, Weizmann Institute of Science, Rehovot, Israel e-mail: yosef.yarden@weizmann.ac.il Contact: Michael Sela, same affiliation as above e-mail: michael.sela@weizmann.ac.il
Cancer	TTK protein kinase (TTK; MPS1)	<i>In vitro</i> and rat studies suggest a new class of MPS1 inhibitors could help treat cancer. <i>Ttk</i> knockdown has previously been shown to reduce survival and induce apoptosis in cancer cells. Chemical synthesis, SAR and <i>in vitro</i> testing identified several indazole analogs as selective, potent, nanomolar inhibitors of MPS1. Two lead compounds inhibited proliferation of a human lung cancer cell line at nanomolar IC ₅₀ values and exhibited modest oral bioavailability in rats. Future studies could include improving the bioavailability of the lead compounds. SciBX 6(20); doi:10.1038/scibx.2013.490 Published online May 23, 2013	Patent and licensing status unavailable	Kusakabe, K.-i. <i>et al. J. Med. Chem.</i> ; published online May 1, 2013; doi:10.1021/jm4000215 Contact: Ken-ichi Kusakabe, Shionogi Pharmaceutical Research Center, Osaka, Japan e-mail: ken-ichi.kusakabe@shionogi.co.jp

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Tubulin	<p>A mouse study suggests photodynamic therapy (PDT) with red light-activated prodrugs could help treat cancer with fewer side effects than existing chemotherapeutics. A prodrug composed of a tubulin-binding compound linked to a photosensitizing agent was designed such that free drug would be released upon exposure to red light. In a human breast cancer cell line, the prodrug plus red light increased apoptosis compared with the prodrug alone. In a mouse model for colon cancer, prodrug plus irradiation with red light decreased tumor growth compared with prodrug or vehicle alone, without causing observable toxicity. Future studies could include synthesizing and testing prodrugs of other classes of cancer drugs.</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.491 Published online May 23, 2013</p>	Patent and licensing status unavailable	<p>Bio, M. <i>et al. J. Med. Chem.</i>; published online April 30, 2013; doi:10.1021/jm400139w Contact: Youngjae You, University of Oklahoma, Oklahoma City, Okla. e-mail: youngjae-you@ouhsc.edu</p>
Leukemia	Telomerase reverse transcriptase (TERT)	<p>A mouse study suggests adoptive transfer of T cells expressing a TERT-specific T cell receptor (TCR) and additional small interfering RNAs could help treat adult T cell leukemia (ATL). A retroviral vector was engineered to express both a TERT-specific TCR and siRNAs that suppressed expression of endogenous TCRs, then transduced into CD8⁺ T cells. In mouse models for ATL, infusion of autologous or allogeneic T cells modified with the vector decreased tumor growth compared with infusion of unmodified cells. Next steps include determining whether the approach could be toxic to TERT-expressing normal tissues and measuring the proliferation of the adoptive T cells <i>in vivo</i>.</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.492 Published online May 23, 2013</p>	Patent and licensing status undisclosed	<p>Miyazaki, Y. <i>et al. Blood</i>; published online May 2, 2013; doi:10.1182/blood-2012-11-465971 Contact: Hiroshi Fujiwara, Ehime University Proteo-medicine Research Center, Toon, Japan e-mail: yunarief@m.ehime-u.ac.jp</p>
