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mAb about FGF21

By Chris Cain, Senior Writer

Amgen Inc. has developed an antibody that mimics fibroblast growth factor 21 and has antidiabetic effects in monkeys.¹ The findings cap a year of advances that have greatly increased understanding of the protein's tissue-specific actions, and work from groups including **Eli Lilly and Co.** and **Roche's Genentech Inc.** unit is informing drug development by at least six companies.

Fibroblast growth factor 21 (FGF21) is a secreted metabolic regulator that improves insulin sensitivity, induces weight loss and lowers levels of blood glucose, triglycerides and low-density lipoproteins (LDLs) when injected in mice and monkeys.

Eli Lilly scientists were the first to describe these functions in 2005 for the protein,² and the results prompted widespread industry interest in the therapeutic potential of targeting the FGF21 pathway to treat type 2 diabetes and obesity.

David Moller, VP of endocrine and cardiovascular research and clinical investigation at Eli Lilly, told *SciBX* that the potential to simultaneously treat multiple type 2 diabetes symptoms is the driving force behind pharma interest in FGF21.

"One of our major strategic goals is to find a way to treat the underlying disease pathophysiology in a way that can yield multiple beneficial effects. That's what is exciting about the FGF21 pathway—there is nothing else, practically speaking, that has the same effect."

Despite the enticing functions, multiple hurdles have slowed the development of drugs targeting the FGF21 pathway.³ Native FGF21 is not suitable as a drug because of its short half-life. Development of drugs that mimic FGF21 function has been difficult because the precise receptors, cell types and downstream mechanisms responsible for the protein's beneficial effects need to be worked out.

Junichiro Sonoda, a scientist at Genentech, told *SciBX* that these unanswered questions spurred intense industry and academic study of the pathway. "One thing that really excites people about FGF21 is this novel biology. Nobody knows exactly how FGF21 does all these fantastic things," he said.

A breakthrough in understanding came in 2007, when a team at **The University of Texas Southwestern Medical Center** identified the transmembrane protein klotho- β (KLB) as a co-receptor required for FGF21 function.⁴ However, KLB pairs with multiple fibroblast growth

"If you can target the FGF21 pathway in a tissue-specific way, I think you would have a drug."

—David Mangelsdorf,
The University of Texas
Southwestern Medical Center

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factor receptors (FGFRs), and it was unclear which receptor complex was required for FGF21's antidiabetic effects.

Now, Amgen and Genentech have built the case that FGFR 1c isoform (FGFR1c) and KLB is the key complex and have shown antibodies designed to agonize the target can mimic FGF21's therapeutic effect. Together with academic studies describing essential pathways downstream of the receptor, a clearer picture of FGF21 function has emerged that suggests a possible path forward to tap into FGF21's therapeutic potential (see Figure 1, "FGF21 gets detailed").

Getting specific

The biotechs bookended 2012 with two separate studies published in *Science Translational Medicine* that described distinct FGF21-mimicking antibodies.

The first study was published in December 2011 by a Genentech team led by Sonoda.⁵ The researchers identified an antibody that could bind to and agonize FGFR1 (CD331) and tested it in a mouse model of diabetes. The antibody lowered blood glucose compared with IgG control for up to a month after a single injection and also caused weight loss.

The effect was likely mediated by the antibody's action on adipose tissue, as mice genetically engineered to lack the tissue did not show a reduction in blood glucose when injected with the antibody.

Sonoda told SciBX that it was a surprise that targeting FGFR1 alone could cause such significant antidiabetic effects. "We knew FGF21 acts through the liver, adipose tissue and potentially the pancreas, and FGF receptors were expressed in different patterns in each tissue. It was really a surprise that we could get this dramatic effect just by activating FGFR1 and not other FGF21 targets."

Despite the promising efficacy, Genentech is not pursuing further development of this antibody. Sonoda said the molecule binds FGFR1 but is not specific for the FGFR1c and KLB complex, and widespread activation of a major growth factor receptor could cause unpredictable side effects. Indeed, the antibody caused a reduction in serum phosphate levels in mice.

Instead of targeting FGF1R directly, Sonoda said the company would pursue the pathway by specifically targeting FGFR1c and KLB.

Less than 12 months later, a team at Amgen has published results showing the feasibility of doing exactly that.¹ By screening against the FGFR1c and KLB complex, the company identified an antibody that specifically agonized FGFR1c and KLB but not FGFR1c alone. In diabetic monkeys, the antibody caused weight loss and decreased blood glucose and triglyceride levels compared with vehicle control. The antibody had no significant effect on serum phosphate levels.

To advance the argument that the FGFR1c and KLB complex in adipose tissue is responsible for these effects, the team showed that FGF21 no longer reduced blood glucose levels when administered to tissue-specific FGFR1 knockout mice. These findings were in line with a study published by Eli Lilly in August 2012.⁶

"It was a surprise that this antibody could activate a complex receptor structure. This has never been seen before—there have been descriptions of agonistic antibodies, but in this case it is a receptor complex. This is a special antibody, and a major takeaway from the paper is that it opens up our eyes in terms of thinking about what antibodies can do," said Yang Li, the scientist at Amgen who led the team.

Amgen has filed a patent covering antibodies targeting KLB and

Figure 1. FGF21 gets detailed. Researchers from **Amgen Inc.** and **Roche's Genentech Inc.** unit have separately published studies that suggest using antibodies to mimic fibroblast growth factor 21 (FGF21) action could help treat metabolic diseases, including type 2 diabetes and obesity.

In addition, separate teams at **Eli Lilly and Co., Harvard Medical School** and **The University of Texas Southwestern Medical Center** have elucidated downstream cellular functions that help explain how FGF21 exerts its antidiabetic effects.

In adipose tissue, FGF21 binds to and activates an FGF receptor 1c isoform (FGFR1c) and klotho- β (KLB) complex [a]. This triggers a signaling cascade that leads to activation of peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ) and PPARG coactivator 1 α (PPARGC1A; PGC-1 α) [b]. These transcriptional regulators then act to upregulate downstream targets that trigger uptake of glucose, browning of white adipose tissue, induction of thermogenesis and increases in oxidative metabolism [c].

In obese monkeys, an Amgen antibody designed to specifically activate the FGFR1c and KLB complex mimicked the antidiabetic actions of FGF21. In mice, adipocyte-specific deletion of *Fgfr1c* blocked the blood glucose-lowering effects of Fgf21 compared with no deletion. Together, these results suggest that targeting the FGFR1c and KLB complex in adipocytes is primarily responsible for the therapeutic action of FGF21.

FGFRs, and the company said that it is evaluating data from the current study and has not yet determined next steps.

