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By Kai-Jye Lou, Senior Writer

Roche's Genentech Inc. unit has shown that mutations in *ERBB3* can drive oncogenesis by enhancing the receptor's ability to form a heterodimer with HER2.¹ Because the process appears to depend on HER2, the results suggest existing HER2-targeted therapies could also be effective in cancers driven by mutations in *ERBB3*.

Epidermal growth factor receptor 3 (EGFR3; HER3; ErbB3) is a member of the ErbB family of receptor tyrosine kinases. The membrane-bound receptor is comprised of an extracellular domain (where ligand binding and dimerization interactions occur), an α -helical transmembrane segment and an intracellular tyrosine kinase domain to phosphorylate downstream targets.

Unlike other members of the ErbB family, ErbB3's kinase domain is impaired and does not show significant kinase activity on its own.² To activate downstream cellular signaling pathways via phosphorylation, a ligand such as neuregulin 1 (NRG1) must first bind to ErbB3's extracellular domain.³

This ligand binding promotes the formation of a heterodimer between ErbB3 and other members of the ErbB family, such as HER2 (EGFR2; ErbB2; neu), which have functional kinase domains.^{4,5}

"We noticed that there were recurrent mutations in *ERBB3* in the context of colon and gastric cancers, although the functional relevance of such mutations was unclear," said Somasekar Seshagiri, a principal scientist in molecular biology at Genentech. "We were especially curious about these mutations in *ERBB3*, as it is the only member of the ErbB family that by itself does not show significant kinase activity. Thus, we sought to find out why cancer patients still accumulate recurrent somatic mutations in *ERBB3* when the protein is not able to phosphorylate and activate downstream targets on its own."

Now, Seshagiri's group has characterized the functional relevance of protein-altering somatic mutations in *ERBB3* and also assessed the frequency of such mutations across a range of cancers.

Whole-exome sequencing of 507 human primary tumor samples covering 20 types of cancer found *ERBB3* mutations in 12% of gastric cancer samples, 11% of colon cancer samples and occurring sporadically in samples of other cancer types. The majority of the mutations occurred in the receptor's extracellular domain.

In mouse and human cell lines, most of the cancer-associated ErbB3 mutants tested by the group promoted oncogenic transformation and signaling but only when co-expressed with functional HER2. In cells that expressed mutant ErbB3, antibody-mediated neutralization of

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NRG1 did not significantly affect cell survival or impair the mutant receptor's ability to form a heterodimer with HER2.

The latter result suggests that oncogenic mutations in the receptor enhance its ability to dimerize with HER2 independently of its ligand (see Figure 1, "Model of oncogenesis driven by mutant ErbB3").

In a mouse model for *ErbB3*-mutant murine leukemia, mAbs such as MEHD7945A or the anti-HER2 mAb Herceptin trastuzumab, which inhibit ErbB3 signaling, decreased disease severity and increased survival compared with a control mAb.

Results were published in *Cancer Cell*.

Genentech markets Herceptin to treat HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinomas.

The company's MEHD7945A, a humanized IgG1 mAb targeting ErbB3 and the closely related EGFR, is in Phase II testing to treat metastatic colorectal cancer or metastatic squamous cell carcinomas of the head and neck. The mAb is also in Phase I testing to treat metastatic epithelial tumors.

"Our hypothesis is that these somatic mutations that accumulate in *ERBB3* shift the protein towards an active conformation that enhances its ability to cooperate with HER2," said Seshagiri, the corresponding author. "We believe these mutations tend to make ErbB3 ligand-independent in that the protein no longer needs its ligand to bind to form a heterodimer with HER2."

"This work is interesting, as it shows that a protein that is generally considered to be inactive on its own can acquire mutations that allow it to promote oncogenesis," said Heidi Greulich, an instructor in medicine at the Dana-Farber Cancer Institute and a visiting scientist at the Broad Institute of MIT and Harvard.

"At Merrimack, we are developing ErbB3-directed drugs that primarily target ligand-dependent mechanisms, which have previously been shown to play a prominent role in mediating resistance to both targeted therapy and chemotherapy," said Gavin MacBeath, cofounder and VP of translational research at Merrimack Pharmaceuticals Inc.

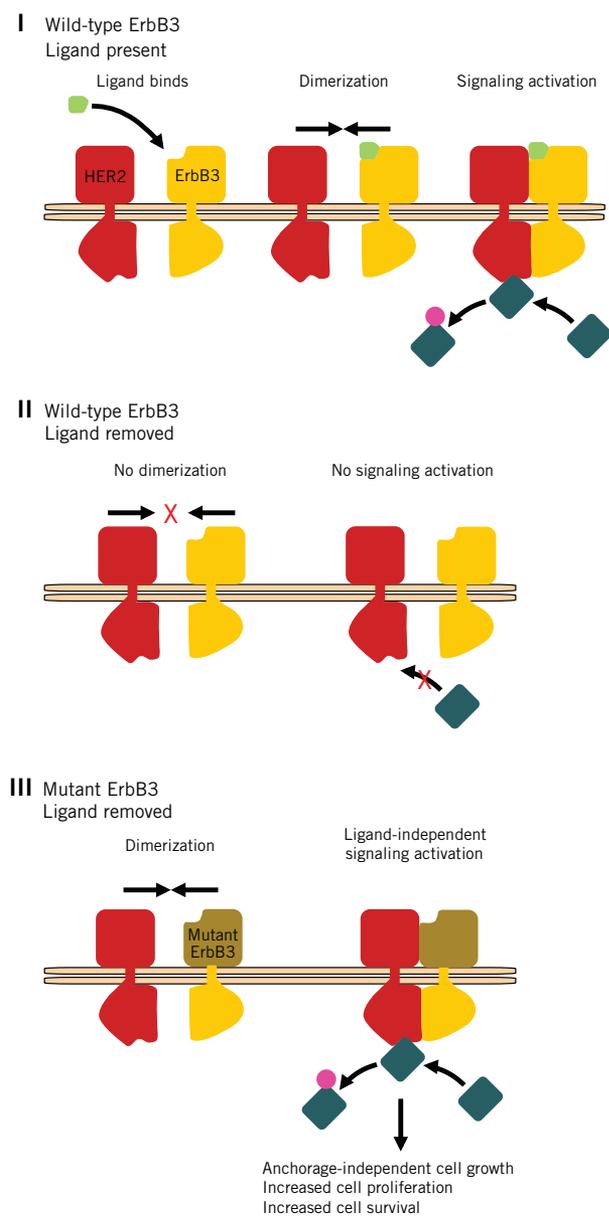
"These results now show that mutated ErbB3 may also play a role in cancer. This suggests that as ErbB3-directed drugs are developed clinically, it may be important not only to detect ligand-driven signaling in patient tumors but also identify any mutations that are driving ErbB3 signaling in a ligand-independent manner."

Previously, the rationale for targeting ErbB3 in cancer primarily stemmed from studies linking increased expression of the receptor or NRG1 to resistance against tyrosine kinase inhibitors and chemotherapy.⁶⁻⁸

The new data further support the case for targeting ErbB3 in cancer and also suggest that patients who have cancers driven by mutations in *ERBB3* could potentially benefit from treatment with existing HER2-targeted drugs (see Table 1, "Targeted therapies against HER2 and ErbB3").

"We sought to find out why cancer patients still accumulate recurrent somatic mutations in *ERBB3* when the protein is not able to phosphorylate and activate downstream targets on its own."

**—Somasekar Seshagiri,
Genentech Inc.**



“The most important potential translational aspect of this work is in showing that it may be possible to expand the use of existing HER2-targeted therapies into cancer patients who have oncogenic *ERBB3* mutations,” Greulich told *SciBX*.

