

THIS WEEK

ANALYSIS

COVER STORY

1 Interfacing with Ras

A German team has identified a compound that disrupts a protein-protein interaction that localizes K-Ras to the cell membrane, thus selectively inhibiting tumor growth. The interface provides a new small molecule binding site for the handful of companies and academics working on ways to tackle the previously undruggable Ras family.

TARGETS & MECHANISMS

5 Rationalizing CF combos

A McGill University–led team has shown that CFTR corrector compounds target only one of two sequential steps required for proper folding of the mutated protein. The findings suggest there is a clear rationale for developing combinations of correctors to treat patients with cystic fibrosis.

7 FGF9 for baldness

A University of Pennsylvania team has found that increasing FGF9 levels in wounded skin can promote the growth of hair follicles in mice. Follica has licensed the findings and plans to test the effects of FGF9 in hair growth indications.

TOOLS

9 Transferring flu protection

Two independent studies provide proof of concept that gene transfer could be used to establish broad protection against influenza. Both groups are working to move their influenza A virus hemagglutinin–expressing vectors into humans.

THE DISTILLERY

11 This week in therapeutics

Treating IBD and psoriasis by selectively inhibiting TYK2; alleviating ischemia/reperfusion injury with C3AR agonists; preventing epileptic seizures with SEMA4D-Fc; and more...

16 This week in techniques

A microchip platform to model heart failure; peptidyl arginine deiminase type III autoantibodies as prognostic markers for rheumatoid arthritis; mAb antagonists of glucose-dependent insulinotropic polypeptide receptor; and more...

INDEXES

18 Company and institution index**18 Target and compound index**

Interfacing with Ras

By Amy Donner, Senior Editor

A German team has identified a compound that disrupts a protein-protein interaction that localizes K-Ras to the cell membrane, thus inhibiting tumor growth.¹ The interface provides a new small molecule binding site for the handful of companies and academics working on ways to tackle the previously undruggable Ras family.

Ras proteins are molecular switches that control cell growth and proliferation. Mutations and other mechanisms that aberrantly activate Ras signaling can promote tumorigenesis.

Collectively, mutations in genes encoding the three Ras isoforms—K-Ras, v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS) or neuroblastoma Ras viral (v-Ras) oncogene (NRAS)—occur in nearly 20% of all cancers.

K-Ras is by far the most commonly mutated isoform, with activating mutations occurring in about 80% of pancreatic cancers.

“If one is diagnosed with pancreatic cancer based on a mutation in *K-Ras*, the life expectancy is months. And there is hardly anything the doctors can do,” said Herbert Waldmann, professor of chemistry and managing director at the **Max Planck Institute of Molecular Physiology**.

“K-Ras is a particularly important driver in pancreatic cancer. This is essentially an untreatable cancer—there is a huge unmet clinical need,” added John Hancock, integrative biology and pharmacology chair and professor at **The University of Texas Health Science Center at Houston**.

Until 2012, nobody had been able to target any form of Ras with a small molecule because the proteins lacked well-defined surface pockets suitable for binding drug molecules (*see Box 1, “A complex question”*).

Last year, independent teams at **Roche’s Genentech Inc.** unit and the **Vanderbilt University School of Medicine** identified small molecules that disrupted Ras, but the compounds were not potent and were not tested against oncogenic Ras.^{2–4}

In April, a **Kobe University** team developed small molecule inhibitors of wild-type and oncogenic forms of Ras, but the compounds were far from drug-like in terms of potency.^{5,6}

Now, a German team has overcome these shortcomings by targeting a distinct protein-protein interface that modulates oncogenic K-Ras activity.

K-Ras activation depends on its localization at the plasma membrane. Farnesyl protein transferases add a lipid modification called a prenyl group to the C-terminal end of K-Ras, which anchors K-Ras to the membrane. The phosphodiesterase δ subunit (PDE δ), a prenyl-binding protein, binds lipid-modified Ras and delivers it to the plasma membrane.⁷

With that mechanism in mind, Waldmann, Philippe Bastiaens and

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Alfred Wittinghofer led a structure-based initiative to identify small molecules that bind to PDE δ and disrupt its interaction with K-Ras. The goal was to delocalize K-Ras from the plasma membrane and inhibit its activity.

Bastiaens is professor of systemic cell biology at the Max Planck Institute of Molecular Physiology, and Wittinghofer is professor emeritus at the institute.

A high throughput screen identified small molecules that bound to the prenyl-binding pocket of PDE δ . The screen yielded several hits with a shared chemical scaffold. After validating these hits in secondary, *in vitro* PDE δ -binding assays, the scientists solved the crystal structure of PDE δ in complex with several compounds.

Using the cocrystal structures as guides, the team modified the initial hits to optimize interaction with and affinity for PDE δ . For cellular studies the group selected one compound—deltarasin—that bound PDE δ with a K_d of 38 nM *in vitro* but did not interact with off-target prenyl-binding proteins.

In cultured cells, deltarasin disrupted PDE δ -K-Ras interactions. Deltarasin delocalized K-Ras from the plasma membrane in pancreatic ductal adenocarcinoma cell lines. The molecule also produced dose-dependent decreases in oncogenic K-Ras-driven proliferation and signaling compared with vehicle in pancreatic cancer cell lines. In xenograft mouse models, deltarasin abrogated oncogenic K-Ras-driven pancreatic tumor growth.

“Within the next two years we are going to profile and optimize several compound series, including deltarasin and analogs, to generate a lead package.”

—Thomas Hegendörfer,
Lead Discovery Center GmbH

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Box 1. A complex question.

Whereas German researchers have uncovered a way to target K-Ras, a team from Texas has shown that a prior approach of disrupting Ras interactions with rho guanine nucleotide exchange factors (ARHGGEFs; GEFs) may be more clinically relevant than previously believed.

GEFs such as son of sevenless homolog 1 (SOS1) catalyze the rate-limiting step in Ras activation. They promote the dissociation of GDP so GTP can bind and reactivate Ras. Two groups, one from **Roche's Genentech Inc.** unit and the other from the **Vanderbilt University School of Medicine**, independently reported compounds that act via Ras-GDP to disrupt the Ras-SOS1 interface and block Ras activation.

Nevertheless, other researchers had questioned whether blocking the Ras-GDP complex would be an effective therapeutic strategy because oncogenic Ras mutants are locked in a GTP-bound conformation, rendering them constitutively active. The expectation was that these mutants could be insensitive to small molecules that act via the GDP-bound conformation.

Now, John Hancock and Alemayehu Gorfe have shown that this is not exactly the case.⁹

Hancock is integrative biology and pharmacology chairman and professor at **The University of Texas Health Science Center at Houston**. Gorfe is assistant professor of integrative biology and pharmacology at the university.

In cells cultured for six hours, the team's inhibitors of Ras-GDP did not block oncogenic Ras signaling. However, when incubation periods were prolonged to three days, the compounds decreased oncogenic Ras signaling and oncogenic K-Ras-driven proliferation of multiple cancer cell lines compared with vehicle.

According to Hancock, these prolonged assays demonstrate that "GTP turnover is slow—not absent—so exchange

activity is still inhibited. Therefore, this study shows that blocking exchange factor interaction is a viable approach to inhibiting oncogenic mutant Ras function."

The research was published in the *Proceedings of the National Academy of Sciences*. The team also included scientists from the **University of Putra Malaysia**.

Hancock said, "It is very hard to predict which of the different approaches to inhibit Ras will be most successful. Inhibiting Ras at multiple

levels will likely be the way to go. As we have learned from kinase inhibitors, we need to use two, possibly three drugs to achieve maximal inhibition at the lowest levels of toxicity."

Hancock and Gorfe declined to disclose the patent and licensing status of their work. —AD

"It is very hard to predict which of the different approaches to inhibit Ras will be most successful. Inhibiting Ras at multiple levels will likely be the way to go."

—John Hancock,
The University of Texas Health
Science Center at Houston

Results were published in *Nature*. The team also included scientists from **Ruhr University Bochum**.

Building momentum against Ras

Waldmann said a drug discovery project based on deltarasin is ongoing at the **Lead Discovery Center GmbH**, which is the drug discovery arm of the **Max Planck Society**.⁸

"Within the next two years we are going to profile and optimize several compound series, including deltarasin and analogs, to generate a lead package," said Thomas Hegendörfer, head of business development at Lead Discovery Center.

Hegendörfer said projects usually start to attract interest from industry after showing efficacy in therapeutically relevant animal models. In the case of deltarasin, however, he said there are already pharma suitors.

One reason for the early interest, said Waldmann, is that deltarasin is more potent than other reported Ras inhibitors. "It also differentiates between wild-type- and K-Ras-dependent cell lines," he said. "The target is entirely novel."