Solid tumors	Insulin-like growth factor-1 receptor (IGF1R; CD221); insulin receptor substrate 1 (IRS1); IRS2	<p>SAR, cell culture and mouse studies suggest compounds that cause degradation of IRS1 and IRS2 could be useful for treating cancer. SAR and cell culture studies identified allosteric inhibitors of IGF1R that caused hyperphosphorylation and degradation of IRS1 and IRS2. In mouse xenograft tumor models, the most effective of these compounds decreased tumor growth and increased survival compared with vehicle. In cell lines derived from BRAF inhibitor-resistant tumors, the compounds increased cancer cell death compared with no treatment. Next steps include long-term toxicology studies and other preclinical development work.</p> <p>At least 18 products that target IGF1R or IRS1 are in preclinical through Phase III testing for various cancer indications (<i>see IRS audit for tumors, page 1</i>).</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.493 Published online May 23, 2013</p>	Patent pending; available for licensing or partnering from NovoTyr Therapeutics Ltd.	<p>Reuveni, H. <i>et al. Cancer Res.</i>; published online May 7, 2013; doi:10.1158/0008-5472.CAN-12-3385 Contact: Alexander Levitzki, The Hebrew University of Jerusalem, Jerusalem, Israel e-mail: alex.levitzki@mail.huji.ac.il</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Depression; pain	Regulator of G-protein signaling 4 (RGS4)	<p>Mouse studies suggest modulating RGS4 activity could help enhance the efficacy of antidepressant drugs. In mice, viral vector-mediated overexpression of <i>Rgs4</i> in the nucleus accumbens region of the brain increased the antidepressant and antiallodynia effects of three monoamine-targeting antidepressant drugs compared with overexpression of a control gene. In mice, knockout of <i>Rgs4</i> in all tissues or specifically in the nucleus accumbens increased the antidepressant and antiallodynia effects of two non-monoamine-targeting antidepressant drugs compared with no knockout. Next steps could include screening for small molecule modulators of RGS4 activity and evaluating their effects in combination with different classes of antidepressant drugs.</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.494 Published online May 23, 2013</p>	Patent and licensing status unavailable	<p>Stratinaki, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 29, 2013; doi:10.1073/pnas.1214696110 Contact: Venetia Zachariou, Mount Sinai School of Medicine, New York, N.Y. e-mail: venetia.zachariou@mssm.edu</p>
Neurology	Histone deacetylase 2 (HDAC2)	<p>Mouse studies suggest inhibiting HDAC2 in the brain could help improve cognitive function in neuropsychiatric and neurodegenerative diseases. Mice with forebrain-specific disruption of <i>Hdac2</i> showed better performance on tests of conditioned associative learning and had higher hippocampal synaptic function than wild-type controls. Next steps include identifying and testing brain-penetrant, selective inhibitors of HDAC2 in murine models for cognitive dysfunction.</p> <p>Acetylon Pharmaceuticals Inc. has an inhibitor of HDAC1 and HDAC2 in preclinical development for thalassemia and sickle cell disease.</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.495 Published online May 23, 2013</p>	Unpatented; licensing status not applicable	<p>Morris, M.J. <i>et al. J. Neurosci.</i>; published online April 10, 2013; doi:10.1523/JNEUROSCI.1001-12.2013 Contact: Lisa M. Monteggia, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: lisa.monteggia@utsouthwestern.edu</p>
Other				
Cushing's disease	Nuclear receptor subfamily 2 group C member 2 (NR2C2; TR4)	<p>Patient sample and mouse studies suggest inhibiting TR4 could help treat Cushing's disease. In corticotroph tumors from patients with the disease, TR4 was overexpressed compared with expression in normal corticotroph cells. In mice, injection of the mouse corticotroph tumor cell line pretreated with <i>Nr2c2</i> small hairpin RNA decreased tumor growth and levels of circulating adrenocorticotrophic hormone (ACTH) compared with injection of cells pretreated with scrambled control shRNA. Planned studies include identifying and testing TR4 inhibitors.</p> <p>SciBX 6(20); doi:10.1038/scibx.2013.496 Published online May 23, 2013</p>	Patent and licensing status unavailable	<p>Du, L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 7, 2013; doi:10.1073/pnas.1306182110 Contact: Anthony P. Heaney, University of California, Los Angeles, Calif. e-mail: aheaney@mednet.ucla.edu Contact: Ronald M. Evans, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: evans@salk.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Various				