Merrimack has three antibody therapies in clinical development that target ErbB3. MM-121 is being developed with **Sanofi** and is a human mAb against ErbB3 in multiple Phase II trials in patients who have breast, ovarian or non-small cell lung cancers (NSCLCs). MM-111, a bispecific antibody that targets ErbB3 and HER2, is in Phase II testing to treat gastric cancers. MM-141, a tetravalent antibody that targets insulin-like growth factor-1 receptor (IGF1R; CD221) and ErbB3, is in a Phase I trial in patients who have advanced solid tumors.

Taking functional insights to the clinic

Seshagiri said the group at Genentech is now trying to further flesh out the mechanisms by which mutations in *ERBB3* drive oncogenesis. To

Figure 1. Model of oncogenesis driven by mutant ErbB3.

Epidermal growth factor receptor 3 (EGFR3; HER3; ErbB3) is a receptor tyrosine kinase that is ineffective at activating downstream cellular signaling pathways by itself owing to its impaired kinase domain. Instead, downstream signaling via ErbB3 depends on the binding of an appropriate ligand to the receptor. As reported in Jaiswal *et al.*, oncogenic mutations in *ERBB3* are primarily found in the receptor’s extracellular domain and render the protein ligand-independent. Binding of a ligand to the wild-type ErbB3 receptor (I) promotes its ability to undergo dimerization with HER2 (EGFR2; ErbB2; neu), which has an active kinase domain. The resulting HER2–ErbB3 heterodimer can then activate downstream signaling pathways. Without an appropriate ligand (II), wild-type ErbB3 is unable to form a heterodimer with HER2 and activate downstream signaling pathways in an effective manner. Oncogenic mutant ErbB3 can form a heterodimer with HER2 in the absence of an appropriate ligand (III) and activate downstream signaling pathways. Addition of an ErbB3 ligand can further stimulate this activity.

help with this, the researchers are looking into generating additional structural information on the target.

“We are also considering the creation of mouse models that will help us better understand at what stage of disease mutant ErbB3 contributes to tumorigenesis,” he said.

Seshagiri noted that such models also could provide the opportunity to do some preclinical testing of product candidates being developed at Genentech but declined to disclose details. Seshagiri added it will be important to do follow-up studies in samples from larger patient cohorts to establish the baseline frequency of oncogenic mutations in *ERBB3*.

“Looking at additional clinical samples could help better determine the prognostic value of these mutations and also could help better predict how tumors with such mutations would respond to a particular treatment,” he told *SciBX*. “Once you have obtained such information, then you may be able to incorporate the mutational status of *ERBB3* into the design of a clinical trial.

“The picture that is emerging is that some tumors may be driven by ligand-dependent ErbB3 signaling in the absence of mutations, while others may be driven by oncogenic mutations, either in the presence or absence of ligands,” added MacBeath. “As such, a comprehensive biomarker strategy for ErbB3-directed drugs may require detecting both of these mechanisms.”

Greulich thinks it will be important to identify additional ErbB3-mutant cancer cell lines and determine how they respond to HER2 inhibition. She said such studies will help determine how useful current HER2-targeted therapies could be against ErbB3-mutant tumors.

“The most important potential translational aspect of this work is in showing that it may be possible to expand the use of existing HER2-targeted therapies into cancer patients who have oncogenic *ERBB3* mutations.”

—Heidi Greulich,
Dana-Farber Cancer Institute

Table 1. Targeted therapies against HER2 and ErbB3. In Jaiswal *et al.*, researchers report data suggesting that cancers driven by oncogenic mutations in epidermal growth factor receptor 3 (EGFR3; HER3; ErbB3) could respond to existing therapies against HER2 (EGFR2; ErbB2; neu). The data also further support the idea of developing ErbB3-targeting therapies to treat cancer. There are at least four HER2-targeting therapies marketed to treat various types of cancer with another five in late-stage clinical development or under regulatory review. The most advanced ErbB3-targeting therapies are in Phase II testing.

Source: BCIQ; BioCentury Archives

Company	Product	Description	Latest stage of development
Marketed and late-stage therapies that target HER2			
Genentech Inc. / Chugai Pharmaceutical Co. Ltd. (Tokyo:4519) / Roche (SIX:ROG; OTCQX:RHHBY)	Herceptin trastuzumab	Humanized mAb against HER2	Marketed
Genentech Inc. / Chugai Pharmaceutical Co. Ltd. / Roche	Perjeta pertuzumab	Humanized mAb HER dimerization inhibitor that prevents HER2 from binding to other HER receptors (EGFR, ErbB3 and ErbB4)	Marketed
Genentech Inc. / Chugai Pharmaceutical Co. Ltd. / ImmunoGen Inc. (NASDAQ:IMGN) / Roche	Kadcyla ado-trastuzumab emtansine	Humanized mAb against HER2 linked to ImmunoGen's DM1 cytotoxic agent	Marketed
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) / Eddingpharm Inc.	Tykerb lapatinib	Small molecule EGFR and HER2 receptor kinase inhibitor	Marketed
Boehringer Ingelheim GmbH	Tomtovok afatinib	Small molecule dual inhibitor of EGFR, HER2 and ErbB4 (HER4)	Registration
Biocon Ltd. (NSE:BIOCON; BSE:BIOCON) / Mylan Inc. (NASDAQ:MYL)	Biosimilar trastuzumab	Humanized mAb against HER2	Phase III
Celltrion Inc. (KOSDAQ:068270) / Nippon Kayaku Co. Ltd. (Tokyo:4272)	CT-P6	Humanized mAb against HER2	Phase III
Pfizer Inc. (NYSE:PFE) / SFJ Pharmaceuticals Inc.	Dacomitinib	Small molecule inhibitor of human EGFR, HER2 and ErbB4	Phase III
Symphony Evolution Inc. / Exelixis Inc. (NASDAQ:EXEL) / Kadmon Corp. LLC	XL647; KD019	Spectrum selective small molecule inhibitor of EGFR, HER2 and VEGF	Phase III
Clinical-stage therapies that target ErbB3			
Genentech Inc. / Roche	MEHD7945A	Humanized IgG1 mAb targeting EGFR and ErbB3	Phase II
Merrimack Pharmaceuticals Inc. (NASDAQ:MACK) / Sanofi (Euronext:SAN; NYSE:SNY)	MM-121	Human mAb against ErbB3	Phase II
Merrimack Pharmaceuticals Inc.	MM-111	Bispecific antibody targeting HER2 and ErbB3	Phase II
Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568) / Amgen Inc. (NASDAQ:AMGN)	U3-1287, AMG 888	Human mAb against ErbB3	Phase I/II
Aveo Pharmaceuticals Inc. (NASDAQ:AVEO)	AV-203	ErbB3-targeted antibody	Phase I
Merrimack Pharmaceuticals Inc.	MM-141	Tetavalent antibody targeting insulin-like growth factor 1 receptor (IGF1R; CD221) and ErbB3	Phase I
Novartis AG (NYSE:NVS; SIX:NOVN) / MorphoSys AG (Xetra:MOR; Pink:MPSYF)	LJM716	Human HuCAL antibody against ErbB3	Phase I
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN)	REGN1400	Human ErbB3 antibody	Phase I
Roche	RG7116	Anti-HER3/ADCC mAb	Phase I
Zensun (Shanghai) Sci. & Tech. Co. Ltd.	rhErbB3-f	Recombinant human ErbB3 fragment vaccine	Phase I

Seshagiri said the group's findings also strengthen the case for developing bispecific antibodies that target both HER2 and ErbB3 but declined to say whether the company itself plans to develop such an antibody.

Genentech declined to disclose patent details.

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COMPANIES AND INSTITUTIONS MENTIONED

Broad Institute of MIT and Harvard, Cambridge, Mass.

Dana-Farber Cancer Institute, Boston, Mass.

Genentech Inc., South San Francisco, Calif.

Merrimack Pharmaceuticals Inc. (NASDAQ:MACK), Cambridge, Mass.