Safety signals

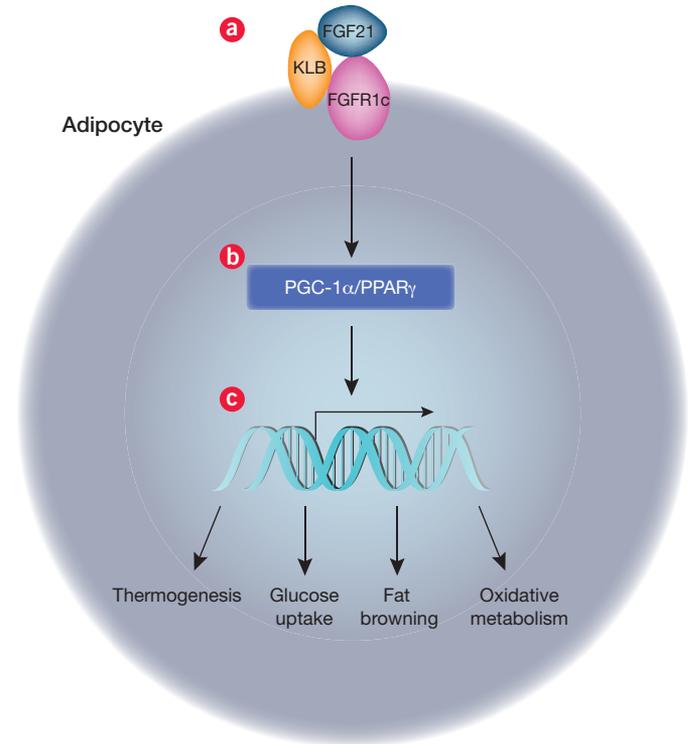
Although the companies have shown proof of concept that antibodies can mimic the positive metabolic effects of FGF21, additional studies published in 2012 identified potential FGF21-mediated side effects that will need to be monitored.

Last February, a team at UT Southwestern Medical Center led by David Mangelsdorf and Steven Kliewer published papers in *Cell* and the *Proceedings of the National Academy of Sciences* that showed FGF21 can cause severe bone loss in mice.^{7,8} The authors traced this effect to peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ), which they found is activated by FGF21.

Mangelsdorf told *SciBX* that these safety concerns are particularly worrisome given the potential chronic administration of a diabetes drug. "This is not an acute condition; these are hormones or compounds that you will put into people for a long, long time, so the safety bar is a lot higher," he said. "FGF21 has some substantial side effects. The bone effect is really pronounced. It may also suppress female reproduction, and there are going to be others."

Mangelsdorf is chair of the Department of Pharmacology at UT Southwestern Medical Center and an investigator of the **Howard Hughes Medical Institute**. Kliewer is a professor of pharmacology at UT Southwestern Medical Center. He said his results argue against developing long-acting forms of FGF21.

Long-acting derivatives of FGF21 have been developed by multiple companies. **Ambrx Inc.** and partner **Bristol-Myers Squibb Co.** have ARX618, a pegylated form of FGF21, in preclinical development.⁹ Amgen also has published work describing a long-acting FGF21



analog, and **Novo Nordisk A/S** and Eli Lilly have filed patents covering composition of matter on FGF21 derivatives.¹⁰

Mangelsdorf said he sees more promise in the targeted approach presented by the Amgen team. "If you can target the FGF21 pathway in a tissue-specific way, I think you would have a drug," he said. He added that he would like to see the tissue-specific effect of an FGFR1c and KLB antibody examined in more detail in mouse models.

Jasbir Sehra, CSO at **Ember Therapeutics Inc.**, agreed that tissue-specific targeting may be key to exploiting the tissue-specific effects of FGF21.

"While this may be particular to mice, the potential for bone loss in humans will need to be closely monitored in clinical studies. FGFR is expressed on cells in many tissues, but KLB shows a restricted expression pattern in the pancreas, liver and adipose tissue. In principle, an agonist antibody may be safer with limited side effects because it targets only the tissues that express KLB," he said.

Sehra said Ember is evaluating the FGF21 pathway for therapeutics that could induce brown fat-like properties, including increased glucose uptake and energy expenditure. Earlier this year, FGF21 was shown by a team at **Harvard Medical School** to induce the browning of white adipose tissue by activating the metabolic transcription factor PPARG coactivator 1 α (PPARGC1A; PGC-1 α).¹¹

Mangelsdorf said this may explain how FGF21 is exerting its positive effects on metabolism. "FGF21 is normally a starvation-induced hormone—it is a cry from the body for energy. If you look at how it works in obese individuals, it acts on adipose tissue to increase energy expenditure by stimulating glucose uptake and inducing a thermogenic response."

Mangelsdorf's team is continuing to uncover new physiological effects of FGF21. In October 2012, his team showed that mice engineered

to constitutively overexpress FGF21 lived about 33% longer than wild-type mice, though these mice suffer bone loss and females are infertile.¹² The team is now trying to understand pathways downstream of FGF21 that cause this effect on aging.

Genentech's Sonoda said that the advances made in the last year are critical for translating FGF21 to the clinic. "Every company that is working on this pathway has to be aware of these findings. It is not clear to me yet whether this approach would eliminate the safety liability of targeting the FGF21 pathway, but this is something we will need to work out with specific molecules."

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COMPANIES AND INSTITUTIONS MENTIONED

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DUX4 partnership

By Lauren Martz, Staff Writer

Researchers at the **Fred Hutchinson Cancer Research Center** have identified a mutation that induces expression of the transcription factor *double homeobox 4* and could be targeted in facioscapulohumeral muscular dystrophy.¹ Based on this and previous research, the team has partnered with **GlaxoSmithKline plc** to develop small molecule inhibitors against this target, or its downstream effectors, to treat the disease.

The collaboration is the company's third partnership as part of the Discovery Partnerships with Academia program and the first with a U.S.-based institution.

Facioscapulohumeral muscular dystrophy (FSHD) is an inherited disease that causes muscle weakness and loss of function beginning in the muscles of the face and upper extremities. Although researchers have started to uncover FSHD's genetic causes and underlying mechanisms, there are no approved therapeutics to treat or even slow disease progression.

In 2009, a Fred Hutchinson group led by Stephen Tapscott found that mutations causing expression of *double homeobox 4 (DUX4)* mRNA and protein in skeletal muscle tissues could be responsible for FSHD pathology.² DUX4 is a transcription factor that normally is expressed in germline tissues and repressed in somatic tissues.

Tapscott, a member of the Division of Human Biology at Fred Hutchinson and professor of neurology at the **University of Washington**, built on work from a group at **Leiden University**. In 1990, the Leiden team mapped FSHD to a mutation in chromosome 4q.³ Three years later, the same group found that the mutation caused a reduction in the number of *D4Z4* macrosatellite repeat units in the subtelomere of the chromosome.⁴

Whereas healthy individuals express 11–100 unit repeats of *D4Z4*, patients with FSHD express 1–10.