Bacterial infections; inflammation	Lipopolysaccharide (LPS)	Cell culture studies suggest a cathelicidin polypeptide isolated from the skin of the frog <i>Paa yunnanensis</i> could help treat bacterial infections or reduce inflammation. In a panel of bacteria and fungi, cathelicidin decreased growth in 13 of 14 microorganisms at micromolar concentrations compared with saline. In mouse macrophages, cathelicidin inhibited LPS-induced production of inflammatory cytokines. Next steps could include optimizing the potency and pharmacokinetic profile of cathelicidin. <i>SciBX</i> 6(20); doi:10.1038/scibx.2013.497 Published online May 23, 2013	Patent and licensing status unavailable	Wei, L. <i>et al. J. Med. Chem.</i> ; published online April 17, 2013; doi:10.1021/jm4004158 Contact: Ren Lai, Life Sciences College of Nanjing Agricultural University, Nanjing, China e-mail: rlai72@njau.edu.cn Contact: Xiuwen Yan, same affiliation as above e-mail: yanxw@njau.edu.cn Contact: Donghai Lin, Xiamen University, Xiamen, China e-mail: dhlin@xmu.edu.cn

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This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Fluorescence labels in phosphatase (FLiP) assay to detect allosteric inhibitors of phosphatases	A FLiP assay could help identify allosteric inhibitors of phosphatases. An allosteric inhibitor of protein tyrosine phosphatase 1B (PTP-1B; PTPN1) bound a pocket about 20 Å from the enzyme's active site and blocked phosphatase activity by displacing the $\alpha 7$ helix from the phosphatase core. A high throughput FLiP assay was created by labeling the PTP-1B $\alpha 7$ helix with a red fluorophore, which produced altered emission spectra when displaced. In this assay, the allosteric inhibitor shifted the emission spectra readout, whereas an active site-targeting inhibitor or nonbinding control molecule did not. Next steps could include using the screen to identify additional phosphatase inhibitors.	Patent and licensing status unavailable	Schneider, R. <i>et al. J. Am. Chem. Soc.</i> ; published online April 23, 2013; doi:10.1021/ja4030484 Contact: Daniel Rauh, Technical University of Dortmund, Dortmund, Germany e-mail: daniel.rauh@tu-dortmund.de
SciBX 6(20); doi:10.1038/scibx.2013.498 Published online May 23, 2013			
Disease models			
Postsurgical resection model for metastatic breast cancer	A mouse model for postsurgical resection metastatic breast cancer could be useful for evaluating therapeutic regimens to treat the disease. In mice with metastatic human breast cancer, Sutent sunitinib when given after surgical resection of the primary tumor did not significantly increase survival compared with vehicle. However, an antibody against rodent Vegf receptor 2 (Kdr/Flk-1; Vegfr-2) plus paclitaxel when given after resection of the primary tumor increased survival compared with either compound alone or vehicle. Next steps could include using the model to predict efficacy of therapeutic regimens. Pfizer Inc. markets the receptor tyrosine kinase (RTK) inhibitor Sutent sunitinib to treat gastrointestinal stromal tumors (GISTs) and advanced renal cell carcinoma (RCC). The drug was discontinued in advanced breast cancer after missing the endpoints in Phase III trials. Paclitaxel is a generic platinum chemotherapy drug.	Patent and licensing status unavailable	Guerin, E. <i>et al. Cancer Res.</i> ; published online April 22, 2013; doi:10.1158/0008-5472.CAN-12-4183 Contact: Robert S. Kerbel, University of Toronto, Toronto, Ontario, Canada e-mail: robert.kerbel@sri.utoronto.ca