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

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

Not-so-fast track

By Lev Osherovich, Senior Writer

GlaxoSmithKline plc's [Discovery Fast Track competition](#) has hit a roadblock at the **University of California, Los Angeles**, as the university's technology transfer office has barred researchers from competing for access to GlaxoSmithKline (GSK) screening and assay development facilities because of potential IP concerns.

The logjam is a cautionary tale for companies trying to lower barriers to collaboration across the academia-industry divide and highlights the need to bring tech transfer offices to the table prior to launching new partnerships.

Discovery Fast Track launched officially last month¹ with the aim of accelerating direct collaboration between academia and industry by giving individual researchers access to GSK's drug discovery resources. Under the program, GSK solicits brief, nonconfidential proposals from academic researchers that lay out a hypothesis and a compound-screening strategy to establish proof of concept for emerging drug targets in collaboration with GSK counterparts.

The program was envisioned as an entry point into the Discovery Partnerships in Academia (DPAc) program, in which GSK and academics collaborate over the long term under negotiated deals that may involve financial terms and the development of new IP.

The Fast Track program focuses on precompetitive, exploratory science, so GSK had been hoping to establish connections with academic researchers without the need for negotiated agreements with their host institutions.

But this relatively informal approach has raised a red flag with UCLA's Office of IP and Industry Sponsored Research following an e-mail sent by GSK to UCLA faculty who had previously opted to receive applications to the program.

Last week, Brendan Rauw, associate vice chancellor and executive director of entrepreneurship at the UCLA Office of IP and Industry Sponsored Research, told UCLA researchers to stop participating in GSK's program.

Rauw's concern is that prospective participants in the program could divulge confidential information that may be covered by prior agreements between the University of California (UC) and third parties. Rauw told *SciBX* that the program puts faculty members in a position to represent things that are outside of their authority. In fact, UC researchers must disclose any ideas to their tech transfer offices prior to disclosing them to outside companies.

In an e-mail to UCLA researchers, Rauw and James Economou, UCLA vice chancellor of research, explained that the terms of the contest "do not adhere to UC policy because faculty have prior and ongoing obligations under the patent policy to disclose all discoveries to the university and have assigned patent rights to the university. Participation in the GSK competition would violate these policies and obligations."

GSK spokeswoman Melinda Stubbee told *SciBX* that the terms and

conditions of participation in Discovery Fast Track require the consent of researchers' host institutions.

Indeed, according to GSK's Discovery Fast Track website, the contest rules stipulate that "each Applicant represents that his/her institution has authorized his/her entry into the Competition, that he/she is complying with the policies and instructions of his/her institution at all times during his/her participation in the Competition and that participation in the Competition, including if selected as a finalist or winner, will not result in the Applicant being in violation of any such policies or instructions or in breach of any agreement with a third party."

Rauw countered that it is impossible for researchers to comply with this requirement without a careful vetting of each application by a tech transfer office.

"If you look at the conditions, they ask people to represent that any ideas are not subject to and do not infringe upon any on third-party rights," said Rauw. "We cannot ask individual researchers to make that determination."

Thus, Rauw believes his stance on Discovery Fast Track participation could potentially be adopted throughout the UC system, not just UCLA.

"We're the only campus that has made a statement about this so far, but in collaboration with the [UC] Office of General Counsel we came to the conclusion this was not in compliance with UC policy," said Rauw.

Erik Lium, assistant vice chancellor of the Office of Innovation, Technology and Alliances at **UCSF**, told *SciBX* in an e-mail that "our position on this issue is very similar if not the same as UCLA's."

Intellectual turf war

At the end of the day, the dispute highlights the difficulty of forging collaborations between industry and academia in a landscape of complex, sometimes competing, IP claims and third-party agreements.

Alicia Löffler, executive director of the Innovation and New Ventures Office and associate VP of research at **Northwestern University**, said the terms of the GSK contest were clearly stated but that the pharma may not have fully considered the implications of asking researchers to submit their own proposals.

"No company would allow its employees to enter into signed agreements, and the same thing happens in academia. At universities, the employees don't own their IP, and employees aren't allowed to sign deals," said Löffler.

In theory, Löffler said, tech transfer offices should vet all disclosures by academic researchers, including conference presentations, posters and papers, for patentability and potential conflict with pre-existing agreements.

In practice, it's impossible to vet everything that academic researchers disclose, so tech transfer offices typically are unable to oversee disclosures made in academic venues such as conferences and peer-reviewed journals.

"It's very difficult to control what a faculty member writes in a poster or says at a conference," said Löffler. "If they disclose something that would be eventually patentable, too bad, we can't do anything about that."

"If you look at the conditions, they ask people to represent that any ideas are not subject to and do not infringe upon any on third-party rights. We cannot ask individual researchers to make that determination."

—Brendan Rauw,
University of California, Los Angeles

Löffler said the terms of the Discovery Fast Track contest may have crossed the line into tech transfer office territory.

“The moment you are asked to say that none of what you’re disclosing has been committed to a third party, that evaluation can only be done at a tech transfer office,” she said. “This was probably the deal killer for UCLA.”

If Rauw’s argument takes hold at other campuses, applications to Discovery Fast Track would need to be individually evaluated by tech transfer offices. The upshot for the pharma could be a slower influx of fresh science ideas.

“There’s a common perception that universities let a lot of ideas go undeveloped,” said Rauw. “GSK is looking for ways to streamline the process and I fully support them in that, but there are proper steps required for good reason. We don’t want our faculty sending over their ideas before we’ve evaluated them for patent protection or for pre-existing third-party rights.”

A potential solution is for GSK to enter into a master agreement with the UC system that would authorize tech transfer offices to rapidly evaluate Discovery Fast Track applications.

Löffler noted that under a series of agreements with **Baxter International Inc.** that began in 2002, Northwestern researchers submit 36 early stage proposals a year to the pharma. Those proposals are vetted by her office.

Another example is a 2010 deal between **Pfizer Inc.**’s Centers for Therapeutic Innovation (CTI) and UCSF that covers the development of biologics for new targets discovered by UCSF researchers. Last month, the CTI-UCSF deal was expanded to cover small molecules.

“No company would allow its employees to enter into signed agreements, and the same thing happens in academia. At universities, the employees don’t own their IP, and employees aren’t allowed to sign deals.”

—*Alicia Löffler,*
Northwestern University

CTI CSO Anthony Coyle said that the master agreement allows UCSF researchers to submit exploratory research proposals akin to those solicited by GSK.

“A typical collaboration begins with CTI, in conjunction with its academic medical center partners, holding a call for proposals,” said Coyle. “Researchers submit nonconfidential pre-proposals for review to begin the process of vetting research projects for potential funding.”

Coyle said that UCSF’s tech transfer office handles third-party IP issues concerning the

proposals. UCSF’s Lium said that his office examines proposals prior to submitting them to CTI. The CTI-UCSF deal has thus far yielded eight biologics discovery projects.

Stubbee said that GSK has thus far received seven Discovery Fast Track proposals.

Rauw and Stubbee said GSK and UCLA will hold discussions today to try to resolve their issues.

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COMPANIES AND INSTITUTIONS MENTIONED

Baxter International Inc. (NYSE:BAX), Deerfield, Ill.

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

Northwestern University, Evanston, Ill.

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

University of California, Los Angeles, Calif.

University of California, San Francisco, Calif.

Watching obesity on a new channel

By C. Simone Fishburn, Senior Editor

Researchers at the **University of California, Irvine**, have found a potassium channel Kv1.3 inhibitor that may help treat obesity-related diseases.¹ The team had previously licensed one inhibitor, ShK-186, to **Kineta Inc.** for autoimmune indications—the biotech is now planning to test it also in obesity or metabolic syndrome.