The Hutchinson team showed that *D4Z4* represses transcription of *DUX4* in somatic tissues of healthy controls. When fewer *D4Z4* repeats are expressed than normal—as is the case in most patients with FSHD—*DUX4* repression is lower than that in healthy individuals, leading to decreased levels of *DUX4* mRNA and protein expression in skeletal muscle.

In the current paper, published in late 2012, the team found that a mutation in *structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1)* decreased epigenetic repression of *DUX4* in somatic tissues compared with no mutation and thus helped cause the disease.

Tapscott and his team identified mutations in *SMCHD1* that reduce protein levels and cause *D4Z4* CpG hypomethylation. They found that a subset of patients with FSHD, classified as patients with FSHD2, carry mutations in *SMCHD1* that cause *DUX4* expression despite normal numbers of *D4Z4* repeat units.

Data were published in *Nature Genetics*.

Prior to this study, Tapscott and colleagues also used *in vitro* models of FSHD based on their mechanistic data in order to examine the link between DUX4 expression and disease pathology. Indeed, expression of DUX4 in the FSHD model upregulated genes involved in RNA processing, ubiquitin pathways and immunity.⁵ These upregulated genes could be new targets to help treat the disease.

GSK collaboration

Based on the new mechanistic insights, the next steps for the Hutchinson team are to choose the best target and develop a therapeutic. To do so, Tapscott partnered with GSK under the pharma's first Discovery Partnerships with Academia (DPAc) collaboration with a U.S.-based institution.

DPAc started in 2011 and involves partnerships with academic researchers to develop early stage projects and facilitate their translation to the clinic by combining academic expertise with GSK's drug discovery and development capabilities.

Under the DPAc agreements, GSK provides financial support for a project based on the achievement of milestones, and the academics are eligible for royalties.

GSK already has formed DPAc collaborations with academics from the

“We know many of the genes regulated by DUX4, and they suggest different possible mechanisms for the disease. Future work will need to determine which of the candidate mechanisms are dominant contributors to the disease phenotype, and those could be targeted individually.”

—Stephen Tapscott,
Fred Hutchinson Cancer Research Center

University of Cambridge and the **University of Dundee**.

Tapscott's team will work with GSK to identify new small molecule therapeutics for FSHD. He told *SciBX* that they will be testing both direct inhibitors of DUX4 and inhibitors of the transcription factor's downstream targets.

“We know many of the genes regulated by DUX4, and they suggest different possible mechanisms for the disease. Future work will need to determine which of the candidate mechanisms are dominant contributors to the disease phenotype, and those could be targeted individually,” he said.

Tapscott said a therapeutic that blocks DUX4 or its downstream targets should be able to treat most, if not all, patients with FSHD. “These are the only known genetic causes for the condition, and we know that while there may be other causal factors, these mutations account for the vast majority of cases,” he said.

He added, “It is also important to note that both *DUX4* and *SMCHD1* mutations are involved in the same pathway, so if there is another mutation responsible for the disease, it would also most likely be expressed in this pathway. These patients should also respond to a drug developed to block the pathway.”

Additionally, Tapscott said, “inhibitors of DUX4 should prevent disease progression if our model of the disease is correct.” He said that the patent status of the work and any development timelines are undisclosed. GSK declined to comment.

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Targeting inflammation in AD

By Lev Osherovich, Senior Writer

German researchers have implicated the inflammasome, an intracellular sensor of proinflammatory signaling, as a key player in Alzheimer's disease.¹ The findings provide additional evidence that Alzheimer's disease could be treated with anti-inflammatory agents that act upstream of β -amyloid deposition.

The accumulation of β -amyloid ($A\beta$) is thought to underlie the neurodegeneration at the heart of AD, and as a result most efforts to treat the disease have focused on directly blocking $A\beta$ production or the accumulation of $A\beta$ plaques.

Although the central role of $A\beta$ in AD is widely accepted, Michael Heneka, professor of clinical neuroscience at the **University of Bonn**, said academic researchers observed in the 1980s "that people in advanced age either have plaques or plaques plus inflammation."

However, it was unclear whether brain inflammation is a cause or consequence of AD. "Inflammation has really been the stepchild of the AD field. People would laugh and say that inflammation is a complete bystander that is secondary to disease," Heneka said.

Now, Heneka's team has found that AD progression in mice requires the Nlr family pyrin domain containing 3 (Nlrp3; Nalp3) inflammasome. The team showed that Nalp3 inflammasome activity was essential for the accumulation of dysfunctional microglia, the brain's innate immune cells, at AD lesions.

If NALP3-mediated inflammation is indeed a key player in AD-associated inflammation, "we now know what is the motor of disease and how to stop it," said Heneka.

Prince Casp1

Heneka's team hypothesized that $A\beta$ aggregates trigger proinflammatory signaling. Thus, the group tested whether known players in inflammation were active in the brains of patients with AD. Indeed, postmortem brain tissue from patients with AD and AD model mice had higher levels of IL-1 β -converting enzyme (CASP1), a protease that activates proinflammatory cytokines, than tissue from healthy controls.

The team then tested whether the NALP3 inflammasome, which activates CASP1, also played a role in AD. Indeed, AD model mice lacking either *Nalp3* or *Casp1* performed similarly to non-AD controls in a range of neurophysiological and behavioral assays for AD-associated neurological dysfunction.

Nalp3 and *Casp1* knockouts also had lower levels of $A\beta$, suggesting that proinflammatory signaling affected either production or accumulation of amyloid plaques.

Heneka suspected this reduction of $A\beta$ might relate to changes in the behavior of microglia. Indeed, microglia from *Nalp3* or *Casp1* knockout AD model mice were more effective at ingesting and disposing of $A\beta$

aggregates than microglia from wild-type AD mice. Microglia from *Nalp3*-deficient AD mice had biomarkers that indicated a productive, short-lived inflammatory response, whereas microglia from wild-type AD mice had markers associated with chronic inflammation.

Altogether, Heneka's findings suggest that chronic activation of the NALP3 inflammasome in AD leads to abnormally aggressive microglia that are unable to ingest and break up $A\beta$ aggregates and instead secrete neuron-killing proinflammatory cytokines and proteases.

Results were reported in *Nature*.

Nalp help

The findings argue that blocking some combination of NALP3 and its downstream effectors could be useful for treating AD. More work is needed to identify which target in this pathway would be most suitable for early intervention in AD.

Heneka is skeptical about whether blocking any steps in this pathway would be useful in patients with advanced disease and instead thinks that anti-inflammatory therapy could be useful in slowing progression of early forms of AD such as mild cognitive impairment (MCI).