SciBX 6(20); doi:10.1038/scibx.2013.499 Published online May 23, 2013			
Drug delivery			
Collagen-like, cell-penetrating peptides for drug delivery	Cell-penetrating peptides structurally similar to collagen could be used to deliver therapeutics into cells. The peptides contain a collagen-like, triple-helical scaffold that can resist cleavage by proteases. In cell culture, peptides conjugated with a toxin complex that induces cell death after entering the cytosol decreased cell viability compared with unconjugated peptides. In human serum, the collagen-like peptides had a longer half-life than related peptides that lacked the triple-helical scaffold. Next steps could include evaluating the use of the collagen-like peptides for drug delivery.	Patent and licensing status unavailable	Yamazaki, C.M. <i>et al. Angew. Chem. Int. Ed.</i> ; published online April 16, 2013; doi:10.1002/anie.201301266 Contact: Takaki Koide, Waseda University, Tokyo, Japan e-mail: koi@waseda.jp
SciBX 6(20); doi:10.1038/scibx.2013.500 Published online May 23, 2013			
Improved safety for blood brain barrier (BBB)-penetrating antibodies	Mouse studies suggest bispecific antibodies that cross the BBB can be made safer by modifying the effector portion of the antibody. Previous studies identified a BBB-penetrant, bispecific mAb against the Alzheimer's disease (AD) target β -site APP-cleaving enzyme 1 (BACE1) and transferrin receptor protein 1 (TFRC; TFR; CD71). In mice, a variant of the mAb that was unable to bind the Fc γ -receptor (FCGR) showed BBB penetration levels comparable to those of the original mAb. In mice, the mAb variant showed a better toxicity profile than the original mAb. Next steps include humanizing the FCGR binding-compromised mAb and conducting further preclinical development.	Patent pending; licensing status undisclosed	Couch, J.A. <i>et al. Sci. Transl. Med.</i> ; published online May 1, 2013; doi:10.1126/scitranslmed.3005338 Contact: Ryan J. Watts, Genentech Inc., South San Francisco, Calif. e-mail: rwatts@gene.com Contact: Mark S. Dennis, same affiliation as above e-mail: msd@gene.com
SciBX 6(20); doi:10.1038/scibx.2013.501 Published online May 23, 2013			

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Using modified hyperbranched polyglycerol (HPG) to guide stem cell localization	Modified HPG could be used to target injected stem cells to specific tissues. HPG was modified with octadecyl chains and vasculature-binding peptides and then coated onto the surface of mesenchymal stem cells (MSCs). In an <i>in vitro</i> model for blood vessel circulation, MSCs coated with the modified HPGs showed greater adhesion to inflamed endothelium than MSCs coated with unmodified HPGs. Next steps include assessing the ability of the HPG carrier to guide cells to target tissues <i>in vivo</i> . SciBX 6(20); doi:10.1038/scibx.2013.502 Published online May 23, 2013	Patent application filed; unavailable for licensing	Jeong, J.H. <i>et al. J. Am. Chem. Soc.</i> ; published online April 16, 2013; doi:10.1021/ja400636d Contact: Hyunjoon Kong, University of Illinois at Urbana-Champaign, Urbana, Ill. e-mail: hjkong06@illinois.edu
Drug platforms			
<i>N</i> -Glycosylation of Fc regions to improve antibody half-life and specificity	<i>In vitro</i> studies yielded a monomeric Fc fragment of IgG that could help extend antibody half-life and decrease off-target effects. <i>N</i> -Glycosylation of the IgG Fc fragment at two sites in the dimeric binding domain prevented dimerization, which could help decrease the risk of off-target effects caused by bivalent antibodies. In mice, a Fab fused with a tandem repeat of monomeric Fc fragments had a threefold longer half-life than a Fab fused with a single monomeric Fc fragment. Next steps could include designing therapeutic antibodies that incorporate monomeric Fc fragment repeats. SciBX 6(20); doi:10.1038/scibx.2013.503 Published online May 23, 2013	Patent and licensing status unavailable	Ishino, T. <i>et al. J. Biol. Chem.</i> ; published online April 24, 2013; doi:10.1074/jbc.M113.457689 Contact: Tetsuya Ishino, Pfizer Inc., Cambridge, Mass. e-mail: tetsuya.ishino@pfizer.com