The deltarasin compound class is patented by the Max Planck Society and will be available for licensing from **Max Planck Innovation GmbH**.

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Kobe University, Kobe, Japan

Lead Discovery Center GmbH, Dortmund, Germany

Max Planck Innovation GmbH, Munich, Germany

Max Planck Institute of Molecular Physiology, Dortmund, Germany

Max Planck Society, Munich, Germany

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

Ruhr University Bochum, Bochum, Germany

University of Putra Malaysia, Selangor, Malaysia

The University of Texas Health Science Center at Houston, Houston, Texas

Vanderbilt University School of Medicine, Nashville, Tenn.

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Rationalizing CF combos

By Chris Cain, Senior Writer

A McGill University–led team has shown that Vertex Pharmaceuticals Inc.'s lumacaftor and other cystic fibrosis transmembrane conductance regulator corrector compounds target only one of two sequential steps required for proper folding of the mutated protein.¹ The findings suggest there is a clear rationale for developing combinations of correctors to treat patients with cystic fibrosis, three of which have been detailed at recent scientific meetings.

Cystic fibrosis is caused by mutations that reduce the function of cystic fibrosis transmembrane conductance regulator (CFTR), an anion channel that helps keep the lung and intestinal epithelium hydrated and prevents mucous buildup that leads to airway obstruction and infection.

Kalydeco ivacaftor (VX-770), a small molecule CFTR potentiator from Vertex that increases chloride transport through the channel, is the only marketed disease-modifying treatment for CF. The drug was approved in January 2012 and is indicated to treat only the 4% of patients with CF that have the *G551D CFTR* gating mutation, which decreases ion transport through the channel but does not impair its localization to the cell surface.

About two-thirds of patients with CF inherit a different mutation, the $\Delta F508$ CFTR allele, which encodes for a misfolded version of the protein that is degraded and does not reach the surface of the cell. Because Kalydeco can only improve the function of CFTR that reaches the cell surface, corrector compounds are needed to repair the folding defect caused by the $\Delta F508$ mutation.

Two correctors are in clinical development. Lumacaftor (VX-809) is in Phase III testing in combination with Kalydeco to treat patients with $\Delta F508$ CFTR. VX-661, a compound in the same chemical class as lumacaftor, is in Phase II testing in the same population.

In separate Phase II trials, lumacaftor or VX-661 in combination with Kalydeco significantly increased lung function compared with placebo. The Kalydeco-lumacaftor combination has received breakthrough therapy designation from the FDA.

However, *in vitro* studies have suggested that combining Kalydeco plus lumacaftor can at best restore up to about 25% of CFTR function, leaving open the question of whether further correction of CFTR folding could lead to additional clinical improvements for patients with CF.²

Last year two groups, one led by McGill researchers and one from The University of Texas Southwestern Medical Center, used a combination of biophysical studies and mutational analyses to show that restoring normal function to $\Delta F508$ CFTR requires correcting two distinct folding steps.^{3,4} The first step consists of the folding of CFTR's nucleotide binding domain 1 (NBD1), in which F508 is located, and the second step concerns the proper folding of CFTR through interactions between NBD1 and other distinct structural regions within CFTR.

“What is important is that it shows there are no compounds in the set people have been looking at that are effective at correcting the first step, namely NBD1 folding.”

—Philip Thomas,
The University of Texas
Southwestern Medical Center

The researchers involved in those studies told *SciBX* at the time that the next logical advance would be to use the knowledge to guide the identification of compounds that act on each step.⁵

Now, the McGill-led team has taken a step in that direction by providing the most complete analysis to date of the mechanisms of action for available corrector compounds.

The team, led by McGill professor of physiology Gergely Lukacs, took advantage of previously identified suppressor mutations that restore $\Delta F508$ CFTR function by correcting either of the two steps. Combining both sets of suppressor mutations leads to a synergistic and dramatic increase in $\Delta F508$ CFTR function, bringing it to wild-type CFTR levels.

Thus, by testing corrector compounds on $\Delta F508$ CFTR variants with suppressor mutations that correct one of the two steps, the researchers could deduce which folding step the compounds act upon.

In cell lines expressing $\Delta F508$ CFTR variants carrying suppressor mutations that improved NBD1 interaction with other regions of CFTR, lumacaftor and other corrector compounds increased the amount of $\Delta F508$ CFTR at the cell surface, but the total amount was still only about one-third of wild-type CFTR levels.

In cell lines expressing $\Delta F508$ CFTR variants carrying suppressor mutations that improved the folding of NBD1, the compounds restored $\Delta F508$ CFTR cell surface localization to levels comparable to those in wild-type cell lines. This suggested existing corrector compounds do not act to improve NBD1 folding but instead stabilize the interaction between NBD1 and other regions of CFTR.

To probe the mechanism of action for these corrector compounds in more detail, the authors performed *in vitro* experiments in which $\Delta F508$ CFTR variants were reconstituted in an artificial

lipid bilayer. In this assay, lumacaftor and a related compound directly acted on CFTR, and a combination of computational modeling, mutational analysis and biophysical experiments pinpointed the interface between NBD1, membrane spanning domain 1 (MSD1) and MSD2 as their likely site of action.

According to Lukacs, this is the most detailed public description of lumacaftor's mechanism of action to date and complements previously published work by Vertex. "Without photocrosslinkable variants in hand, we don't have absolute evidence of direct drug binding and its location. However, the artificial lipid bilayer study is the closest evidence we have that the compound is directly interacting," he said.

He added that this is in line with data published earlier this year by a group at The University of North Carolina at Chapel Hill School of Medicine that suggested the compound was acting to stabilize the interaction of NBD1 with other regions of CFTR.⁶

The McGill team went on to characterize additional correctors that are structurally unrelated to lumacaftor and found that some were in fact mechanistically distinct from the compound and likely stabilized interactions between the NBD1 and NBD2 regions of CFTR. No correctors repaired the NBD1 folding defect.

"It was disappointing that we did not find any compounds that corrected the folding defect in NBD1," said Lukacs.

Finally, the team tested how clinically relevant combinations of correctors could be developed by combining them with chemical chaperones that stabilize NBD1 folding, such as glycerol and myo-inositol. These chemical chaperones are not drug-like but served as tools to demonstrate proof of concept for functional $\Delta F508$ correction.

In cultured human bronchial cell lines and in a recently developed organoid model system,⁷ lumacaftor plus the chemical chaperones led to substantial increases in $\Delta F508$ CFTR function compared with either lumacaftor or chaperones alone. The effect was enhanced when a third compound was added that stabilized NBD1-NBD2 interactions, supporting the idea that multiple compounds that act on distinct folding steps could be combined to restore $\Delta F508$ function.

Results were published in *Nature Chemical Biology*.

Cocktail mixing

Philip Thomas, professor of physiology at UT Southwestern Medical Center and a cofounder of **Reata Pharmaceuticals Inc.**, told *SciBX* that the study was the natural follow-on to the two-step folding hypothesis described by his lab and the Lukacs lab last year.

"This work underlines what was in the two earlier papers in *Cell*, but what is important is that it shows there are no compounds in the set people have been looking at that are effective at correcting the first step, namely NBD1 folding," he said.

Fred Van Goor, head of biology for Vertex's CF research program, agreed with Thomas. "This is a follow-on to the earlier work that set the foundation by showing that just deleting F508 causes multiple structural defects. It provides a mechanistic rationale for why two CFTR correctors could be additive for each other."

Only one corrector of the NBD1 folding defect has been reported so far. According to Thomas, a screen carried out by Reata, with screening technology licensed from the UT Southwestern Medical Center and developed in Thomas' lab, identified a compound that corrected NBD1 folding and synergized with an analog of lumacaftor. Data were presented in March at the **European Cystic Fibrosis Society Basic Science Conference** by Andre Schmidt, a member of Thomas' lab. Reata did not respond to interview requests.

At last week's European Cystic Fibrosis Society Conference, Vertex presented data on a corrector that synergizes with Kalydeco and lumacaftor to improve chloride transport in $\Delta F508$ human bronchial epithelial cells. Vertex did not provide details of the development status or mechanism of action for this compound but said the company has an active research program to identify second-generation correctors for use in future combination regimens. Vertex also said it hopes to have a second-generation corrector in clinical development by the end of 2014.

Proteostasis Therapeutics Inc. has also disclosed data on small molecule proteostasis modulators that show that the compounds can synergize with lumacaftor to improve chloride transport in human bronchial epithelial cells. The data were presented at the 26th Annual North American Cystic Fibrosis Conference last October and the **EMBO** meeting on May 21. The compounds are currently in lead optimization.

Proteostasis' approach is distinct from that of the other companies in that it does not specifically target CFTR but rather goes after cellular protein trafficking mechanisms.