"I have a hard time imagining that any of these targets would be suitable for acute treatment, but if we initiate anti-inflammatory treatment at early stages of disease, this could prevent or delay disease," he said.

Heneka is collaborating with some of his coauthors to screen for brain-penetrating NALP3 inhibitors. He cautioned that mouse studies suggest the lack of *Nalp3* could compromise innate immunity and increase susceptibility to bacterial pathogens, so hitting this pathway might elicit side effects.

It also remains unclear whether the NALP3 pathway relates to other recently discovered inflammatory players in AD. Last November, separate

teams at **deCode genetics ehf** and **University College London** identified genetic variants in the proinflammatory cell-surface receptor triggering receptor expressed on myeloid cells 2 (TREM2) that led to increased AD risk compared with that for noncarrier controls.^{2,3}

deCode is being acquired by **Amgen Inc.**

Also in November, Swiss and German researchers reported that blocking IL-12 or IL-23 signaling could reduce pathological microglial activity in AD.⁴

Heneka said that experiments are under way to clarify how the NALP3 inflammasome affects IL-12, IL-23 and TREM2 activity.

Although no companies are directly targeting NALP3 or CASP1 in AD, at least one biotech—**Transition Therapeutics Inc.**—has preclinical AD compounds that block proinflammatory mechanisms downstream of the inflammasome.

The results published in *Nature* are not patented.

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"Inflammation has really been the stepchild of the AD field. People would laugh and say that inflammation is a complete bystander that is secondary to disease."

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COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.

deCode genetics ehf, Reykjavik, Iceland

Transition Therapeutics Inc. (TSX:TTH; NASDAQ:TTHI), Toronto,
Ontario, Canada

University of Bonn, Bonn, Germany

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Scaling up iPS cells

By Joanne Kotz, Senior Editor

A Memorial Sloan-Kettering Cancer Center team has conducted one of the first large-scale screens of a small molecule library using patient-derived induced pluripotent stem cells.¹ The approach was applied to neuronal cells derived from patients with familial dysautonomia and provides early evidence of its potential for identifying new leads.

Separately, a public-private partnership led by Roche and the University of Oxford is aiming to establish a repository comprising 1,500 induced pluripotent stem (iPS) cells—triplicate samples from 500 patients with diabetes or a wide range of neurological diseases—in an effort to provide a tool for finding new targets and therapeutic leads.

Patient-derived iPS cells are generated by reprogramming skin fibroblasts. These cells can subsequently serve as the starting material for obtaining disease-relevant cell types through redifferentiation. The goal is to obtain cells from patients that will display phenotypes characteristic of the disease and thus can be used to explore disease mechanisms or screen for small molecules that reverse the disease phenotype.

“For the first time, we have human cells from patients and can differentiate them into different cell types in a dish. If we can identify disease-relevant phenotypes, this has huge potential,” said Martin Graf, head of the stem cell platform at Roche.

However, there are many practical challenges in using iPS cells to characterize disease, including identifying strong disease-associated phenotypes and patient-to-patient genetic variations.

For high throughput screening, there is the added need to have a large number of relatively pure cells and an assay that can be scaled up. Because it is difficult to conduct small molecule screens with iPS cells, initial screens to look for compounds that modulate a target or phenotype typically have been conducted with standard, non-patient-derived human cell lines.

“The challenge has been getting a population of cells at a sufficient purity and scale that behaves well in plates. There is often a lot of heterogeneity when people try to differentiate iPS cells,” said Lorenz Studer, director of the Center for Stem Cell Biology and member of the Developmental Biology Program at Memorial Sloan-Kettering.

In 2009, Studer led a team that generated iPS cells from patients with familial dysautonomia, a rare and fatal peripheral neuropathy caused by a mutation in *IKBKAP* (*inhibitor of κ -light polypeptide gene enhancer in B cells kinase complex-associated protein*) that leads to incorrect gene splicing and reduced protein levels.²

When these iPS cells were differentiated into five cell types, *IKBKAP* expression was lowest in neural crest precursors, which suggested an explanation for the tissue specificity of the disease and provided a disease phenotype for high throughput screening.

Now, Studer’s team has screened about 7,000 small molecules to look for compounds that increase expression of *IKBKAP* in patient-derived neural crest precursors.

Eight hits were further characterized, with all of them boosting

IKBKAP expression more potently in neural crest precursors than in the parent iPS cells or in the same iPS cells differentiated into fibroblasts or lymphoblasts. This result suggests it may be important to screen for therapeutic leads in the appropriate genetic disease background and also in the relevant cell type.

One of the top screening hits was the research compound SKF-86466, an adrenergic receptor α_2 (ADRA2) antagonist.

Results were published in *Nature Biotechnology*.

“This is an excellent example of why screening in cells from patients can be important,” said Stephen Haggarty. “It turns out that none of these compounds significantly increased *IKBKAP* expression in cells from healthy controls. Finding these hits required the specific genotype relevant to the disease” and benefitted from use of iPS cells that were differentiated to disease-relevant neural crest cells.

Haggarty is an assistant professor of neurology at Harvard Medical School, director of neuropharmacology for the Massachusetts General Hospital psychiatry center for experimental drugs and diagnostics and a senior associate member of the Broad Institute of MIT and Harvard.

Studer told *SciBX* that his team will now look in more detail at the mechanism of action for some of the other hits from the screen.

The researchers also have developed a protocol for making mature neurons to test whether the compounds work in the later neurodegenerative stages of the disease.

BANCC-ing on it

Separately, a European consortium is betting that patient-specific iPS cells will aid disease understanding and therapeutic discovery in a wide range of neurological diseases—peripheral and central, as well as monogenic and complex.

A public-private partnership dubbed StemBANCC will create a repository of 1,500 iPS cells, comprised of triplicate samples from 500 patients, over the next 5 years.

The partnership was announced in December and is being led by Roche and the University of Oxford. The consortium includes 23 academic institutions, 3 small- and medium-sized enterprises and 10 pharmas. StemBANCC has a 5-year budget of €55.6 million (\$72.6 million), which includes €26 million (\$34 million) from the Innovative Medicines Initiative and €21 million (\$27.4 million) of in-kind contributions from pharma partners.

Graf, who is coordinator for the StemBANCC project at Roche, said the pharma has existing academic collaborations around stem cells, for instance one with Harvard Medical School and MGH and another with Boston Children’s Hospital. Each of these deals has generated iPS cells from about 20 patients.

“This consortium is something completely different. We are talking about 500 patients. We could hardly undertake such a big project on our own,” he said.