Potassium channel Kv1.3 (KCNA3) has long been associated with immune regulation owing to its expression on effector-memory T cells.² Indeed, four companies have KCNA3 inhibitors in preclinical development for autoimmunity: **conoGenetix biosciences GmbH**, **Axxam S.p.A.**, **Bionomics Ltd.** and **Circassia Ltd.**

However, evidence has been mounting that inhibiting the channel may have additional regulatory functions.

In 2003, a group at **Yale University** reported the target was involved in regulating body weight. That team produced *Kcna3*^{-/-} knockout mice and found the animals were protected from diet-induced obesity and had an increased basal metabolic rate compared with wild-type animals.³

In 2011, researchers at Kineta were studying ShK-186 in monkeys and noticed that treated animals consistently had lower cholesterol levels than untreated controls.

These results led Shawn Iadonato, CSO at Kineta, to initiate a collaboration with George Chandy, professor of physiology and biophysics at UC-Irvine and a member of Kineta's scientific advisory board, to test the potential therapeutic use of ShK-186 in obesity.

First the researchers showed that mice receiving ShK-186 gained significantly less weight than vehicle-treated animals when given a high-fat diet to induce obesity.

In obese mice, the peptide decreased adiposity, hyperglycemia and insulin resistance, as measured by normalized blood levels of cholesterol, glucose, hemoglobin A1c (HbA1c), insulin, leptin and thyroid hormones. The molecule also decreased body weight and fatty liver.

Mice fed a normal chow diet showed no weight loss when given ShK-186, suggesting the high-fat diet itself may affect *Kcna3*-related pathways and make the target more sensitive to inhibition.

Mechanistic studies showed the peptide acts on brown adipose tissue (BAT) and the liver. BAT is a thermogenic form of fat that can take up triglycerides from white adipose tissue (WAT) and use them to generate heat, resulting in increased energy expenditure.

In BAT, the peptide affects β -oxidation, glycolysis and BAT transcription factors, all of which indicate activation of brown fat metabolism. The compound also increased glucose uptake specifically in BAT and increased sensitivity in an insulin tolerance test, while producing comparable changes in insulin levels to control treatment in a glucose tolerance test.

Together, these results suggest ShK-186 elicits anti-diabetic effects by increasing peripheral insulin sensitivity rather than by increasing insulin secretion from the pancreas.

In the liver, the peptide altered pathways of energy and lipid metabolism, including markers of gluconeogenesis, fatty acids and peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ)-activating metabolites, which most likely contribute to its effects on adiposity and blood markers of obesity.

Finally, ShK-186 decreased levels of tumor necrosis factor- α (TNF- α) in WAT, suggesting it can decrease obesity-induced inflammation.

Data were reported in *Proceedings of the National Academy of Sciences*.

Many mechanisms

Chandy and Iadonato think ShK-186's action on multiple pathways sets it apart from other drugs for obesity-related disorders.

According to Chandy, ShK-186 could work in obesity via a trio of distinct mechanisms: decreased peripheral insulin resistance, decreased obesity-induced inflammation and increased brown-fat activation.

"No other drug acts on type 2 diabetes and cholesterol, and enhances brown-fat activation," Chandy told *SciBX*.

Kineta completed a Phase I trial of ShK-186 in autoimmune disease in March; the molecule was well tolerated. ShK-186 produced no significant off-target effects in toxicity studies in rats and monkeys.

Next steps include examining ShK-186's role in obesity-related disorders in humans. Kineta has not yet decided whether it will pursue an obesity or metabolic syndrome indication.

Nora Volkow, director of NIH's **National Institute on Drug Abuse**, thinks the effects ShK-186 has in obesity and diabetes make it well suited to treat patients with metabolic syndrome who are candidates for bariatric surgery.

"What is very impressive is to be able to come out with an intervention that might eliminate the need for surgery," said Volkow, who is interested in the field owing to the role of food addiction in the growing incidence of obesity.

Volkow also believes that BAT activation is a key attribute of the compound. "If you can accelerate energy utilization via peripheral tissues, this is a major issue," she told *SciBX*.

Kineta has licensed the patent to ShK-186 from **Airmid Inc.**, a company cofounded by Chandy. Kineta is now in discussions with partners to co-develop the compound in metabolic syndrome or obesity.

Fishburn, C.S. *SciBX* 6(22); doi:10.1038/scibx.2013.537
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COMPANIES AND INSTITUTIONS MENTIONED

Airmid Inc., Redwood City, Calif.
Axxam S.p.A., Milan, Italy
Bionomics Ltd. (ASX:BNO; OTCBB:BMICY), Thebarton, SA, Australia
Circassia Ltd., Oxford, U.K.
conoGenetix biosciences GmbH, Martinsried/Planegg, Germany
Kineta Inc., Seattle, Wash.
University of California, Irvine, Calif.
Yale University, New Haven, Conn.
National Institutes of Health, Bethesda, Md.
National Institute on Drug Abuse, Bethesda, Md.

Nanoparticles for the flu

By Tracey Baas, Senior Editor

An NIH team has created a self-assembling influenza nanoparticle that induces the production of antibodies against a wider range of flu strains than traditional vaccines.¹ The team hopes to test the immunogenicity of the vaccine in humans once a GMP manufacturing process is developed.

The nanoparticle consists of a fusion of the influenza A virus hemagglutinin (HA) from New Caledonia H1N1 1999 strain and ferritin, an iron-storage protein from *Helicobacter pylori*.

Ferritin self-assembles into nanoparticles, and previous work has shown nanoparticles made up of 24 ferritin monomers could be used to display 24 peptides on the capsid surface by engineering an N-terminal fusion peptide with ferritin. The researchers used the peptide-ferritin nanoparticles in rats to generate high titers of antibody to an HIV Tat protein antigen.²

The NIH team hypothesized that the spacing between the ferritin units in the nanoparticle could yield HA proteins in the form of spike-like trimers that would mimic exactly the presentation of the protein on the surface of the influenza virus.

The group expressed the HA-ferritin fusion protein in mammalian cells and showed using electron microscopy that the self-assembled spherical nanoparticle presented eight trimeric viral spikes. To confirm the antigenicity of the HA trimer, the group showed that two mAbs against the H1N1 New Caledonia 1999 HA—one against the stem and one against the head—bound to the HA-ferritin nanoparticle.

In mice, an adjuvant plus the HA-ferritin nanoparticle led to about seven times more neutralizing antibodies than adjuvant plus a conventional trivalent inactivated influenza vaccine containing the same strain.

The HA-ferritin vaccine also induced broadly neutralizing antibodies that cross-reacted with mismatched virus.

The team then used the strategy to create a trivalent vaccine formulated as a single dose. They incorporated three HA-ferritin nanoparticles, presenting HA from the H1N1 California 2009 strain, the H3N1 Perth 2009 strain and the Florida 2006 strain.

Mice vaccinated with the trivalent HA-ferritin nanoparticle formulation plus adjuvant showed higher levels of neutralizing antibodies than mice vaccinated with a conventional trivalent vaccine plus adjuvant.

Ferrets immunized with the HA-ferritin nanoparticle plus adjuvant produced about ten times more neutralizing antibody than ferrets immunized with a conventional vaccine plus adjuvant. In addition, sera from the nanoparticle-immunized ferrets neutralized four of six different types of H1N1 viruses, whereas sera from conventionally immunized ferrets neutralized only one type of H1N1 virus.

Ferrets that were immunized with adjuvant plus HA-ferritin nanoparticles containing HA from New Caledonia H1N1 1999 and then challenged with a different strain of the virus showed less viral shedding and weight loss than ferrets immunized with adjuvant plus a regular trivalent vaccine.

Finally, the researchers performed detailed neutralization assays to help explain the broadly neutralizing capability of the antibodies induced by the HA-ferritin.

Those studies showed that the HA-ferritin nanoparticle vaccine induced antibodies targeting conserved regions of both the HA stem and the HA head in all the nanoparticle-immunized ferrets, in contrast to those given the conventional trivalent vaccine.