"Many of the current corrector approaches seek compounds directly interacting with CFTR itself. I think of them as molecular staples that

in some way enhance folding and/or correct a folding deficit that allows CFTR to pass some of its quality control checkpoints," said Peter Reinhart, president and CSO of Proteostasis.

According to Reinhart, his company has "a fundamentally different approach, which is to identify modulators of the cells' endogenous quality control machinery, which will ultimately handle CFTR by enhancing its folding and trafficking."

Last May, the **Cystic Fibrosis Foundation** announced it would collaborate with Proteostasis to develop therapies to treat patients with $\Delta F508$ CFTR. The foundation also is collaborating with Vertex, **Pfizer Inc.** and **Sanofi's Genzyme Corp.** unit. CFF, Pfizer and Sanofi did not respond to interview requests.

David Thomas, a professor in the Department of Biochemistry at McGill, told *SciBX* that the McGill work provides a template for characterizing compounds as they emerge from screening efforts. "You can think of it as a funnel. People have found lots of correctors, and now they have a nice way to identify which step they are involved in."

Thomas was not involved in the studies by Lukacs.

In 2011, Thomas and McGill University colleagues began collaborating with **GlaxoSmithKline plc** to characterize the functions of correctors identified in high throughput screens, and Thomas and John Hanrahan, professor of physiology at McGill, are developing some of the correctors from the screens. In addition, the pair have recently founded **Traffic Therapeutics Inc.** to develop CFTR correctors.

Earlier this year, GSK also began collaborating with a team at **The Hospital for Sick Children** and the **University of Toronto** to discover CFTR correctors.⁸

Lukacs said his lab now plans to identify compounds that act to correct the NBD1 folding defect in $\Delta F508$ CFTR using structural defect-targeted, new high throughput screening assays based on monitoring the channel's biochemical appearance at the cell surface.

He added that ultimately, additional structural information about CFTR will be needed to move the field beyond phenotypic screening and toward rational drug design.

"The interesting question is how we can rationally design correctors for NBD1 stabilization," he said. "What has been done is a random search, and to make the process more successful it should be more targeted than a random chemical library screen. The question is how best to do that."

Results from the study are not patented.

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(Continues on p. 7)

FGF9 for baldness

By Lauren Martz, Staff Writer

A **University of Pennsylvania** team has found that increasing fibroblast growth factor 9 levels in wounded skin can promote the growth of hair follicles in mice.¹ **Follica Inc.** has licensed the findings and plans to test the effects of the growth factor in hair growth indications.

Male pattern baldness, or androgenic alopecia, occurs when circulating hormones cause hair follicles to shrink and eventually stop producing hair. Treatments include Rogaine minoxidil from **Johnson & Johnson**, a vasodilator thought to increase nutrient supply to the follicles and prevent miniaturization, and Propecia finasteride from **Merck & Co. Inc.**, which converts testosterone to dihydrotestosterone.

Minoxidil needs to be applied twice a day and can actually cause hair loss in some patients. Finasteride's effects on hormone balance can lead to side effects such as loss of libido. Both molecules are indicated to prevent future hair loss but do not regrow lost hair.

An alternative to therapeutically inhibiting hair loss is hair transplantation, which involves relocating a patient's healthy follicles to sites of baldness. The procedure is the only approved method that actually replaces lost hair, but it is invasive and requires that a patient have some hair to transplant.

Also, the transplanted hairs remain subject to the same factors that caused follicle miniaturization in the first place, suggesting the solution is not permanent.

In a search for alternatives, George Cotsarelis and colleagues at the University of Pennsylvania have been studying the process in mice. In 2007, the team found that skin wounds in mice initiated the formation of new hair follicles, a process called hair follicle neogenesis, through upregulation of the wingless-type MMTV integration site (Wnt) pathway.²

Now, the researchers have zeroed in on fibroblast growth factor 9 (FGF9; GAF) as a key player in the process.

The group injured healthy adult mice and saw that new hair follicles began to form around day 14 post-injury. Gene expression profiling during the wound healing process showed that Fgf9 was upregulated just before new follicle formation.

In the same mouse model, injection of an FGF9-neutralizing antibody into the wounded skin decreased the number of new follicles compared with injection of an isotype-matched IgG control antibody. Adenovirus-mediated overexpression of Fgf9 increased new follicle formation compared with normal expression of Fgf9.

The team fluorescently labeled $\gamma\delta$ T cells, which are known to

produce Fgf9, and found that the immune cells accumulated at the wounds right before Fgf9 upregulation. Knockout of the T cell subset in the mice decreased new follicle growth. The effects were partially reversed by administration of exogenous Fgf9.

Finally, the group found that mouse fibroblasts at the wound sites expressed two receptors for Fgf9—the keratinocyte growth factor receptor (Kgf9; Fgfr2; Cd332) and fibroblast growth factor receptor 3 (Fgfr3; Cd333).

When activated by Fgf9, the receptors increased Wnt activity and transcript levels. The higher Wnt activation in turn increased Fgf9 expression on fibroblasts.

These studies suggest FGF9 produced by $\gamma\delta$ T cells initiates a feedback loop in wound fibroblasts that amplifies the signaling components required for follicle neogenesis (see Figure 1, "Wound-induced hair follicle neogenesis").

In human dermal samples, the $\gamma\delta$ T cells required to initiate the process were scarce, unlike in mouse skin. This finding potentially explains why humans do not undergo hair follicle neogenesis when wounded.

Results were published in *Nature Medicine*.

Cotsarelis told *SciBX* that the next steps for this research include testing the effects of FGF9 on human skin in xenograft models and then in the clinic.

Cotsarelis is chairman of dermatology at the **Perelman School of Medicine at the University of Pennsylvania**, director of the program on epithelial regeneration and stem cells at the University of Pennsylvania's Institute for Regenerative Medicine and director of the university's Hair and Scalp Clinic.

The paper also included researchers from the **Seoul National University College of Medicine**, the **New York University Langone Medical Center**, **Chungnam National University**, **Texas A&M University** and the **Washington University in St. Louis School of Medicine**.

Follica advancement

Follica plans to test FGF9 as a potential component of its follicle neogenesis technology.

The technology is a combination of a device that the company says removes the top layers of skin and undisclosed topical molecules that

"FGF9 modulation could be used in combination with skin disruption alone or in combination with skin disruption and other compounds."

—Bernat Olle,
Follica Inc.

(Continued from "Rationalizing CF combos," p. 6)

COMPANIES AND INSTITUTIONS MENTIONED

Cystic Fibrosis Foundation, Bethesda, Md.

EMBO, Heidelberg, Germany

European Cystic Fibrosis Society, Karup, Denmark

Genzyme Corp., Cambridge, Mass

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

The Hospital for Sick Children, Toronto, Ontario, Canada

McGill University, Montreal, Quebec, Canada

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Proteostasis Therapeutics Inc., Cambridge, Mass.

Reata Pharmaceuticals Inc., Irving, Texas

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

Traffic Therapeutics Inc., Montreal, Quebec, Canada

The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, N.C.

The University of Texas Southwestern Medical Center, Dallas, Texas

University of Toronto, Toronto, Ontario, Canada

Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Cambridge, Mass.

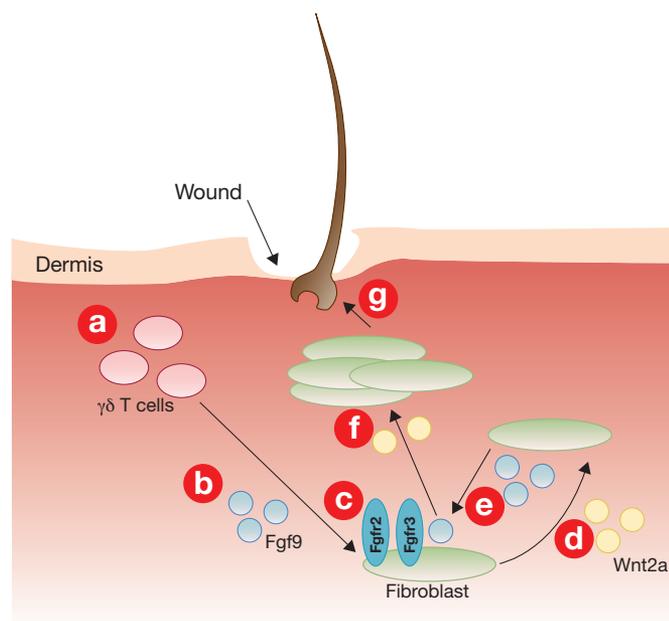


Figure 1. Wound-induced hair follicle neogenesis. In mice, skin wounds create an embryonic-like state in the surrounding cells that allows for the generation of new skin and hair follicles. The wounded dermis causes the recruitment of $\gamma\delta$ T cells to the site of injury [a]. The T cells produce fibroblast growth factor 9 (Fgf9; Gaf) [b], which binds to keratinocyte growth factor receptor (Kgfr; Fgfr2; Cd332) and fibroblast growth factor receptor 3 (Fgfr3; Cd333) [c]. This leads to the activation of Fgfr2 and Fgfr3 and production and activation of wntless-type MMTV integration site family member 2a (Wnt2; Wnt2a) [d]. The protein stimulates the production of Fgf9 by some fibroblasts to initiate a feedback loop to generate more activated Wnt2a [e]. Wnt2a then activates a signaling pathway that causes fibroblast proliferation [f] and dermis cell-fate determination to promote development of new hair follicles [g].

help regenerate hair follicles. The company says that the process is not very painful but the region can easily be numbed.