StemBANCC will focus on neuropathic pain, neurodegenerative diseases and psychiatric diseases. The project also will generate iPS cells from patients with diabetes.

Zameel Cader, a group leader in the division of clinical neurology at University of Oxford and the academic coordinator of StemBANCC,

“For the first time, we have human cells from patients and can differentiate them into different cell types in a dish. If we can identify disease-relevant phenotypes, this has huge potential.”

—Martin Graf,
Roche

said the partnership is focusing on neurological diseases because these are “very hard-to-treat conditions where access to relevant tissue is difficult and where pharmas have been turning away.”

In addition to banking the iPS cells, the consortium will look for molecular and cellular abnormalities that correlate with disease. “Within each disease we’ll stratify and focus on monogenic disorders first to ‘cut our teeth’ before moving on to more complex disorders,” said Cader.

All of the iPS cell lines, along with accompanying profiling data, will be made publicly available over the course of the program.

Cader said that after disease phenotypes are identified, high throughput screens could be run during later stages of the program and will “almost certainly be undertaken principally within pharmas.” Any resulting compounds and IP would rest with the project partner, added Graf.

Screen play

A key unknown is whether sufficiently strong and reproducible phenotypes can be identified for more complex neurological diseases.

Graf said recent work has shown *in vitro* phenotypes in iPS cell-derived neural cells from, for example, patients with schizophrenia or Alzheimer’s disease (AD). However, he noted that “if you go into detail, many phenotypes are relatively weak at this stage. We need to have much more robust and reproducible models because we would like to be able to do high throughput screens of more than a million compounds. I am fully convinced in some cases this will be a game changer. In other cases we may not be able to find a robust phenotype.”

Studer said finding a compelling phenotype is just one of the major challenges. “We have iPS cell-based models of Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and others, but none is ready for a screen,” he said. “For PD, there are phenotypes, but they are pretty subtle in my opinion—and on top of that there is heterogeneity and on top of that you need to get to pretty mature neurons to get a phenotype.”

“For many disorders like PD, we can’t make enough sufficiently pure and large enough quantities of the relevant subtypes of neurons at the moment,” agreed Haggerty. “But that is likely going to change very quickly as investigators learn to direct differentiation toward defined lineages using a variety of emerging techniques. The bigger issue will be reproducibility across patients and understanding precise genotype-phenotype correlations.”

Studer noted a last caveat: “Many neurodegenerative disorders are late onset. How do you model a late-onset disease in a dish? How do you get a cell to behave like an 80-year-old neuron?”

The results published in *Nature Biotechnology* have not been patented.

Kotz, J. *SciBX* 6(1); doi:10.1038/scibx.2013.4

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2. Lee, G. *et al. Nature* 461, 402–406 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

Boston Children’s Hospital, Boston, Mass.

Broad Institute of MIT and Harvard, Cambridge, Mass.

Harvard Medical School, Boston, Mass.

Innovative Medicines Initiative, Brussels, Belgium

Massachusetts General Hospital, Boston, Mass.

Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

University of Oxford, Oxford, U.K.