Scaffolds with endothelial cell cords to promote vascularization of tissue transplants	Mouse studies suggest scaffolds containing cords made of endothelial cells could help improve tissue transplant outcomes. Cords that consist of a cylindrical segment of endothelial cells that surround a collagen core were generated and embedded within a fibrin scaffold. In mice, fat pad implantation of a scaffold containing the endothelial cell cords led to greater vascularization of the scaffold than implantation of a similar scaffold with randomly organized endothelial cells. In mice, transplantation of scaffolds containing the endothelial cell cords plus hepatocytes resulted in increased tissue vascularization and hepatocyte functionality compared with transplantation of scaffolds with randomly organized endothelial cells or hepatocytes alone. Next steps could include testing the patterned scaffolds in additional transplantation models. SciBX 6(20); doi:10.1038/scibx.2013.504 Published online May 23, 2013	Patent application filed; licensed to an undisclosed company	Baranski, J.D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 22, 2013; doi:10.1073/pnas.1217796110 Contact: Christopher S. Chen, University of Pennsylvania, Philadelphia, Pa. e-mail: chrischen@seas.upenn.edu
Markers			
Adrenomedullin (ADM; AM) and calcitonin receptor-like (CRLR; CALCRL) levels to diagnose preeclampsia	Mouse studies suggest monitoring levels of ADM or its receptor, CRLR, could enable early diagnosis of preeclampsia in pregnant women. In mice, placentas of <i>Adm</i> - or <i>Crlr</i> -deficient mouse fetuses showed less remodeling of vasculature and greater recruitment of maternal uterine NK cells, which are features of preeclampsia, than placentas of wild-type mouse fetuses. In maternal uterine NK cells from normal mice, <i>Adm</i> increased the secretion of cytokines, chemokines and metalloproteases involved in remodeling of placental vasculature compared with no treatment. Planned studies include investigating serum ADM as a marker of preeclampsia in pregnant women (<i>see Revisiting adrenomedullin in preeclampsia, page 5</i>). SciBX 6(20); doi:10.1038/scibx.2013.505 Published online May 23, 2013	Unpatented; unlicensed; <i>Adm</i> -deficient mouse models available for partnering	Li, M. <i>et al. J. Clin. Invest.</i> ; published online May 1, 2013; doi:10.1172/JCI67039 Contact: Kathleen M. Caron, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, N.C. e-mail: kathleen_caron@med.unc.edu
Classification system for endometrial cancers	<i>In vitro</i> studies were used to develop a classification system for endometrial cancers that could help guide treatment regimens for patients after initial therapy. Endometrial cancers are traditionally divided into the endometrioid and serous subtypes, with favorable and poor prognoses, respectively. In 373 samples from patients who have endometrial carcinoma, genome, proteome and transcriptome analyses were used to subdivide the cancers into four categories based on high or low levels of somatic copy number variants (CNVs), mutation status of DNA-directed DNA polymerase ϵ (POLE) and microsatellite instability. Genetic analysis showed that high somatic CNVs correlated with a poor prognosis independent of subtype classification. Next steps could include determining whether there is a relationship between the identified disease subtypes and treatment response. SciBX 6(20); doi:10.1038/scibx.2013.506 Published online May 23, 2013	Patent and licensing status unavailable	Cancer Genome Atlas Research Network. <i>Nature</i> ; published online May 1, 2013; doi:10.1038/nature12113 Contact: Douglas A. Levine, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: levine2@mskcc.org