“Follica’s technology platform is based on Cotsarelis’ discovery that when skin is perturbed, some cells revert to a more basic state from which they can develop into either skin or hair follicles,” said cofounder Bernat Olle. “During a limited time window after the perturbation, these cells can be directed to form new hair follicles by modulating pathways involved in hair neogenesis with exogenous compounds.”

In a Phase IIa trial, the device and undisclosed molecules showed hair follicle neogenesis, according to the company. Further details were not disclosed.

“FGF9 modulation could be used in combination with skin disruption alone or in combination with skin disruption and other compounds,” said Olle.

Basil Hantash, founder, chairman and CEO of **Escape Therapeutics Inc.**,

said it is still unclear whether the mouse studies of Fgf9 will translate to humans.

“We know that mouse hair cycles differ from humans in numerous ways. The study would have to be performed in a human *ex vivo* hair model or in a human clinical trial,” he said.

Escape has human epidermal stem cells with hair growth capacity in preclinical development.

“Topical FGF9 would be catabolized readily in the skin,” noted Hantash. “Thus, delivering adequate sustained levels is not a simple task even if FGF9 maintains the same results in humans.”

Desmond Tobin, professor of cell biology and director of the Centre for Skin Sciences at the **University of Bradford**, wanted to know about the duration of effect for FGF9 modulation.

Tobin did acknowledge that hormone-induced miniaturization of hair follicles is a long process. Even if the new follicles are susceptible to the same processes, the treatment could be effective for some time, he said.

According to Luis Garza, assistant professor of dermatology at **The Johns Hopkins University School of Medicine**, “FGF9 will not treat the underlying cause of any specific hair disease. Its best use might be in burn scars, for example, where the trauma occurred in the past but is not an ongoing disease.”

Cotsarelis told *SciBX* that in the mouse, “new follicles that form behave like neonatal follicles. There may be a period of time when the new follicles do not respond to testosterone. The goal is to regenerate a large follicle and keep it that way.”

The University of Pennsylvania has filed a patent application covering the FGF9 work. Follica has licensed the approach and other IP from the group and has filed additional patents to protect the technology.

Martz, L. *SciBX* 6(24); doi:10.1038/scibx.2013.590
Published online June 20, 2013

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e-mail: cotsarel@mail.med.upenn.edu
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COMPANIES AND INSTITUTIONS MENTIONED

Chungnam National University, Daejeon, South Korea
Escape Therapeutics Inc., San Jose, Calif.
Follica Inc., Boston, Mass.
The Johns Hopkins University School of Medicine, Baltimore, Md.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
New York University Langone Medical Center, New York, N.Y.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa.
Seoul National University College of Medicine, Seoul, South Korea
Texas A&M University, College Station, Texas
University of Bradford, Bradford, U.K.
University of Pennsylvania, Philadelphia, Pa.
Washington University in St. Louis School of Medicine, St. Louis, Mo.

Transferring flu protection

By Tracey Baas, Senior Editor

Two independent teams have shown proof of concept that gene transfer could be used to establish broad protection against influenza A viruses.^{1,2} Both laboratories are working to move their influenza A virus hemagglutinin-expressing vectors into humans for immunogenicity and safety testing.

Despite the availability of flu vaccines, the morbidity and mortality associated with influenza A-triggered seasonal and pandemic flu outbreaks are still high. Multiple groups have identified broadly neutralizing antibodies that target a range of influenza virus types and immunotherapies based on such antibodies that could be used as prophylactics or as treatments for already infected patients.^{3,4}

Two teams have now engineered recombinant adeno-associated viruses (AAVs) expressing broadly neutralizing antibodies targeting influenza A. These vectors could be used to transfer the capability to produce such antibodies to humans.

A team led by James Wilson developed an intranasal formulation of recombinant AAV serotype 2/9 expressing FI6, which is an antibody previously shown to protect mice against H1, H3 and H5 viruses.⁵

Wilson is professor of pathology and laboratory medicine at the **University of Pennsylvania** and scientific founder of **ReGenX Biosciences LLC**, which develops

recombinant AAV vectors for gene delivery.

FI6 is being developed by **Humabs BioMed S.A.**, which has licensed the product to an undisclosed pharma.

Meanwhile, a group led by David Baltimore, professor of biology and president emeritus of the **California Institute of Technology**, has used AAV2/8 to direct muscle to produce stable levels of F10, a broadly neutralizing human mAb known to protect mice against H1 and H5 viruses.⁶

Breathing deep

The Wilson team showed that mice receiving prophylactic nasal doses of AAV2/9 expressing FI6 survived a lethal influenza challenge three, four or seven days later. Mice pretreated one day before lethal challenge did not survive, although the symptoms of infection were delayed.

These results suggest the method provides relatively rapid onset of protection and would be useful for prophylaxis during pandemic outbreaks, or it could provide additional time to start therapeutic interventions.

In ferrets, nasal immunization with the FI6-expressing vector decreased virus replication and increased survival compared with administration of empty vector after lethal challenge with pandemic H1 or H5 influenza virus.

Macaques given an intranasal dose of AAV2/9 with a reporter gene expressed the gene product for more than 100 days. Peak vector expression was greater than that needed to protect ferrets from influenza challenge.

“The transient expression of the gene provides another layer of safety,” said Wilson. “Nasal delivery allows the gene to be expressed locally in the nasal epithelia and not in other tissue. The vector does not integrate, and the nasal epithelial cells turn over naturally. Our goal is to provide a vector that protects for an influenza season with the option of re-administration.”

Wilson said he is in discussions with an undisclosed funding agency to move the vector into humans.

He previously led a team that developed an AAV2/8 vector that replicates in epithelial cells in the lung and could be used to treat cystic fibrosis and α_1 -antitrypsin (AAT; A₁AT; SERPINA1) deficiency.⁷

Muscle for hire

The Baltimore group showed that mice intramuscularly injected with AAV2/8 encoding F10 were protected from lethal challenge with either of three different influenza H1 strains. Protection lasted for at least 11 months after gene transfer.

The vector also protected aged or immunocompromised mice from lethal influenza infection. These findings suggest the strategy might be useful to protect the elderly—a population in which the majority of deaths occur from seasonal influenza.

However, in ferrets immunized with the same vector, antibody production was 100-fold less than that seen in mice and did not protect ferrets from influenza challenge.

The researchers hypothesized that the expression difference could be because of the human antibody's decreased half-life in ferrets compared with in mice.

Baltimore said he was not concerned about the ferret data. “The antibodies are human, and so we are predicting they will have the greatest half-life and immunogenicity in human sera,” he told *SciBX*. “Our ultimate goal for AAV vectors, whether targeting influenza or HIV, is lifelong protection. The primary focus of my team right now is targeting HIV. Influenza is a secondary goal.”

Baltimore has previously used AAV2/8 to direct muscle to produce stable levels of broadly neutralizing anti-HIV mAbs. The mAbs resulted in protection against HIV in humanized mice, in which they persisted for over a year.⁸ The team is now manufacturing a clinical product and plans to start clinical trials in the next year or two in collaboration with the Vaccine Research Center at the **NIH**.

Positioning the vector

For both gene transfer approaches, showing adequate expression and safety in the clinic should be the next step, according to Gary Nabel, SVP and CSO of **Sanofi**.

“Safety will be a significant issue since long-term expression is intended, and it would be advisable to have a mechanism to terminate gene expression in the event that adverse events are encountered,” he

“Nasal delivery allows the gene to be expressed locally in the nasal epithelia and not in other tissue. The vector does not integrate, and the nasal epithelial cells turn over naturally. Our goal is to provide a vector that protects for an influenza season with the option of re-administration.”

—James Wilson,
University of Pennsylvania

told *SciBX*. “It will also be important to determine whether immune responses to either the antibody or to the vector are observed in significant numbers of subjects.”

“The biggest challenge will be proving the safety of the approach,” agreed Philip Johnson, CSO and EVP director of **The Children’s Hospital of Philadelphia Research Institute**. “Because there are existing efficacious vaccines, this approach for influenza might meet more resistance than, say, for HIV, malaria, tuberculosis or hepatitis C,” for which no vaccines exist.