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				
Cancer	Sirtuin 6 (SIRT6)	<p>Patient tissue and mouse studies suggest activating SIRT6 could help modulate tumor metabolism to treat cancer. In cancer patient data from The Cancer Genome Atlas, <i>SIRT6</i> was deleted in 20% of all cancers. In a genetic mouse model of colorectal adenomatosis, <i>Sirt6</i> deletion in the intestines increased the frequency, size and invasiveness of adenomas compared with no deletion. In that model, the <i>Sirt6</i> deletion also increased glucose uptake and glycolytic gene expression in tumors. Next steps include screening studies to identify molecules that activate SIRT6.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.5 Published online Jan. 10, 2013</p>	Unpatented; licensing status not applicable	<p>Sebastián, C. <i>et al. Cell</i>; published online Dec. 7, 2012; doi:10.1016/j.cell.2012.10.047 Contact: Raul Mostoslavsky, Massachusetts General Hospital and Harvard Medical School, Boston, Mass. e-mail: rmostoslavsky@mg.harvard.edu Contact: David B. Lombard, University of Michigan, Ann Arbor, Mich. e-mail: davidlom@umich.edu</p>
Colorectal cancer	β-Catenin (CTNNB1); yes-associated protein 1 (YAP1); v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1 (YES1; Yes)	<p>Studies in cancer cell lines suggest inhibiting YES1 could help treat CTNNB1-driven colon cancers. In a panel of colon cancer cell lines with high CTNNB1 activity, YAP1 knockdown decreased proliferation compared with no knockdown. In CTNNB1-driven colon cancer cell lines, knockdown of YES1, which phosphorylates YAP1 to regulate its transcriptional activity, or nonspecific inhibition of YES1 with Sprycel dasatinib decreased proliferation compared with no knockdown or inhibition. Next steps include designing clinical studies to test whether inhibiting YES1 has a therapeutic benefit and setting up screens to identify YES1 inhibitors.</p> <p>Bristol-Myers Squibb Co. markets Sprycel to treat acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML).</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.6 Published online Jan. 10, 2013</p>	Patent application filed; available for licensing	<p>Rosenbluh, J. <i>et al. Cell</i>; published online Dec. 13, 2012; doi:10.1016/j.cell.2012.11.026 Contact: William C. Hahn, Dana-Farber Cancer Institute, Boston, Mass. e-mail: william_hahn@dfci.harvard.edu</p>
Diffuse large B cell lymphoma (DLBCL)	Enhancer of zeste homolog 2 (EZH2)	<p><i>In vitro</i> studies identified an EZH2 inhibitor that could help treat DLBCL. <i>In vitro</i>, the lead compound EI1 inhibited EZH2 with an IC₅₀ value of about 10 nM and about 90-fold specificity for EZH2 over the related enzyme EZH1. In DLBCL cell lines carrying mutant <i>EZH2</i>, EI1 inhibited cell growth at low micromolar concentrations. Next steps could include additional preclinical studies of EI1 in mouse models of cancer.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.7 Published online Jan. 10, 2013</p>	Patent and licensing status undisclosed	<p>Qi, W. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 10, 2012; doi:10.1073/pnas.1210371110 Contact: En Li, Novartis Institutes for BioMedical Research, Shanghai, China e-mail: en.li@novartis.com</p>
Leukemia	Myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX); WD repeat domain 5 (WDR5)	<p><i>In vitro</i> studies identified inhibitors of the protein-protein interaction between WDR5 and MLL protein-protein interactions that could help treat leukemias. In an enzymatic assay, peptide inhibitors of the MLL binding site on WDR5 blocked MLL's H3K4 methyltransferase activity. In leukemia cells with MLL fusion protein expression, the most potent peptide inhibitor blocked cell growth in leukemia cells with MLL fusion protein expression but not in leukemia cells expressing wild-type MLL. Next steps include improving the cellular potency and <i>in vivo</i> properties of the inhibitor peptides.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.8 Published online Jan. 10, 2013</p>	Patent applications filed; licensed by Ascentage Pharma Group Corp. Ltd.; available for partnerships	<p>Karatas, H. <i>et al. J. Am. Chem. Soc.</i>; published online Dec. 4, 2012; doi:10.1021/ja306028q Contact: Shaomeng Wang, University of Michigan, Ann Arbor, Mich. e-mail: shaomeng@umich.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Neurofibromatosis	Neurofibromin 1 (NF1); MEK	Two studies in mice suggest MEK inhibitors could help treat cancers with mutations in <i>NF1</i> . In a mouse model of neurofibromatosis type 1, a familial cancer in which mutations in <i>NF1</i> increase the risk of juvenile myelomonocytic leukemia, the MEK inhibitor PD-0325901 decreased blood leukocyte counts and spleen size and increased survival compared with vehicle. In the second study, PD-0325901 decreased the size of neurofibromas and increased survival compared with vehicle in a patient xenograft mouse model of neurofibromatosis type 1. Next steps could include clinical trials of MEK inhibitors in patients with neurofibrosis type 1.	Patent and licensing status unavailable for both papers	Chang, T. <i>et al. J. Clin. Invest.</i> ; published online Dec. 10, 2012; doi:10.1172/JCI63193 Contact: Kevin Shannon, University of California, San Francisco, Calif. e-mail: shannonk@peds.ucsf.edu
		Pfizer Inc.'s combination of PD-0325901 and PF-04691502 is in Phase I testing in cancer. At least seven other companies have MEK inhibitors in clinical testing for various cancers. SciBX 6(1); doi:10.1038/scibx.2013.9 Published online Jan. 10, 2013		Jessen, W.J. <i>et al. J. Clin. Invest.</i> ; published online Dec. 10, 2012; doi:10.1172/JCI60578 Contact: Nancy Ratner, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio e-mail: nancy.ratner@cchmc.org
Pancreatic cancer	DNA methyltransferase	<i>In vitro</i> and mouse studies suggest hypomethylating agents could help treat pancreatic ductal adenocarcinoma (PDAC). In a mouse model of aggressive, stroma-rich PDAC, the demethylating agent Dacogen decitabine decreased tumor burden and increased survival compared with vehicle control. Next steps include testing Dacogen plus therapeutic cytokines and immunotherapy. Astex Pharmaceuticals Inc., Eisai Co. Ltd. and Johnson & Johnson market Dacogen, a DNA methyltransferase inhibitor, to treat acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). SciBX 6(1); doi:10.1038/scibx.2013.10 Published online Jan. 10, 2013	Patent and licensing status unavailable	Shakya, R. <i>et al. Cancer Res.</i> ; published online Nov. 29, 2012; doi:10.1158/0008-5472.CAN-12-1880 Contact: Benjamin Tycko, Columbia University, New York, N.Y. e-mail: bt12@columbia.edu
Prostate cancer	Enhancer of zeste homolog 2 (EZH2); protein kinase B (PKB; PKBA; AKT; AKT1)	Cell culture studies suggest inhibiting the histone methyltransferase EZH2 could help treat prostate cancer. In androgen-independent prostate cancer cells, EZH2 methyltransferase activity and AKT-dependent phosphorylation of EZH2 were required for activation of target genes associated with castration-resistant disease. Next steps could include designing EZH2 inhibitors that block enzymatic activity and prevent AKT-mediated activation or testing the AKT plus EZH2 inhibitors in preclinical models of androgen-independent prostate cancer. SciBX 6(1); doi:10.1038/scibx.2013.11 Published online Jan. 10, 2013	Patent and licensing status undisclosed	Xu, K. <i>et al. Science</i> ; published online Dec. 14, 2012; doi:10.1126/science.1227604 Contact: Myles Brown, Dana-Farber Cancer Institute, Boston, Mass. e-mail: myles_brown@dfci.harvard.edu Contact: X. Shirley Liu, same affiliation as above e-mail: xslu@jimmy.harvard.edu
Cardiovascular disease				
Ischemia/reperfusion injury	Sirtuin 2 (SIRT2)	Mouse studies suggest inhibiting SIRT2 could help treat ischemia/reperfusion injury. In a mouse model of ischemia/reperfusion injury, <i>Sirt2</i> knockout or an inhibitor of SIRT2 decreased necrosis and infarct size compared with no knockout or vehicle. Next steps include determining the time frame during which SIRT2 inhibitors have a therapeutic benefit in ischemia and testing whether modulating necrosis via SIRT2 inhibition could have benefit in other indications, such as neurodegenerative diseases. Indus Biotech Pte. Ltd.'s SIRT2 inhibitor INDUS815B is in preclinical development for Parkinson's disease (PD) and renal disease. The company also has the SIRT2 inhibitor INDUS815C in discovery for Huntington's disease (HD) and ophthalmic indications. SciBX 6(1); doi:10.1038/scibx.2013.12 Published online Jan. 10, 2013	Patent application filed; available for licensing or partnering	Narayan, N. <i>et al. Nature</i> ; published online Nov. 28, 2012; doi:10.1038/nature11700 Contact: Toren Finkel, National Institutes of Health, Bethesda, Md. e-mail: finkelt@nih.gov
Endocrine/metabolic disease				