Antibodies that target conserved regions of the HA stem and the receptor binding site on the HA head should help limit viral escape.

Results were published in *Nature*.

“The studies are quite impressive to show that the vaccine can generate antibodies that recognize a conserved epitope within the receptor binding site of HA,” said JoAnn Suzich, VP and head of infectious disease and vaccines research at **MedImmune LLC**, the global biologics research and development arm of **AstraZeneca plc**.

The protein sequence of the HA head allows the virus to bind and enter host cells and is made up of conserved and variable regions that are used to categorize the different strains of influenza A virus. A vaccine that generates broadly neutralizing antibodies against the conserved receptor binding site on

the HA head could thus protect against multiple viral strains.

HA's humors

The NIH team now plans to test the safety and immunogenicity of the HA-ferritin nanoparticle in humans.

“Immunogenicity can be assessed both with hemagglutination-inhibition and virus-neutralization assays. These tests will determine whether the nanoparticle vaccine can elicit similar cross-protective antibodies in humans,” said Gary Nabel, who led the NIH team and was previously director of the NIH Vaccine Research Center. “Typically as you test immune responses in higher species, vaccine potency decreases, but the potent responses seen in both mice and ferrets give us hope that the potency will also be seen in humans.”

Nabel, who became SVP and CSO of **Sanofi** at the end of 2012, added, “because the vaccine leads to generation of antibodies that target both the HA stem and the receptor binding site on the HA head, we think the possibility that viruses will escape neutralization from either of two different antibodies is low.”

Sanofi had no involvement in the *Nature* work.

Steffen Mueller, president and CSO of viral vaccine company **Codagenix Inc.**, thinks manufacturing will be a challenge.

“The big question is, will they be able to make the nanoparticles in the amounts needed in a cost-effective way,” noted Mueller. “The science is very intriguing at the research laboratory scale, but to make this commercially feasible, they are going to have to take it to GMP levels, and that may be difficult because you’re going to have to produce a lot

“Typically as you test immune responses in higher species, vaccine potency decreases, but the potent responses seen in both mice and ferrets give us hope that the potency will also be seen in humans.”

—Gary Nabel,
National Institutes of Health

“What I would really be interested in seeing is for them to move closer to providing a universal vaccine by further modifying the HA so that it would produce even more broadly neutralizing antibodies.”

—JoAnn Suzich, MedImmune LLC

of nanoparticles.”

Nabel agreed: “Ultimately, the Vaccine Research Center team at NIH is going to have to see if it can manufacture the HA-ferritin nanoparticles in a simple way that can be scaled up before going on to

production. It’s possible because it’s essentially one gene being expressed in mammalian cell culture.”

The NIH team is also deciding which HA-ferritin nanoparticle vaccination strategy is most attractive.

“If the goal is to simply try to replace the seasonal trivalent or quadrivalent vaccines with a comparable formulation using the nanoparticles, the team can do that right now,” said Nabel. “In terms of a universal vaccination, they could use multiple, sequential vaccinations of nanoparticles with different HA strains to provide broad protection. They could also attempt to create an HA that doesn’t exist in nature but stimulates broad protection. At this stage, there is a lot of flexibility to develop different therapeutic strategies.”

“What I would really be interested in seeing is for them to move closer to providing a universal vaccine by further modifying the HA so that it would produce even more broadly neutralizing antibodies,” said Suzich.

Mueller also wanted to see whether the HA-ferritin nanoparticles provide better immunogenicity than another vaccination strategy in clinical development—influenza virus-like particles (VLPs).

Medicago Inc. and **Novavax Inc.** each have VLP-based vaccines against pandemic influenza and seasonal influenza in Phase I and II testing.

“Basically the NIH team’s HA-ferritin nanoparticle is acting like a VLP that presents only HA. Other VLPs are being developed that present not only HA but also neuraminidase and sometimes matrix proteins,” said Mueller.

Nabel thinks nanoparticles might provide better surface protein presentation to the immune system than do VLPs.

“The HA is displayed on the particle in a regular conformation but not too tightly packed so that the immune system can better see the viral spike,” he said. “In the traditional vaccine or some VLPs, HA is more crowded and may be less accessible.”

Beyond the flu

The NIH researchers also are interested in using the nanoparticle as a template to create vaccines that present proteins from other pathogens.

“There is a lot of interest in using the nanoparticle to express proteins that have a similar intermolecular distance between monomeric units of trimers, like the team did with influenza’s HA trimers,” said Nabel. “Some possibilities would be HIV, herpes simplex virus (HSV) or respiratory syncytial virus (RSV).”

He said that the NIH team is most interested in HIV. “Preliminary structural preparations show that the trimeric structure of the HIV-1 envelope protein would be amenable to this strategy. They’ve also got their eye on malaria but would have to determine which protein might be best incorporated into nanoparticle presentation.”

A patent application has been filed and is available for licensing from the NIH Office of Technology Transfer.

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COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Codagenix Inc., Stonybrook, N.Y.
Medicago Inc. (TSX:MDG; OTCQX:MDCGF), Quebec City, Quebec, Canada
MedImmune LLC, Gaithersburg, Md.
National Institutes of Health (NIH), Bethesda, Md.
Novavax Inc. (NASDAQ:NVAX), Rockville, Md.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