Johnson’s lab has used an AAV2/8 vector to produce broadly neutralizing anti-HIV mAbs in nonhuman primates. The mAbs protected against simian immunodeficiency virus (SIV) and persisted for up to one year.⁹

Adolfo García-Sastre, professor of microbiology and co-director of the Emerging Pathogens Institute at the **Icahn School of Medicine at Mount Sinai**, thinks the most logical population for the new flu vaccine approaches is elderly or immune-compromised individuals. “The most obvious advantage of the method is the ability to protect individuals at risk of severe disease for which traditional vaccine efficacy is low,” he said.

Nabel agreed. “Commercial flu vaccines are much less effective in elderly individuals because they generate less robust immune responses,” he said. “The elderly suffer much higher mortality and may have greater exposure in hospital and chronic care settings. The risk-benefit ratio of such an approach is therefore more favorable in this group.”

García-Sastre did say that relying on only one antibody to provide universal protection might be overly optimistic.

“Although some influenza cross-reactive antibodies have been described that neutralize H1, H3 and influenza B viruses, these antibodies neutralize only a few specific virus strains,” he said.

Both the Baltimore and Wilson teams plan to test their vectors in

humans to determine safety and immunogenicity. The teams have filed for patents covering their respective findings, and the IP is available for licensing.

Baas, T. *SciBX* 6(24); doi:10.1038/scibx.2013.591
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e-mail: limberis@mail.med.upenn.edu
Contact: James M. Wilson, same affiliation as above
e-mail: wilsonjm@mail.med.upenn.edu
2. Balazs, A.B. *et al. Nat. Biotechnol.*; published online June 2, 2013; doi:10.1038/nbt.2618
Contact: David Baltimore, California Institute of Technology, Pasadena, Calif.
e-mail: baltimo@caltech.edu
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The Children’s Hospital of Philadelphia Research Institute, Philadelphia, Pa.
Humabs BioMed S.A., Bellinzona, Switzerland
Icahn School of Medicine at Mount Sinai, New York, N.Y.
National Institutes of Health, Bethesda, Md.
ReGenX Biosciences LLC, Washington, D.C.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
University of Pennsylvania, Philadelphia, Pa.