Company and institution index

A	
Acetylon Pharmaceuticals Inc.	14
Amgen Inc.	1
Arisaph Pharmaceuticals Inc.	12
Astellas Pharma Inc.	1
C	
California Institute for Regenerative Medicine	7
Cellular Dynamics International Inc.	7
Chugai Pharmaceutical Co. Ltd.	11
D	
Daiichi Sankyo Co. Ltd.	3
Duke University Medical Center	5
E	
Eli Lilly and Co.	1
G	
Genentech Inc.	11
Glenveigh Medical LLC	5
H	
Hebrew University of Jerusalem	1
I	
iPierian Inc.	7
J	
Johnson & Johnson	10
L	
Li Ka Shing Foundation	4
M	
McGill University	3
Merck & Co. Inc.	10
Meytav Technological Incubator	3
N	
New York Stem Cell Foundation	7
NovoTyr Therapeutics Ltd.	1,13
O	
Office of the Chief Scientist in the Ministry of Economy	3
OncoSynergy Inc.	11
Oregon Health & Science University	7
Oregon National Primate Research Center	7
P	
Pfizer Inc.	1,16
R	
Regents of the University of California	11
Roche	3,11
S	
SGC Oxford	4
Structural Genomics Consortium	4
T	
Taiho Pharmaceutical Co. Ltd.	10
Takeda Pharmaceutical Co. Ltd.	1,10

Teva Pharmaceutical Industries Ltd.	3
Thermo Fisher Scientific Inc.	6
U	
UK Biobank	4
University of Minnesota Masonic Cancer Center	3
University of Minnesota Medical School	3
University of North Carolina at Chapel Hill	5
University of North Carolina at Chapel Hill School of Medicine	5
University of Oxford	4
University of Tennessee College of Medicine Chattanooga	5
V	
Vantia Therapeutics Ltd.	12
W	
Weizmann Institute of Science	12
Y	
Yeda Research and Development Co. Ltd.	12

Target and compound index

A	
ADM	5,17
Adrenomedullin	5,17
AKT	3
AKT1	3
AM	5,17
AMG 479	1
AML1-ETO oncogenic fusion protein	10
Aromatase	11
ASP7487	1
Avastin	11
B	
β -Site APP-cleaving enzyme 1	16
BACE1	16
Bevacizumab	11
Boronic acid	12
Bortezomib	10
BRAF	3,13
C	
Calcitonin receptor-like	5,17
CALCRL	5,17
CD8	13
CD29	11
CD71	16
CD221	1,13
Cixutumumab	1
COX-2	10
CP-751,871	1
CP-751871	1
CRLR	5,17
Cyclooxygenase-2	10
D	
Dipeptidyl peptidase	12
DNA-directed DNA polymerase ϵ	17

DPP	12
E	
EGFR2	12
ErbB2	12
ERK-1	2
ERK-2	2
Estrogen receptor	11
F	
FAP	12
FCGR	16
Fc γ -receptor	16
Fibroblast activation protein	12
Figitumumab	1
FRAP	3
G	
Ganitumab	1
H	
HDAC	10
HDAC1	14
HDAC2	14
Heat shock protein 90	12
HER2	12
Histone deacetylase	10
Histone deacetylase 2	14
Hsp90	12
I	
IGF-1	1
IGF1R	1,13
IMC-A12	1
Indazole	12
INSR	3
Insulin-like growth factor-1	1
Insulin-like growth factor-1 receptor	1,13
Insulin receptor	3
Insulin receptor substrate 1	1,13
Insulin receptor substrate 2	1
Integrin β_1	11
IRS1	1,13
IRS2	1,13
J	
JMJD2B	12
K	
KDM4B	12
Kdr/Flk-1	16
L	
Linsitinib	1
Lipopolysaccharide	15
LPS	15
Lysine-specific demethylase 4B	12
M	
Mammalian target of rapamycin	3
MAPK1	2
MAPK3	2
MAP kinase 1	2
MPS1	12
mTOR	3
N	
Neu	12
NR2C2	14
Nuclear receptor subfamily 2 group C member 2	14
O	
OS2966	11
P	
Paclitaxel	16
Phosphoinositide-3 kinase	11
PI3K	11
PKB	3
PKBA	3
PLX4032	3
POLE	17
PREP	12
Prolyl endopeptidase	12
Proteasome	10
Protein kinase B	3
Protein tyrosine phosphatase 1B	16
PTP-1B	16
PTPN1	16
R	
RAFT1	3
Receptor tyrosine kinase	1,16
Regulator of G-protein signaling 4	14
RET	11
Ret proto-oncogene	11
RGS4	14
Ribosomal protein S6 kinase 90 kDa polypeptide 2	11
RPS6KA2	11
RPS6KA6	11
RSK3	11
RSK4	11
RTK	16
S	
Src	3
Sunitinib	16
Sutent	16
T	
T cell receptor	13
TCR	13
Telomerase reverse transcriptase	13
TERT	13
TFR	16
TFRC	16
TR4	14
Transferrin receptor protein 1	16
TTK	12
TTK protein kinase	12
Tubulin	13
V	
VA999260	12
VEGF	11
Vegfr-2	16
Vegf receptor 2	16
Velcade	10
Vemurafenib	3
Vorinostat	10
Z	
Zelboraf	3
Zolanza	10