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	Epidermal growth factor receptor 3 (EGFR3; HER3; ErbB3); HER2 (EGFR2; ErbB2; neu)	<p>Patient sample and mouse studies identified oncogenic somatic mutations in <i>ERBB3</i> that could guide the use of HER2 and ErbB3 inhibitors. Whole-exome sequencing of 507 human primary tumor samples identified protein-altering somatic mutations in <i>ERBB3</i> in 12% of gastric cancers, 11% of colon cancers and sporadically in other types of cancer. In both mouse and human cell lines, <i>ERBB3</i> mutations plus <i>ErbB2</i> expression promoted oncogenic transformation, anchorage-independent growth and IL-3-independent cell survival. In a mouse model for <i>ErbB3</i> mutant leukemia, anti-ErbB3 mAbs or the anti-HER2 mAb Herceptin trastuzumab decreased disease severity and increased survival compared with a control mAb. Next steps include conducting studies to further elucidate the mechanisms by which mutant <i>ERBB3</i> drives oncogenesis.</p> <p>Roche's Genentech Inc. unit markets Herceptin to treat breast and gastric cancers (see <i>Driving cancer through ErbB3</i>, page 1).</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.539 Published online June 6, 2013</p>	Patent and licensing status undisclosed	<p>Jaiswal, B.S. <i>et al. Cancer Cell</i>; published online May 13, 2013; doi:10.1016/j.ccr.2013.04.012 Contact: Somasekar Seshagiri, Genentech Inc., South San Francisco, Calif. e-mail: sekar@gene.com</p>
Cancer	Integrin $\alpha_4\beta_1$ (CD49D/CD29)	<p>Human and mouse studies suggest inhibiting integrin $\alpha_4\beta_1$ could help prevent metastasis. In patient samples, integrin $\alpha_4\beta_1$ was expressed on 75% of lymphatic vessels from metastatic breast cancer samples and on 50% of lymphatic vessels from nonmetastatic breast cancer samples but at low levels in healthy samples. In mice with Lewis lung carcinoma, melanoma or pancreatic carcinoma cells, anti-integrin $\alpha_4\beta_1$ antibodies decreased metastasis compared with control antibodies. Next steps are to develop a human or humanized anti-integrin $\alpha_4\beta_1$ antibody for imaging lymph nodes associated with cancer and for therapeutic blockade of lymphangiogenesis and metastasis.</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.540 Published online June 6, 2013</p>	Therapeutic targeting and diagnostic analysis of vascular integrin $\alpha_4\beta_1$ patented; patent application filed for lymph node-specific findings; available for licensing	<p>Garmy-Susini, B. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 13, 2013; doi:10.1073/pnas.1219603110 Contact: Judith Varner, University of California, San Diego, La Jolla, Calif. e-mail: jvarner@ucsd.edu</p>
Cancer	Poliovirus receptor-related 4 (PVRL4)	<p><i>In vitro</i> and mouse studies suggest inhibiting PVRL4 could help treat cancer. A genetic screen to identify genes that promote anchorage-independent growth identified <i>PVRL4</i> as a top candidate. In a series of human cell lines, <i>PVRL4</i> drove cell-to-cell attachment, which was required for anchorage-independent growth. In mouse xenograft models for human breast cancer, small hairpin RNA knockdown of <i>PVRL4</i> or treatment with a mAb that disrupts PVRL4-mediated cell-to-cell attachment decreased tumor growth compared with no knockdown or treatment. Next steps include studies to understand the mechanisms by which <i>PVRL4</i> is upregulated in tumors.</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.541 Published online June 6, 2013</p>	Unpatented; licensing status not applicable	<p>Pavlova, N.N. <i>et al. eLife</i>; published online April 30, 2013; doi:10.7554/eLife.00358 Contact: Stephen J. Elledge, Harvard Medical School, Boston, Mass. e-mail: selledge@genetics.med.harvard.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Thrombospondin-1 (TSP-1; THBS1); prosaposin (PSAP)	Cell-based and mouse studies suggest increasing TSP-1 expression could help treat metastatic cancer. In a <i>Tsp-1^{-/-}</i> mouse xenograft model for metastatic cancer, transplant of Tsp-1-secreting bone marrow cells decreased metastasis compared with transplant of Tsp-1-deficient cells. Injection of a pentapeptide derived from PSAP, a protein that induces expression of Tsp-1, decreased metastasis compared with a control peptide. Next steps include mining additional components of the Tsp-1 pathway for therapeutic targets. SciBX 6(22); doi:10.1038/scibx.2013.542 Published online June 6, 2013	Patented; available for licensing	Catena, R. <i>et al. Cancer Discov.</i> ; published online April 30, 2013; doi:10.1158/2159-8290.CD-12-0476 Contact: Vivek Mittal, Weill Cornell Medical College, New York, N.Y. e-mail: vim2010@med.cornell.edu Contact: Randolph S. Watnick, Harvard Medical School, Boston, Mass. e-mail: randy.watnick@childrens.harvard.edu
Cancer	Tumor necrosis factor receptor 1 (TNFRSF1A; TNFR1; CD120a)	A study in mice suggests decreasing TNFRSF1A could improve the safety of tumor necrosis factor (TNF)-based cancer treatments. In mouse models for cancer, an anti-TNFRSF1A mAb decreased the frequency of lethal toxicity compared with control antibody but preserved the antitumor effect of TNF treatment. In transgenic mice expressing human <i>TNFRSF1A</i> , a pegylated anti-TNFRSF1A Fab fragment prevented acute TNF-mediated lethality but enabled full TNF-mediated tumor regression. Next steps include assessing heterogeneity of TNFRSF1A levels in human patients and confirming safety and efficiency of the antibody in other solid tumors, including in animal models for spontaneous tumor development. SciBX 6(22); doi:10.1038/scibx.2013.543 Published online June 6, 2013	Patent status not applicable; models and tools available for licensing	Van Hauwermeiren, F. <i>et al. J. Clin. Invest.</i> ; published online May 15, 2013; doi:10.1172/JCI65624 Contact: George Kollias, Biomedical Sciences Research Center Alexander Fleming, Vari, Greece e-mail: kollias@fleming.gr Contact: Claude Libert, Flancers Institute for Biotechnology and Ghent University, Ghent, Belgium e-mail: claude.libert@ugent.be
Chronic lymphocytic leukemia (CLL)	RAD51 homolog (RAD51); activation-induced cytidine deaminase (AICDA; AID)	Studies in patient-derived cells and in mice suggest antagonizing RAD51 could be useful for treating AID-expressing CLL. AID and RAD51 are enzymes involved in DNA repair. In a panel of samples from 74 patients with CLL, about 40% of tumors had higher AID expression than nontumor tissue. In cultured human CLL tumors with elevated AID levels, a RAD51 inhibitor decreased tumor growth and increased sensitivity to ionizing radiation compared with vehicle. Next steps include preclinical development of new chemical entities derived from the RAD51 inhibitor used in the study. Cyteir Therapeutics Inc.'s RAD51 inhibitor, C1523, is in preclinical development for AID ⁺ CLL and other AID-overexpressing malignancies. SciBX 6(22); doi:10.1038/scibx.2013.544 Published online June 6, 2013	Patent pending; licensed to Cyteir Therapeutics	Lamont, K.R. <i>et al. J. Exp. Med.</i> ; published online April 15, 2013; doi:10.1084/jem.20121258 Contact: Kevin D. Mills, The Jackson Laboratory, Bar Harbor, Maine e-mail: kevin.mills@jax.org
Melanoma	VEGF receptor 2 (KDR/Flk-1; VEGFR-2)	Mouse studies suggest co-delivery of engineered T cells expressing a chimeric antigen receptor (CAR) targeting VEGFR-2 and engineered T cells expressing tumor-specific T cell receptors (TCRs) could help treat melanoma. In lymphodepleted mice with established melanoma tumors, adoptive transfer of the two T cell populations plus a protocol to stimulate the transferred cells led to complete tumor regression and long-term, tumor-free survival. Next steps include dose-escalation safety studies of the anti-VEGFR-2, CAR-expressing T cells in patients. SciBX 6(22); doi:10.1038/scibx.2013.545 Published online June 6, 2013	Patent application filed; available for licensing	Chinnasamy, D. <i>et al. Cancer Res.</i> ; published online April 30, 2013; doi:10.1158/0008-5472.CAN-12-3913 Contact: Steven A. Rosenberg, National Institutes of Health, Bethesda, Md. e-mail: sar@mail.nih.gov