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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
Autoimmune disease				
Inflammatory bowel disease (IBD); psoriasis	Tyrosine kinase 2 (TYK2)	<i>In vitro</i> and rodent studies suggest selectively inhibiting TYK2 could help treat IBD and psoriasis. In <i>in vitro</i> biochemical and cellular assays, an optimized aminopyridine benzamide derivative showed potent inhibition of TYK2 activity and was selective for TYK2 over off-target Janus kinases. In mice, oral treatment with the lead compound inhibited the IL-12 signaling pathway, which is associated with IBD and psoriasis. Next steps could include evaluating the TYK2 inhibitor in preclinical models for IBD and psoriasis.	Patent and licensing status undisclosed	Liang, J. <i>et al. J. Med. Chem.</i> ; published online May 14, 2013; doi:10.1021/jm400266t Contact: Jun Liang, Genentech Inc., South San Francisco, Calif. e-mail: liang.jun@gene.com
SciBX 6(24); doi:10.1038/scibx.2013.592 Published online June 20, 2013				
Cancer				
Cancer	Apolipoprotein A-1 (APOA1)	Mouse studies suggest APOA1 could help treat solid tumors. In mouse models for melanoma and lung cancer, expression of human <i>APOA1</i> resulted in formation of smaller primary and metastatic tumors than no <i>Apoa1</i> expression. In wild-type mice with murine or human melanomas, APOA1 decreased tumor burden and increased survival compared with vehicle. Next steps could include testing APOA1 in mouse xenograft models for other cancers. Cerenis Therapeutics S.A.'s CER-522, a high-density lipoprotein mimetic based on a peptide analog of APOA1, is in Phase I testing to treat restenosis.	Patented by the Cleveland Clinic; licensing status unavailable	Zamanian-Daryoush, M. <i>et al. J. Biol. Chem.</i> ; published online May 17, 2013; doi:10.1074/jbc.M113.468967 Contact: Stanley L. Hazen, Cleveland Clinic, Cleveland, Ohio e-mail: hazens@ccf.org
SciBX 6(24); doi:10.1038/scibx.2013.593 Published online June 20, 2013				
Cancer	Eukaryotic translation elongation factor 2 kinase (EEF2K)	Patient, mouse and cell culture studies suggest inhibiting EEF2K could help improve the efficacy of nutrient deprivation therapy for cancer. In a human osteosarcoma cell line, small interfering RNA against EEF2K increased nutrient deprivation-induced apoptosis compared with control siRNA. In mice subjected to caloric restriction, injection of transformed fibroblasts overexpressing <i>Eef2k</i> led to larger tumors than injection of transformed fibroblasts not overexpressing <i>Eef2k</i> . In patients who have medulloblastoma or glioblastoma, expression of <i>EEF2K</i> was significantly associated with decreased survival ($p=0.00003$). Next steps could include screening for pharmacological inhibitors of EEF2K and evaluating their effects in cancer models.	Patent and licensing status unavailable	Leprevier, G. <i>et al. Cell</i> ; published online May 23, 2013; doi:10.1016/j.cell.2013.04.055 Contact: Poul H. Sorensen, The University of British Columbia, Vancouver, British Columbia, Canada e-mail: psor@mail.ubc.ca
SciBX 6(24); doi:10.1038/scibx.2013.594 Published online June 20, 2013				
Cancer	Neuropilin 2 (NRP2)	Patient sample and mouse studies suggest inhibiting NRP2 could help prevent cancer metastasis. In multiple mouse xenograft models for human cancer, small hairpin RNA against <i>NRP2</i> decreased metastasis compared with control shRNA but had no effect on primary tumor growth. In patient samples, increased <i>NRP2</i> expression in metastatic tumors correlated with advanced tumor stage. Next steps could include developing NRP2 inhibitors.	Patent and licensing status unavailable	Cao, Y. <i>et al. Cancer Res.</i> ; published online May 20, 2013; doi:10.1158/0008-5472.CAN-13-0529 Contact: Debabrata Mukhopadhyay, Mayo Clinic, Rochester, Minn. e-mail: mukhopadhyay.debabrata@mayo.edu
SciBX 6(24); doi:10.1038/scibx.2013.595 Published online June 20, 2013				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Ninjurin 1 (NINJ1)	Cell culture studies suggest inhibiting NINJ1 could help treat cancer. In human cancer cells, small hairpin RNA-mediated NINJ1 knockdown upregulated the tumor suppressor p53 and prevented colony formation. In cell culture, <i>Ninj1</i> -deficient mouse embryonic fibroblasts had higher p53 levels and showed greater senescence than nondeficient controls. Next steps could include screening for pharmacological inhibitors of <i>Ninj1</i> .	Patent and licensing status unavailable	Cho, S.-J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 20, 2013; doi:10.1073/pnas.1221242110 Contact: Xinbin Chen, University of California, Davis, Calif. e-mail: xbchen@ucdavis.edu
SciBX 6(24); doi:10.1038/scibx.2013.596 Published online June 20, 2013				
Multiple myeloma (MM)	BRAF	Patient studies suggest Zelboraf vemurafenib could help treat BRAF V600E mutant MM. In samples from patients with MM, the BRAF V600E mutant correlated with increased disease severity compared with nonmutant BRAF. In a single patient with BRAF V600E mutant MM, Zelboraf caused tumor regression and increased tumor cell apoptosis compared with baseline. Next steps could include a prospective clinical trial of Zelboraf in patients with BRAF V600E mutant MM. Daiichi Sankyo Co. Ltd., Chugai Pharmaceutical Co. Ltd. and Roche market Zelboraf, an oral small molecule inhibitor of oncogenic BRAF V600E, to treat melanoma. The drug is in Phase II testing for thyroid cancer and Phase I testing for colorectal cancer.	Patent and licensing status unavailable	Andrulis, M. <i>et al. Cancer Discov.</i> ; published online April 23, 2013; doi:10.1158/2159-8290.CD-13-0014 Contact: Marc S. Raab, German Cancer Research Center, Heidelberg, Germany e-mail: m.raab@dkfz.de
SciBX 6(24); doi:10.1038/scibx.2013.597 Published online June 20, 2013				
Cardiovascular disease				
Atherosclerosis	Dickkopf homolog 1 (DKK1)	Cell culture studies suggest inhibiting DKK1 could help treat atherosclerosis. Endothelial-to-mesenchymal transition contributes to calcification and fibrosis in atherosclerosis. In primary bovine aortic endothelial cells, mouse <i>Dkk1</i> induced endothelial-to-mesenchymal morphology and phenotype. In a bovine cell model for atherosclerosis, <i>Dkk1</i> increased calcium deposition and collagen accumulation compared with vehicle. Ongoing work includes evaluating the effect of <i>Dkk1</i> deficiency in mouse models for atherosclerosis. Novartis AG and MorphoSys AG have BHQ880, a HuCAL neutralizing antibody against DKK1, in Phase II testing to treat multiple myeloma (MM).	Unpatented; licensing status not applicable	Cheng, S.-L. <i>et al. Arterioscler. Thromb. Vasc. Biol.</i> ; published online May 16, 2013; doi:10.1161/ATVBAHA.113.300647 Contact: Dwight A. Towler, Sanford-Burnham Medical Research Institute at Lake Nona, Orlando, Fla. e-mail: dtowler@sanfordburnham.org
SciBX 6(24); doi:10.1038/scibx.2013.598 Published online June 20, 2013				
Ischemia/reperfusion injury	Complement component 3a receptor 1 (C3AR1; C3AR)	Mouse studies suggest C3AR agonists could help treat ischemia/reperfusion injury. In mice, C3ar knockout increased neutrophil-mediated damage in response to ischemia/reperfusion injury compared with no knockout. In a mouse model for intestinal ischemia/reperfusion injury, a C3AR agonist decreased circulating neutrophil numbers and intestinal tissue damage compared with vehicle. Next steps include lead optimization of candidate compounds and IND-enabling studies.	Patented by The University of Queensland; available for licensing	Wu, M.C.L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 21, 2013; doi:10.1073/pnas.1218815110 Contact: Trent M. Woodruff, The University of Queensland, Brisbane, Queensland, Australia e-mail: t.woodruff@uq.edu.au
SciBX 6(24); doi:10.1038/scibx.2013.599 Published online June 20, 2013				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Ischemia/ reperfusion injury	NADH dehydrogenase subunit 3 (ND3; MT-ND3)	<i>In vitro</i> and mouse studies suggest S-nitrosylation of MT-ND3 could help prevent ischemia/reperfusion injury. In a mouse model for ischemia/reperfusion injury, injection of a mitochondria-selective S-nitrosylating agent (MitoSNO) during reperfusion decreased infarct size compared with injection of an untargeted S-nitrosylating compound. <i>In vitro</i> , S-nitrosylation at cysteine 39 of MT-ND3 was required for the protective effect of MitoSNO and prevented reactive oxygen species production. Next steps include optimizing the MitoSNO formulation and conducting animal safety and Phase I studies.	Patent issued in the EU; patent application filed in U.S.; available for licensing	Chouchani, E.T. <i>et al. Nat. Med.</i> ; published online May 26, 2013; doi:10.1038/nm.3212 Contact: Michael P. Murphy, Medical Research Council Mitochondrial Biology Unit, Cambridge, U.K. e-mail: mpm@mrc-mbu.cam.ac.uk
SciBX 6(24); doi:10.1038/scibx.2013.600 Published online June 20, 2013				
Dermatology				
Itch	B-type natriuretic peptide (BNP; NPPB); natriuretic peptide receptor A (NPR1; NPRA)	Mouse studies suggest inhibiting NPPB or NPRA could help treat itch. In mouse models for chemical-induced itch, <i>Nppb</i> deficiency or chemical ablation of <i>Npra</i> -expressing spinal neurons decreased scratching behavior compared with no <i>Nppb</i> deficiency or no modification of spinal neurons, respectively. In these mice, the <i>Nppb</i> deficiency or loss of <i>Npra</i> -expressing spinal neurons did not affect responses to thermal, tactile and other stimuli. Next steps could include identifying potential cardiovascular side effects of inhibiting NPPB-NPRA signaling and elucidating itch-inducing targets downstream of NPPB and NPRA.	Unpatented; licensing status not applicable	Mishra, S.K. & Hoon, M.A. <i>Science</i> ; published online May 24, 2013; doi:10.1126/science.1233765 Contact: Mark A. Hoon, National Institutes of Health, Bethesda, Md. e-mail: mark.hoon@nih.gov
SciBX 6(24); doi:10.1038/scibx.2013.601 Published online June 20, 2013				
Endocrine/metabolic disease				
Diabetes	Solute carrier family 10 sodium-dependent bile acid transporter member 2 (SLC10A2; ASBT; IBAT)	<i>In vitro</i> and rodent studies identified benzothiazepine ASBT inhibitors that could help treat diabetes. <i>In vitro</i> , the lead analogs selectively inhibited ASBT with nanomolar IC ₅₀ values. In a rat model for type 2 diabetes, the lead compounds increased plasma insulin and decreased plasma glucose compared with vehicle. GlaxoSmithKline plc has completed Phase I testing of the lead compound (GSK2330672) to treat type 2 diabetes. Albireo AB, Ajinomoto Co. Inc. and Ferring Pharmaceuticals A/S have the ASBT inhibitor elobixibat (A3309) in Phase III testing to treat constipation and Phase II testing to treat irritable bowel syndrome (IBS). Albireo's A4250, an ASBT inhibitor, is in preclinical development for diabetes, cirrhosis and other liver diseases.	Patented; unavailable for licensing	Wu, Y. <i>et al. J. Med. Chem.</i> ; published online May 16, 2013; doi:10.1021/jm400459m Contact: Jon L. Collins, GlaxoSmithKline Research & Development, Research Triangle Park, N.C. e-mail: jon.l.collins@gsk.com
SciBX 6(24); doi:10.1038/scibx.2013.602 Published online June 20, 2013				
Endocrine/ metabolic disease	Branched chain ketoacid dehydrogenase kinase (BCKDK; BDK)	<i>In vitro</i> and mouse studies identified a BDK inhibitor that could help treat diseases associated with accumulation of branched-chain amino acids (BCAAs), including the genetic disorder branched-chain ketoaciduria, obesity and diabetes. Crystal structures of BDK in complex with known inhibitors led to the rational design of (S)- α -chloro-phenylpropionic acid, which inhibits the kinase at an allosteric site. In wild-type mice, injection of the compound decreased both plasma BCAA levels and BDK activity in multiple tissue types compared with vehicle injection. Next steps could include testing the compound in disease models.	Patent and licensing status unavailable	Tso, S.-C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 28, 2013; doi:10.1073/pnas.1303220110 Contact: David T. Chuang, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: david.chuang@utsouthwestern.edu Contact: Uttam K. Tambar, same affiliation as above e-mail: uttam.tambar@utsouthwestern.edu
SciBX 6(24); doi:10.1038/scibx.2013.603 Published online June 20, 2013				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Inflammatory disease	Leukotriene B4 (LTB4); complement 5 (C5)	<i>In vitro</i> and mouse studies suggest inhibitors of both C5 and LTB4 could help treat inflammatory diseases. <i>In vitro</i> , the tick-derived protein <i>Ornithodoros moubata</i> complement inhibitor (OmCI) bound both LTB4 and C5 and blocked their activation. In a mouse model for antigen-induced acute lung injury, OmCI decreased neutrophil recruitment and damage to pulmonary microvasculature compared with inhibition of Ltb4 or C5 alone. Next steps could include testing OmCI in additional animal models for antigen-induced inflammation. Cellceutix Corp.'s Kevetrin thioureidobutyronitrile, an LTB4 and protein kinase B (PKB; PKBA; AKT; AKT1) inhibitor, is in Phase I testing to treat solid tumors. Alexion Pharmaceuticals Inc. markets Soliris eculizumab, a humanized mAb targeting C5, to treat hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. At least seven other companies have C5 inhibitors in Phase II testing or earlier to treat various indications.	Patent and licensing status unavailable	Roversi, P. <i>et al. J. Biol. Chem.</i> ; published online April 26, 2013; doi:10.1074/jbc.M112.420331 Contact: Miles A. Nunn, Centre for Ecology and Hydrology, Wallingford, U.K. e-mail: amn@ceh.ac.uk
SciBX 6(24); doi:10.1038/scibx.2013.604 Published online June 20, 2013				
Neurology				
Addiction; neurology	Glyceraldehyde- 3-phosphate dehydrogenase (GAPDH)	Mouse studies suggest omigapil and other inhibitors of GAPDH nitrosylation could help treat cocaine addiction or overdose. In mice, omigapil decreased cocaine-mediated neurotoxicity compared with no treatment. In mice, omigapil decreased cocaine-induced hyperactivity and cocaine-seeking behavior compared with saline. Ongoing studies at the National Institute on Drug Abuse include evaluating the anticocaine effects of omigapil in animal models. Santhera Pharmaceuticals Holding AG's omigapil, a selegiline derivative that targets GAPDH, is in Phase I testing to treat muscular dystrophy.	Patented; available for licensing	Xu, R. <i>et al. Neuron</i> ; published online May 22, 2013; doi:10.1016/j.neuron.2013.03.021 Contact: Nilkantha Sen, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: nsen@gru.edu Contact: Solomon H. Snyder, same affiliation as above e-mail: ssnyder@jhmi.edu
SciBX 6(24); doi:10.1038/scibx.2013.605 Published online June 20, 2013				
Epilepsy	Semaphorin 4D (SEMA4D)	Cell and tissue culture studies suggest SEMA4D-Fc could be used to treat epilepsy. Sema4d-Fc is produced by conjugating the extracellular domain of mouse Sema4d to the Fc region of mouse IgG. In wild-type, cultured neurons and hippocampal brain slices, Sema4d-Fc increased formation of inhibitory GABAergic synapses compared with a control Fc. In an <i>in vitro</i> model for epilepsy, Sema4d-Fc decreased hyperexcitability compared with a control Fc. Next steps could include testing Sema4d-Fc in mouse models for epilepsy.	Patented; available for licensing from the Brandeis University Office of Technology Licensing	Kuzirian, M.S. <i>et al. J. Neurosci.</i> ; published online May 22, 2013; doi:10.1523/JNEUROSCI.0989-13.2013 Contact: Suzanne Paradis, Brandeis University, Waltham, Mass. e-mail: paradis@brandeis.edu
SciBX 6(24); doi:10.1038/scibx.2013.606 Published online June 20, 2013				
Psychosis	Dopamine D2 receptor; dopamine D3 receptor; serotonin (5-HT _{1A}) receptor; serotonin (5-HT _{1B}) receptor	<i>In vitro</i> and rodent studies suggest coumarin piperazine derivatives could be useful for treating psychosis. <i>In vitro</i> , members of the series bound to the serotonin (5-HT _{1A}) and (5-HT _{1B}) receptors and the dopamine D2 and D3 receptors with nanomolar and subnanomolar affinity. In mice and rats, the lead member of the series decreased multiple psychosis-associated behaviors compared with vehicle. Next steps include evaluating the lead coumarin piperazine derivative in additional preclinical studies.	Patented; unavailable for licensing	Chen, Y. <i>et al. J. Med. Chem.</i> ; published online May 15, 2013; doi:10.1021/jm400408r Contact: Guisen Zhang, Huazhong University of Science & Technology, Wuhan, China e-mail: gszhang@mail.hust.edu.cn
SciBX 6(24); doi:10.1038/scibx.2013.607 Published online June 20, 2013				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pulmonary disease				
Pulmonary disease	Mucin 5B oligomeric mucus/gel-forming (MUC5B)	Patient studies suggest the rs35705950 SNP in the <i>MUC5B</i> promoter region could be a marker of interstitial lung disease risk. In a combined analysis of genomic data and chest CT scans from 2,633 subjects, the rs35705950 SNP in the <i>MUC5B</i> promoter region was associated with a 2.8-fold greater risk of interstitial lung abnormalities and a 6.3-fold greater risk of pulmonary fibrosis ($p < 0.001$). Next steps include studying early forms of interstitial lung disease and developing intervention strategies based on decreasing <i>MUC5B</i> expression. <i>SciBX</i> 6(24); doi:10.1038/scibx.2013.608 Published online June 20, 2013	Patent applications filed; available for licensing	Hunninghake, G.M. <i>et al.</i> <i>N. Engl. J. Med.</i> ; published online May 21, 2013; doi:10.1056/NEJMoa1216076 Contact: David A. Schwartz, University of Colorado Denver, Aurora, Colo. e-mail: david.schwartz@ucdenver.edu Contact: Gary M. Hunninghake, Brigham and Women's Hospital, Boston, Mass. e-mail: ghunninghake@partners.org