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Diabetes	G protein-coupled receptor 119 (GPR119)	<p>Mouse studies identified a series of indolines that act as selective GPR119 agonists and could help treat type 2 diabetes. In mouse islets, a lead indoline-based GPR119 agonist increased glucose-stimulated insulin secretion compared with vehicle. In mice, the agonist increased insulin secretion in response to glucose and decreased gastric emptying without altering food intake compared with vehicle control. GlaxoSmithKline plc did not disclose next steps, which could include testing the agonist in additional diabetes models.</p> <p>At least five companies have GPR119 agonists in clinical and preclinical testing to treat diabetes.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.13 Published online Jan. 10, 2013</p>	Patent and licensing status undisclosed	<p>Katamreddy, S.R. <i>et al. J. Med. Chem.</i>; published online Dec. 5, 2012; doi:10.1021/jm301404a Contact: Andrew J. Carpenter, GlaxoSmithKline Research & Development, Research Triangle Park, N.C. e-mail: andrew.j.carpenter@gsk.com</p>
Infectious disease				
Infectious disease	Protozoan signal peptide peptidase (SPP)	<p>Cell culture studies suggest inhibiting protozoan SPP could help treat parasitic infections. <i>In vitro</i>, a small molecule protozoan SPP inhibitor blocked growth of three different parasites with nanomolar IC₅₀ values without inhibiting host cell growth. Next steps include identifying additional SPP inhibitors in collaboration with the Novartis Institute for Tropical Diseases and evaluating the compounds in mouse models.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.14 Published online Jan. 10, 2013</p>	Unpatented; licensing status not applicable	<p>Harbut, M.B. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 11, 2012; doi:10.1073/pnas.1216016110 Contact: Doron C. Greenbaum, University of Pennsylvania, Philadelphia, Pa. e-mail: dorong@upenn.edu</p>
<i>Staphylococcus</i>	CC chemokine receptor 5 (CCR5; CD195)	<p>Cell culture and mouse studies suggest inhibiting CCR5 could help treat <i>Staphylococcus aureus</i> infections. <i>In vitro</i>, <i>S. aureus</i> leukotoxin killed CCR5-expressing cell lines. The effect was blocked with multiple small molecule CCR5 antagonists. In a model of <i>S. aureus</i> systemic infection, <i>Ccr5</i> knockout mice had lower bacterial load and greater survival than wild-type mice. Next steps include developing animal models that can monitor the efficacy of CCR5 antagonists.</p> <p>Pfizer Inc. markets the CCR5 antagonist Selzentry maraviroc to treat HIV/AIDS.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.15 Published online Jan. 10, 2013</p>	Patent application filed; licensing status undisclosed	<p>Alonzo, F. III <i>et al. Nature</i>; published online Dec. 12, 2012; doi:10.1038/nature11724 Contact: Victor J. Torres, New York University School of Medicine, New York, N.Y. e-mail: victor.torres@nyumc.org</p>
Musculoskeletal disease				
Duchenne muscular dystrophy (DMD)	Dystrophin (DMD)	<p><i>In vitro</i> and mouse studies suggest the ryanodine receptor (RyR) inhibitor dantrolene could enhance the effects of antisense oligonucleotides to treat Duchenne muscular dystrophy. In primary human and mouse muscle cells with disease-associated <i>DMD</i> mutations, dantrolene increased the exon-skipping effect of antisense oligonucleotides compared with vehicle control. In the <i>mdx</i> mouse model of Duchenne muscular dystrophy, dantrolene plus antisense oligonucleotides increased <i>DMD</i> expression and muscle function compared with the antisense alone or antisense plus vehicle. Next steps include dose-optimization studies of the combination therapy.</p> <p>Prosensa B.V. and GlaxoSmithKline plc have PRO51, an antisense oligonucleotide that induces the skipping of exon 51 of <i>DMD</i>, in Phase III trials to treat Duchenne muscular dystrophy.</p> <p>Sarepta Therapeutics Inc. has eteplirsen, a phosphorodiamidate morpholino oligomer (PMO) targeting exon 51, in Phase IIb testing to treat Duchenne muscular dystrophy.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.16 Published online Jan. 10, 2013</p>	Patents pending; licensing status undisclosed	<p>Kendall, G.C. <i>et al. Sci. Transl. Med.</i>; published online Dec. 12, 2012; doi:10.1126/scitranslmed.3005054 Contact: M. Carrie Miceli, University of California, Los Angeles, Calif. e-mail: cmiceli@ucla.edu Contact: Stanley F. Nelson, same affiliation as above e-mail: snelson@ucla.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Muscular atrophy	Transient receptor potential vanilloid 1 (TRPV1; VR1)	<i>In vitro</i> and mouse studies suggest activating TRPV1 in skeletal muscle could help treat or prevent muscular atrophy. In mice, mechanical and functional overload of muscles caused Trpv1 activation and led to muscular hypertrophy. In the mice subjected to muscle overload, the TRPV1 activator capsaicin increased muscle weight and fiber length compared with vehicle. In a mouse model of muscular atrophy, the TRPV1 activator capsaicin prevented muscle weight loss and decreases in fiber length. Next steps could include identifying a muscle-specific TRPV1 activator. NeurogesX Inc. and Astellas Pharma Inc. market Qutenza, a dermal patch containing capsaicin, to manage neuropathic pain associated with postherpetic neuralgia (PHN). NeurogesX's NGX-1998, a topical liquid formulation of synthetic capsaicin, is in Phase II testing for the same indication. SciBX 6(1); doi:10.1038/scibx.2013.17 Published online Jan. 10, 2013	Patent and licensing status unavailable	Ito, N. <i>et al. Nat. Med.</i> ; published online Dec. 2, 2012; doi:10.1038/nm.3019 Contact: Shin'ichi Takeda, National Center of Neurology and Psychiatry, Kodaira, Japan e-mail: takeda@ncnp.go.jp
Osteoporosis	MicroRNA-214 (miR-214)	<i>In vitro</i> and mouse studies suggest inhibiting miR-214 could help treat osteoporosis. In mouse preosteoblast cells, an anti-miR-214 antagomir increased mineral deposits, whereas a miR-214 mimic decreased deposits. In a mouse model of ovariectomy-induced osteoporosis, osteoblast-specific antagomir-214 increased bone mineral density, bone-to-tissue volume ratios and expression of activating transcription factor 4 (Atf4), which is required for osteoblast function, compared with an antagomir control or vehicle. Next steps include identifying a small molecule inhibitor of miR-214 activity. SciBX 6(1); doi:10.1038/scibx.2013.18 Published online Jan. 10, 2013	Patent and licensing status unavailable	Wang, X. <i>et al. Nat. Med.</i> ; published online Dec. 9, 2012; doi:10.1038/nm.3026 Contact: Yingxian Li, China Astronaut Research and Training Center, Beijing, China e-mail: yingxianli@yahoo.cn Contact: Ge Zhang, Hong Kong Baptist University, Hong Kong, China e-mail: zhangge@hkbu.edu.hk
Neurology				
Ataxia	GABA _A receptor	<i>In vitro</i> and mouse studies suggest GABA _A receptor agonists could help treat motor dysfunctions associated with Angelman syndrome, a neurogenetic disorder caused by deletion or inactivation of genes on chromosome 15. In a mouse model of Angelman syndrome, the GABA _A receptor agonist gaboxadol restored normal signaling in cerebellar brain slices and reversed cerebellar ataxia. Next steps include testing the effects of gaboxadol on other brain functions. Merck & Co. Inc. and H. Lundbeck A/S discontinued development of gaboxadol in insomnia after Phase III trials showed that the molecule's profile did not support further development. At least 13 companies have GABA _A agonists in development stages ranging from preclinical to marketed for various neurological indications. SciBX 6(1); doi:10.1038/scibx.2013.19 Published online Jan. 10, 2013	Unpatented; unavailable for licensing	Egawa, K. <i>et al. Sci. Transl. Med.</i> ; published online Dec. 5, 2012; doi:10.1126/scitranslmed.3004655 Contact: Atsuo Fukuda, Hamamatsu University School of Medicine, Hamamatsu, Japan e-mail: axfukuda@hama-med.ac.jp Contact: Kiyoshi Egawa, Massachusetts General Hospital, Boston, Mass. e-mail: cdh67560@par.odn.ne.jp
Neurology	Inhibitor of κ-light polypeptide gene enhancer in B cells kinase complex-associated protein (IKBKAP); adrenergic receptor α ₂ (ADRA2)	A study in neural cells derived from patients with familial dysautonomia (FD) suggests antagonizing ADRA2 could help treat the disease. FD is caused by a mutation in <i>IKBKAP</i> that leads to incorrect splicing and a reduction in IKBKAP protein levels. In neural crest precursors from patient-derived induced pluripotent stem cells, a screen of about 7,000 small molecules identified 43 hits that increased expression of <i>IKBKAP</i> compared with vehicle. Seven of these hits, including a selective ADRA2 antagonist, were further validated in cell culture experiments. Next steps include investigating the mechanism of action for additional screening hits (<i>see Scaling up iPS cells, page 9</i>). SciBX 6(1); doi:10.1038/scibx.2013.20 Published online Jan. 10, 2013	Unpatented; licensing status not applicable	Lee, G. <i>et al. Nat. Biotechnol.</i> ; published online Nov. 25, 2012; doi:10.1038/nbt.2435 Contact: Lorenz Studer, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: studerl@mskcc.org Contact: Gabsang Lee, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: glee48@jhmi.edu