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Cardiomyopathy; heart failure	Growth differentiation factor 11 (GDF11)	Studies in mice suggest GDF11 could be useful for treating age-related cardiac hypertrophy. In an experimental system in which young and old mice share a circulatory system, long-term exposure to young blood reversed cardiac hypertrophy in old mice. In old mice, expression of Gdf11 was lower than that in young mice. In old mice, intraperitoneal injection of recombinant GDF11 decreased cardiac hypertrophy compared with vehicle injection. Next steps include testing levels of GDF11 in young and old humans and optimizing recombinant GDF11 to improve its stability <i>in vivo</i> .	Patent pending; available for licensing	Loffredo, F.S. <i>et al. Cell</i> ; published online May 9, 2013; doi:10.1016/j.cell.2013.04.015 Contact: Richard T. Lee, Brigham and Women's Hospital, Boston, Mass. e-mail: rlee@partners.org Contact: Amy J. Wagers, Harvard University, Cambridge, Mass. e-mail: amy_wagers@harvard.edu
Endocrine/metabolic disease				
Diabetes	Fatty acid binding protein 4 adipocyte (FABP4)	<i>In vitro</i> and mouse studies suggest blocking FABP4 could help treat diabetes. In primary hepatocytes and in lean mice, recombinant Fabp4 stimulated glucose production and gluconeogenesis. In obese mice, secretion of Fabp4 from adipocytes was greater than that in lean mice, and a neutralizing FABP4-targeting antibody decreased Fabp4 serum levels and increased glucose metabolism and clearance compared with a control antibody. Next steps include developing a humanized mAb targeting FABP4.	Patent application filed for the use of antibodies targeting FABP4 in diabetes; exclusively licensed to UCB Group	Cao, H. <i>et al. Cell Metab.</i> ; published online May 7, 2013; doi:10.1016/j.cmet.2013.04.012 Contact: Gökhan S. Hotamisligil, Harvard School of Public Health, Boston, Mass. e-mail: gshotamis@hsph.harvard.edu
Hematology				
Hemophilia	Factor VIII	Mouse studies suggest phosphatidylserine-bound factor VIII could help treat patients with hemophilia A. Patients with hemophilia A lack factor VIII and often develop an antibody response against factor VIII replacement therapy that limits therapeutic benefit. In a mouse model for hemophilia A, pretreatment with factor VIII linked to phosphatidylserine (FVIII-PS) led to a decreased anti-factor VIII antibody response compared with pretreatment using free factor VIII. Next steps include optimizing the FVIII-PS dosage and conducting clinical tests. At least nine companies have factor VIII-based compounds in development stages ranging from Phase II trials to market for treating hemophilia.	Patent application filed; available for licensing	Gaitonde, P. <i>et al. J. Biol. Chem.</i> ; published online May 6, 2013; doi:10.1074/jbc.C112.396325 Contact: Sathy V. Balu-Iyer, University at Buffalo, Buffalo, N.Y. e-mail: svb@buffalo.edu
Inflammation				
Inflammation	Dendritic cell- specific ICAM- 3 grabbing nonintegrin (DC- SIGN; CD209)	Cell culture and mouse studies identified DC-SIGN-binding mannodendrimers that could help treat inflammatory diseases. Mannodendrimers are comprised of poly(phosphorhydrazone) dendrimers grafted with mannose units of varying length. In lipopolysaccharide (LPS)-stimulated human dendritic cells, the mannodendrimers selectively bound to DC-SIGN and decreased tumor necrosis factor- α (TNF- α) secretion compared with vehicle. In a mouse model for LPS-induced acute lung inflammation, a mannodendrimer decreased lung neutrophil recruitment compared with vehicle. Next steps could include testing the mannodendrimer in additional mouse models for inflammatory diseases.	Patent and licensing status unavailable	Blattes, E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 13, 2013; doi:10.1073/pnas.1221708110 Contact: Germain Puzo, Institute of Pharmacology and Structural Biology, Toulouse, France e-mail: germain.puzo@ipbs.fr

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	Peripheral benzodiazepine receptor (TSPO; PBR)	Mouse studies suggest TSPO ligands could be used to treat AD. TSPO ligands have been shown to be neuroprotective. In both young adult and aged adult transgenic mouse models for AD, intraperitoneal injection of the TSPO ligand Ro5-4864 led to increases in working memory and attention compared with vehicle. In these mice, Ro5-4864 also decreased hippocampal β -amyloid ($A\beta$) accumulation, gliosis and anxiety. In normal mice, combined injection of Ro5-4864 and another TSPO ligand, PK-11195, significantly decreased $A\beta$ 40 levels compared with vehicle ($p < 0.001$). Ongoing efforts include evaluating TSPO ligands with neural permeability.	Patent and licensing status undisclosed	Barron, A.M. <i>et al. J. Neurosci.</i> ; published online May 15, 2013; doi:10.1523/JNEUROSCI.1350-13.2013 Contact: Christian J. Pike, University of Southern California, Los Angeles, Calif. e-mail: cjpike@usc.edu
SciBX 6(22); doi:10.1038/scibx.2013.550 Published online June 6, 2013				
Depression	Protocadherin 17 (PCDH17)	Mouse and nonhuman primate studies suggest inhibiting PCDH17 could help treat depression. In those animals, Pcdh17 was expressed in corticobasal ganglia circuits that carry signals between neurons of the cerebral cortex and the thalamus. In mice, knocking out <i>Pcdh17</i> increased synaptic transmission efficacy in corticobasal ganglia circuits and decreased depressive behaviors compared with no knockout. Next steps include solving the crystal structure of the PCDH17 extracellular domain to understand its behavior across synapses.	Unpatented; licensing status not applicable	Hoshina, N. <i>et al. Neuron</i> ; published online May 16, 2013; doi:10.1016/j.neuron.2013.03.031 Contact: Tadashi Yamamoto, Okinawa Institute of Science and Technology Graduate University, Onna-son, Japan e-mail: tadashi.yamamoto@oist.jp
SciBX 6(22); doi:10.1038/scibx.2013.551 Published online June 6, 2013				
Other				
Progeria	Isoprenylcysteine carboxyl methyltransferase (ICMT)	Mouse and cell culture studies suggest inhibiting ICMT could help treat Hutchinson-Gilford progeria syndrome (HGPS), which causes premature aging. In a mouse model for HGPS, expression of an <i>Icmt</i> variant with decreased function improved gait and increased both body weight and survival compared with expression of wild-type <i>Icmt</i> . In fibroblasts from patients with HGPS, <i>ICMT</i> -targeting small hairpin RNA or a competitive ICMT inhibitor delayed senescence and increased proliferation compared with control shRNA or vehicle. Next steps include testing <i>Icmt</i> knockdown or ICMT inhibitors in additional mouse models for progeria.	Patent and licensing status undisclosed	Ibrahim, M.X. <i>et al. Science</i> ; published online May 16, 2013; doi:10.1126/science.1238880 Contact: Martin O. Bergo, University of Gothenburg, Gothenburg, Sweden e-mail: martin.bergo@gu.se
SciBX 6(22); doi:10.1038/scibx.2013.552 Published online June 6, 2013				
Pulmonary disease				
Cystic fibrosis (CF)	Cystic fibrosis transmembrane conductance regulator (CFTR)	<i>In vitro</i> and cell culture studies identified the molecular mechanism of action for CFTR corrector compounds and suggest new combination approaches that could help treat CF. In reconstituted phospholipid bilayers carrying recombinant $\Delta F508$ CFTR, the corrector compound VX-809 directly bound the protein and stabilized the interface between nucleotide binding domain 1 and membrane spanning domains 1 and 2. In cultured cells and samples from patients with CF that have the $\Delta F508$ CFTR mutation, VX-809 plus either of two compounds that help stabilize protein folding increased functional CFTR expression compared with any individual treatment. Next steps include identifying drug-like stabilizers of NBD1 folding, which could be combined with VX-809 or other CFTR correctors. Vertex Pharmaceuticals Inc.'s VX-809, a CFTR corrector, is in Phase III trials to treat $\Delta F508$ mutant CF in combination with the CFTR potentiator Kalydeco ivacaftor (VX-770). Vertex's VX-661, a CFTR corrector that is structurally related to VX-809, is in Phase II trials in combination with Kalydeco to treat $\Delta F508$ CF. Vertex markets Kalydeco to treat CF.	Patent and licensing status unavailable	Okiyoneda, T. <i>et al. Nat. Chem. Biol.</i> ; published online May 12, 2013; doi:10.1038/nchembio.1253 Contact: Gergely L. Lukacs, McGill University, Montreal, Quebec, Canada e-mail: gergely.lukacs@mcgill.ca
SciBX 6(22); doi:10.1038/scibx.2013.553 Published online June 6, 2013				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Transplantation				
Graft-versus-host disease (GvHD)	Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)	TRAIL-overexpressing T cells could be useful for both treating GvHD and improving antitumor immunity following a hematopoietic stem cell transplant (HSCT). Mouse and human T cells were engineered to overexpress TRAIL, which is known to mediate graft-versus-tumor effects after HSCT. In mice receiving allogeneic HSCT and grafted with murine lymphoma cells, adoptive transfer of the TRAIL-overexpressing T cells resulted in 100% survival at 100 days, whereas mice receiving T cells without overexpression died from GvHD and lymphoma. In cell lines and samples from patients who have chronic lymphocytic leukemia (CLL), the human, TRAIL-overexpressing T cells showed more potent killing of both CLL and alloreactive T cells than did T cells with normal TRAIL expression. Next steps include developing a clinical trial to evaluate use of TRAIL-overexpressing T cells in patients whose disease has relapsed after an allogeneic HSCT.	Unpatented; licensing status not applicable	Ghosh, A. <i>et al. J. Clin. Invest.</i> ; published online May 15, 2013; doi:10.1172/JCI66301 Contact: Arnab Ghosh, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: ghosha1@mskcc.org
		<i>SciBX</i> 6(22); doi:10.1038/scibx.2013.554 Published online June 6, 2013		