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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
Disease models			
A microchip platform to model heart failure	A microchip platform could be used to model failing myocardium and identify molecules to prevent myocardial infarction (MI) or hypertension. The device consists of neonatal rat ventricular myocytes seeded on a fibronectin-patterned flexible silicone membrane that is cyclically stretched to induce disease phenotypes. Myocardium that underwent cyclic stretching showed pathologic changes to myocyte shape, sarcomere alignment and gene expression, and it had decreased contractile functions compared with unstretched myocardium. Next steps include using the microchip platform to test compounds currently used to treat heart failure, comparing results to those reported in animal models and the clinic, and adapting the microchip platform to include human stem cell-derived cardiomyocytes.	Patented; licensed to TissueNetix Inc.	McCain, M.L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 28, 2013; doi:10.1073/pnas.1304913110 Contact: Kevin Kit Parker, Harvard University, Cambridge, Mass. e-mail: kkparker@seas.harvard.edu
SciBX 6(24); doi:10.1038/scibx.2013.609 Published online June 20, 2013			
Drug platforms			
Live, attenuated influenza A virus with suppressed hemagglutinin (HA) and neuraminidase (NA) expression as a vaccine	Live, attenuated influenza A virus with suppressed HA and NA expression could be used to develop vaccines. Synthetic, attenuated virus engineering was used to insert multiple suboptimal synonymous codons into the HA and NA regions of a mouse-adapted influenza virus. In mice, the resulting influenza strain showed attenuated replication in lungs. Also in mice, inoculation with the attenuated strain induced a neutralizing antibody response and protected mice from lethal challenge with homologous or two different heterologous, mouse-adapted influenza viruses. Next steps include developing a vaccine using a non-mouse-adapted virus with suppressed HA and NA expression.	Patent applications filed; licensed to Codagenix Inc. to develop human vaccines	Yang, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 20, 2013; doi:10.1073/pnas.1307473110 Contact: Eckard Wimmer, State University of New York at Stony Brook, Stony Brook, N.Y. e-mail: eckard.wimmer@stonybrook.edu Contact: Steffen Mueller, same affiliation as above e-mail: steffen.mueller@stonybrook.edu
SciBX 6(24); doi:10.1038/scibx.2013.610 Published online June 20, 2013			
mAb antagonists against glucose-dependent insulinotropic polypeptide receptor (GIPR)	mAb antagonists against GIPR could be useful as tools to develop improved inhibitors and study receptor function in human disease. Highly specific and potent GIPR antagonists with long <i>in vivo</i> half-lives have not been previously reported. Phage and ribosome display libraries were used to generate Gipg013, which selectively antagonized human GIPR with an <i>in vitro</i> K_d value of 7 nM. In mice, Gipg013 had a half-life of about 10 days. MedImmune LLC did not disclose next steps, which could include evaluating the mAb antagonists in disease models.	Patent status undisclosed; licensing status not applicable	Ravn, P. <i>et al. J. Biol. Chem.</i> ; published online May 20, 2013; doi:10.1074/jbc.M112.426288 Contact: Peter Ravn, MedImmune LLC, Cambridge, U.K. e-mail: ravn@medimmune.com
SciBX 6(24); doi:10.1038/scibx.2013.611 Published online June 20, 2013			
Self-assembling influenza nanoparticle vaccines	Self-assembling influenza nanoparticles could be used as vaccines to induce broadly neutralizing antibodies. A fusion protein of an H1N1 influenza A virus hemagglutinin (HA) ectodomain and <i>Helicobacter pylori</i> ferritin was expressed in mammalian cells and shown to self-assemble into HA-ferritin nanoparticles that display eight trimeric HA spikes on the surface. In mice and ferrets, HA-ferritin nanoparticles plus adjuvant induced higher levels of neutralizing antibodies than an adjuvanted, trivalent, inactivated influenza vaccine. In ferrets infected with an unmatched H1N1 influenza virus, immunization with the nanoparticles decreased viral shedding and weight loss compared with immunization using the trivalent, inactivated influenza vaccine. Next steps include immunogenicity studies in humans.	Patent application filed; available for licensing from the NIH Office of Technology Transfer Contact: Cristina Thalhammer-Reyero, National Institutes of Health, Bethesda, Md. e-mail: thalhmc@mail.nih.gov	Kanekiyo, M. <i>et al. Nature</i> ; published online May 22, 2013; doi:10.1038/nature12202 Contact: Gary J. Nabel, Sanofi, Cambridge, Mass. e-mail: gary.nabel@sanofi.com
SciBX 6(24); doi:10.1038/scibx.2013.612 Published online June 20, 2013			