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology	Unknown	<p>Mouse studies suggest lithium could help treat Down syndrome. In a mouse model of Down syndrome, chronic treatment with the generic mood stabilizer lithium restored hippocampal neurogenesis to levels that were comparable to those in wild-type controls and promoted proliferation of neural precursor cells. In the lithium-treated mice, compared with saline-treated mice, restoration of neurogenesis increased performance on behavioral and memory tests. Next steps include clinical testing of lithium.</p> <p>SciBX 6(1); doi:10.1038/scibx.2013.21 Published online Jan. 10, 2013</p>	Unpatented; licensing status not applicable	<p>Contestabile, A. <i>et al. J. Clin. Invest.</i>; published online Dec. 3, 2012; doi:10.1172/JCI64650 Contact: Laura Gasparini, Italian Institute of Technology, Genoa, Italy e-mail: laura.gasparini@iit.it</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
Assays & screens			
Assays to monitor leucine-rich repeat kinase 2 (LRRK2) activity	Cell-based and pharmacodynamic assays for monitoring LRRK2 activity could help identify compounds to treat Parkinson's disease (PD). The assays were designed to detect autophosphorylation at the Ser ¹²⁹¹ residue of the LRRK2 protein, which has been linked to PD. In a screening study using the assays, the diaminopyrimidine-based compound G1023 was identified as an inhibitor of LRRK2 autophosphorylation with an IC ₅₀ value below 10 nM. In hippocampal neurons from mice carrying PD-associated mutations in <i>Lrrk2</i> , G1023 decreased neurite outgrowth defects compared with vehicle control. Next steps include studies to determine whether blocking LRRK2 activity in mice could reverse the onset and progression of PD. SciBX 6(1); doi:10.1038/scibx.2013.22 Published online Jan. 10, 2013	Patent applications filed; licensing status undisclosed	Sheng, Z. <i>et al. Sci. Transl. Med.</i> ; published online Dec. 12, 2012; doi:10.1126/scitranslmed.3004485 Contact: Haitao Zhu, Genentech Inc., South San Francisco, Calif. e-mail: zhu.haitao@gene.com Contact: Donald S. Kirkpatrick, same affiliation as above e-mail: kirkpatrick.donald@gene.com
Chemistry			
Natural product-based fragment libraries for ligand discovery	Natural product-based fragment libraries could be used to identify ligands against targets that are difficult to drug. A computational analysis of 180,000 natural products identified 2,000 structurally varied fragments that were largely distinct from the molecules found in current fragment libraries. Screening about 200 natural product-based fragments led to the identification of ligands for 4 phosphatases for which inhibitor development had previously been difficult. Next steps could include optimizing inhibitors against these phosphatase targets or screening natural product-based fragment libraries against additional targets. SciBX 6(1); doi:10.1038/scibx.2013.23 Published online Jan. 10, 2013	Unpatented; licensing status not applicable	Over, B. <i>et al. Nat. Chem.</i> ; published online Dec. 2, 2012; doi:10.1038/nchem.1506 Contact: Herbert Waldmann, Max Planck Institute of Molecular Physiology, Dortmund, Germany e-mail: herbert.waldmann@mpi-dortmund.mpg.de
Drug delivery			
Glycosylated triterpene-mediated transdermal delivery of macromolecules	<i>Ex vivo</i> studies suggest glycosylated triterpenes are capable of transdermal transport and could help mediate therapeutic macromolecule delivery. In porcine skin, glycosylated triterpenes (avicins) isolated from the desert plant <i>Acacia victoriae</i> were transported across the skin. In this model, coadministration of avicins with estradiol, dextran or insulin increased transdermal delivery compared with saline control administration. Next steps include designing molecules based on the avicin structure to act as chaperones for macromolecule delivery. SciBX 6(1); doi:10.1038/scibx.2013.24 Published online Jan. 10, 2013	Patent application filed; available for licensing	Pino, C.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 10, 2012; doi:10.1073/pnas.1200942109 Contact: V. Prasad Shastri, Vanderbilt University, Nashville, Tenn. e-mail: prasad.shastri@gmail.com
Imaging			
Probe for functional imaging of legumain (LGMN)	An activity-based fluorescent probe could be used to study the activity of LGMN, a protein associated with cancer and inflammation. The probe is designed to fluoresce after binding covalently to the active form of LGMN. In human monocyte and cancer cell lines, the probe identified different patterns of LGMN activation in response to cytokine stimulation. In a mouse xenograft model of human colorectal cancer, tail vein injection of the probe led to a detectable fluorescence signal at the tumor periphery within 30 minutes and maximum signal contrast between normal and tumor tissues at 7 hours. Next steps include testing the probe in additional models of cancer and inflammation and evaluating the probe's toxicity. SciBX 6(1); doi:10.1038/scibx.2013.25 Published online Jan. 10, 2013	Patent application filed; licensed to Akrotome Imaging Inc.	Edgington, L.E. <i>et al. J. Am. Chem. Soc.</i> ; published online Dec. 8, 2012; doi:10.1021/ja307083b Contact: Matthew Bogyo, Stanford University School of Medicine, Stanford, Calif. e-mail: mbogyo@stanford.edu

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