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
Nuclear localization status of nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2) to distinguish essential thrombocythemia (ET) and primary myelofibrosis (MF)	The nuclear localization status of NRF2 could help differentiate between the myeloproliferative disorders ET and primary MF. In patient biopsies, anti-NRF2 antibodies showed less than 17% nuclear NRF2 localization in erythroid cells from ET samples and greater than 27% nuclear NRF2 localization in erythroid cells from primary MF samples. Computational analysis of the biopsy data sets using NRF2 nuclear localization-based cutoff values distinguished between ET and primary MF with 92% accuracy. Next steps could include testing the method in patients with unclassifiable myeloproliferative disorders. SciBX 6(24); doi:10.1038/scibx.2013.613 Published online June 20, 2013	Patent and licensing status unavailable	Aumann, K. <i>et al. Blood</i> ; published online May 13, 2013; doi:10.1182/blood-2012-11-463257 Contact: Heike L. Pahl, University Medical Center Freiburg, Freiburg, Germany e-mail: heike.pahl@uniklinik-freiburg.de
Peptidyl arginine deiminase type III (PADI3; PAD3) autoantibodies as a prognostic marker for rheumatoid arthritis (RA)	Patient sample studies suggest autoantibodies that recognize PAD3 and activate PAD4 (PADI4) could be used to identify patients at risk for radiographic progression in RA. Autoantibodies against PAD4 have previously been correlated with severe disease in patients with RA, but there is heterogeneity within that group. In serum samples from 150 patients with RA, 80% of those with anti-PAD3 antibodies had radiographic progression, whereas it was only 50% for those with no anti-PAD antibodies. In this patient cohort, the presence of both anti-PAD3 and anti-PAD4 antibodies was associated with increased disease severity compared with the presence of anti-PAD4 antibodies alone. Next steps include looking for anti-PAD3 and anti-PAD4 antibodies in additional patient cohorts and understanding the mechanism by which anti-PAD3 antibodies activate PAD4. SciBX 6(24); doi:10.1038/scibx.2013.614 Published online June 20, 2013	Patent application filed; licensing status undisclosed	Darrach, E. <i>et al. Sci. Transl. Med.</i> ; published online May 22, 2013; doi:10.1126/scitranslmed.3005370 Contact: Antony Rosen, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: arosen@jhmi.edu Contact: Felipe Andrade, same affiliation as above e-mail: andrade@jhmi.edu



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Company and institution index**A**

Ajinomoto Co. Inc. 13
 Albireo AB 13
 Alexion Pharmaceuticals Inc. 14

B

Brandeis University 14

C

California Institute of Technology 9
 Cellceutix Corp. 14
 Cerenis Therapeutics S.A. 11
 Children's Hospital of Philadelphia Research Institute 10
 Chugai Pharmaceutical Co. Ltd. 12
 Chungnam National University 7
 Cleveland Clinic 11
 Codagenix Inc. 16
 Cystic Fibrosis Foundation 6

D

Daiichi Sankyo Co. Ltd. 12

E

EMBO 6
 Escape Therapeutics Inc. 8
 European Cystic Fibrosis Society 6

F

Ferring Pharmaceuticals A/S 13
 Follica Inc. 7

G

Genentech Inc. 1
 Genzyme Corp. 6
 GlaxoSmithKline plc 6,13

H

Hospital for Sick Children 6
 Humabs BioMed S.A. 9

I

Icahn School of Medicine at Mount Sinai 10

J

Johns Hopkins University School of Medicine 8
 Johnson & Johnson 7

K

Kobe University 1

L

Lead Discovery Center GmbH 3

M

Max Planck Innovation GmbH 3
 Max Planck Institute of Molecular Physiology 1
 Max Planck Society 3
 McGill University 5
 MedImmune LLC 16
 Merck & Co. Inc. 7
 MorphoSys AG 12

N

National Institute on Drug Abuse 14

National Institutes of Health 9,16
 New York University Langone Medical Center 7
 Novartis AG 12

P

Perelman School of Medicine at the University of Pennsylvania 7
 Pfizer Inc. 6
 Proteostasis Therapeutics Inc. 6

R

Reata Pharmaceuticals Inc. 6
 ReGenX Biosciences LLC 9
 Roche 1,12
 Ruhr University Bochum 3

S

Sanofi 6,9
 Santhera Pharmaceuticals Holding AG 14
 Seoul National University College of Medicine 7

T

Texas A&M University 7
 TissueNetix Inc. 16
 Traffic Therapeutics Inc. 6

U

University of Bradford 8
 University of North Carolina at Chapel Hill School of Medicine 5
 University of Pennsylvania 7,9
 University of Putra Malaysia 3
 University of Queensland 12
 University of Texas Health Science Center at Houston 1
 University of Texas Southwestern Medical Center 5
 University of Toronto 6

V

Vanderbilt University School of Medicine 1
 Vertex Pharmaceuticals Inc. 5

W

Washington University in St. Louis School of Medicine 7

.....

Target and compound index**A**

α_1 -Antitrypsin 9
 A₁AT 9
 A3309 13
 A4250 13
 AAT 9
 AKT 14
 AKT1 14
 Aminopyridine benzamide 11
 APOA1 11
 Apolipoprotein A-1 11
 ARHGEF 3
 ASBT 13

B

BCKDK 13
 BDk 13

Benzothiazepine 13
 BHQ880 12
 BRAF 12
 Branched chain ketoacid dehydrogenase kinase 13
 B-type natriuretic peptide 13
 BNP 13

C

C3AR 12
 C3AR1 12
 C5 14
 Cd332 7
 Cd333 7
 CER-522 11
 CFTR 5
 Cocaine 14
 Complement 5 14
 Complement component 3a receptor 1 12
 Coumarin piperazine 14
 Cystic fibrosis transmembrane conductance regulator 5

D

Deltarasin 2
 Dickkopf homolog 1 12
 Dihydrotestosterone 7
 DKK1 12
 Dopamine D2 receptor 14
 Dopamine D3 receptor 14

E

Eculizumab 14
 EEF2K 11
 Elobixibat 13
 Eukaryotic translation elongation factor 2 kinase 11

F

F10 9
 Farnesyl protein transferase 1
 Ferritin 16
 FGF9 7
 Fgfr2 7
 Fgfr3 7
 FI6 9
 Fibroblast growth factor 9 7
 Fibroblast growth factor receptor 3 7
 Finasteride 7

G

GAF 7
 GAPDH 14
 GEF 3
 Gipg013 16
 GIPR 16
 Glucose-dependent insulinotropic polypeptide receptor 16
 Glyceraldehyde-3-phosphate dehydrogenase 14
 Glycerol 6
 GSK2330672 13

H

HA 16
 Hemagglutinin 16
 HRAS 1

I

IBAT 13
 IL-12 11

Influenza A virus 9,16
 hemagglutinin 9,16
 Ivacaftor 5

J

Janus kinase 11

K

Kalydeco 5
 Keratinocyte growth factor receptor 7
 Kevetrin 14
 Kgfr 7
 K-Ras 1

L

Leukotriene B4 14
 LTB4 14
 Lumacaftor 5

M

Minoxidil 7
 MitoSNO 13
 MT-ND3 13
 MUC5B 15
 Mucin 5B oligomeric mucus/gel-forming 15
 Myo-inositol 6

N

NA 16
 NADH dehydrogenase subunit 3 13
 Natriuretic peptide receptor A 13
 ND3 13
 Neuraminidase 16
 Neuroblastoma Ras viral (v-Ras) oncogene 1
 Neupilin 2 11
 NFE2L2 17
 NINJ1 12
 Ninjurin 1 12
 NPPB 13
 NPR1 13
 NPRA 13
 NRAS 1
 NRF2 17
 NRP2 11
 Nuclear factor (erythroid-derived 2)-like 2 17

O

OmCI 14
 Omigapil 14
Ornithodoros moubata complement inhibitor 14

P

p53 12
 PAD3 17
 PAD4 17
 PADI3 17
 PADI4 17
 PDE δ 1
 Peptidyl arginine deiminase type III 17
 Phosphodiesterase δ subunit 1
 PKB 14
 PKBA 14

Propecia	7	Serotonin (5-HT _{1A}) receptor	14	SOS1	3	VX-809	5
Protein kinase B	14	serotonin (5-HT _{1B}) receptor	14	T		W	
R		SERPINA1	9	Testosterone	7	Wingless-type MMTV	
Ras	1	(S)- α -Chloro-phenylpropionic acid	13	Thioureidobutyronitrile	14	integration site	7
Rho guanine nucleotide exchange factor	3	SLC10A2	13	TYK2	11	Wingless-type MMTV integration site family member 2a	8
Rogaine	7	Soliris	14	Tyrosine kinase 2	11	Wnt	7
S		Solute carrier family 10 sodium-dependent bile acid transporter		V		Wnt2	8
Selegiline	14	member 2	13	Vemurafenib	12	Wnt2a	8
SEMA4D	14	Son of sevenless	13	V-Ha-ras Harvey rat sarcoma viral oncogene homolog	1	Z	
SEMA4D-Fc	14	homolog 1	3	VX-661	5	Zelboraf	12
Semaphorin 4D	14			VX-770	5		