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			
Clustered, regularly interspaced short palindromic repeats (CRISPR)-based editing system for one-step production of multigene knockout mice	CRISPR-based genome editing could be used to rapidly generate mice with multiple genetic mutations. Injection of one-cell mouse embryos with different concentrations of mRNA encoding CRISPR-associated protein 9 (Cas9) along with guide RNAs targeting two independent genes led to disruption of all four alleles 50%–90% of the time. In mouse embryonic stem cells, the CRISPR-based system was capable of disrupting up to five genes at once. Next steps include further optimizing the efficiency of the approach and determining whole-genome specificity. SciBX 6(22); doi:10.1038/scibx.2013.555 Published online June 6, 2013	Patent and licensing status unavailable	Wang, H. <i>et al. Cell</i> ; published online May 2, 2013; doi:10.1016/j.cell.2013.04.025 Contact: Rudolf Jaenisch, Whitehead Institute for Biomedical Research, Cambridge, Mass. e-mail: jaenisch@wi.mit.edu
Modeling skeletal muscle deficits in Huntington's disease (HD)	Mouse muscle fibers could be useful for modeling HD-associated musculoskeletal deficits and could aid the development of new therapies to treat the disease. In a mouse model for HD, <i>ex vivo</i> skeletal muscle fibers were hyperexcitable because of dysfunction in muscle chloride channel 1 (Clcn1) and in potassium channels. In the affected muscle fibers, <i>Clcn1</i> and potassium channel mRNA levels were both lower than those in wild-type muscle fibers, and the <i>Clcn1</i> mRNA appeared aberrantly spliced. Next steps include assessing the development of the observed muscle fiber deficits in longitudinal studies, assessing other mouse models and determining whether such deficits are present in muscle fibers from patients with HD. SciBX 6(22); doi:10.1038/scibx.2013.556 Published online June 6, 2013	Patent and licensing status undisclosed	Waters, C.W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 13, 2013; doi:10.1073/pnas.1220068110 Contact: Andrew A. Voss, California State Polytechnic University, Pomona, Calif. e-mail: aavoss@csupomona.edu
Mouse model for autosomal-dominant leukodystrophy (ADLD)	A mouse model for adult-onset ADLD could be useful for identifying myelin regeneration therapies to treat ADLD and multiple sclerosis (MS). ADLD is a rare genetic disease caused by duplication of <i>lamin B1</i> (<i>LMNB1</i>) and is often misdiagnosed as chronic progressive MS. Mice engineered to overexpress <i>Lmnb1</i> in oligodendrocytes showed increased myelin abnormalities, demyelination and motor deficits compared with wild-type mice. Next steps include testing the effect of myelin regeneration therapies in the model. SciBX 6(22); doi:10.1038/scibx.2013.557 Published online June 6, 2013	Unpatented; licensing status not applicable	Heng, M.Y. <i>et al. J. Clin. Invest.</i> ; published online May 15, 2013; doi:10.1172/JCI66737 Contact: Ying-Hui Fu, University of California, San Francisco, Calif. e-mail: ying-hui.fu@ucsf.edu Contact: Louis J. Ptáček, same affiliation as above e-mail: ljp@ucsf.edu
Mouse model for partner and localizer of <i>Brca2</i> (<i>Palb2</i>)-deficient breast cancer	A mouse model for <i>Palb2</i> -deficient breast cancer could be useful for evaluating new therapies. Mutations in <i>PALB2</i> are associated with increased risk of breast cancer, but genetically engineered mouse models to study the gene's function were unavailable because <i>Palb2</i> deletion causes embryonic lethality. In the new model, mice were engineered to carry <i>Palb2</i> that could be conditionally inactivated. In this model, <i>Palb2</i> was shown to synergize with <i>p53</i> to suppress breast tumor formation. Next steps could include using the mouse model to evaluate therapies to treat <i>PALB2</i> mutant breast cancer. SciBX 6(22); doi:10.1038/scibx.2013.558 Published online June 6, 2013	Patent and licensing status unavailable	Bowman-Colin, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 8, 2013; doi:10.1073/pnas.1305362110 Contact: David M. Livingston, Dana-Farber Cancer Institute, Boston, Mass. e-mail: david_livingston@dfci.harvard.edu Contact: Chryssa Kanellopoulou, National Institutes of Health, Bethesda, Md. e-mail: chrysi.kanellopoulou@nih.gov

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Direct conversion of fibroblasts to insulin-secreting cells using DNA demethylating agents	<p><i>In vitro</i> and mouse studies suggest demethylating agents could be used to directly convert adult fibroblasts into insulin-producing cells. Adult human skin fibroblasts were exposed first to the DNA demethylating agent Vidaza azacitidine and then to a three-step pancreatic differentiation protocol to produce a population containing about 35% pancreatic cells. In culture, the converted pancreatic cells released insulin in response to glucose challenge. In mice with chemically induced diabetes, injection of the converted pancreatic cells into the spinal cord restored normal glucose levels and tolerance. Next steps include developing a protocol to produce patient-specific pancreatic cells. Celgene Corp., Pfizer Inc. and Nippon Shinyaku Co. Ltd. market the DNA methyltransferase inhibitor Vidaza azacitidine to treat myelodysplastic syndrome (MDS). Celgene and Pfizer also market the drug to treat acute myelogenous leukemia (AML).</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.559 Published online June 6, 2013</p>	Patent application filed; available for licensing	<p>Pennarossa, G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 21, 2013; doi:10.1073/pnas.1220637110 Contact: Tiziana A.L. Brevini, University of Milan, Milan, Italy e-mail: tiziana.brevini@unimi.it</p>
Humanized shark variable new antigen receptors (VNARs)	<p>Humanized versions of VNARs could be used to bind protein epitopes that are difficult to access using traditional antibodies. VNARs are a class of small, immunoglobulin-like molecules from the shark immune system. A VNAR specific for human serum albumin (ALB) was isolated from the spiny dogfish shark, and humanized variants were generated by substituting over 60% of the antibody's non-complementarity-determining region (CDR) residues with those from a human antibody sequence. <i>In vitro</i> immunoassays showed that the lead humanized VNAR retained its specificity and ability to bind human serum ALB. Crystal structures in complex with human serum ALB showed that the VNARs bound in a manner distinct from that of previously described VNARs. Next steps could include generating humanized shark VNARs against known disease targets. Separately, Ossianix Inc. and H. Lundbeck A/S have partnered to develop shark VNARs to treat CNS diseases.</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.560 Published online June 6, 2013</p>	Patent and licensing status unavailable	<p>Kovalenko, O.V. <i>et al. J. Biol. Chem.</i>; published online April 30, 2013; doi:10.1074/jbc.M112.435289 Contact: Oleg V. Kovalenko, Pfizer Inc., Cambridge, Mass. e-mail: oleg.kovalenko@pfizer.com</p>
Imaging			
High-density lipoprotein (HDL)-mimicking nanoparticles to detect vulnerable atherosclerotic plaques	<p><i>In vitro</i> and rat studies identified synthetic, HDL-mimicking nanoparticles that could help detect vulnerable atherosclerotic plaques, which can rupture and cause fatal blood clots. The nanoparticles consist of a poly(lactic-co-glycolic acid) (PLGA) core, cholesteryl oleate and quantum dots plus a phospholipid bilayer containing an apolipoprotein A-1 (APOA1) mimetic and triphenylphosphonium. The nanoparticles accumulated in healthy macrophages but not in apoptotic macrophages, which creates a contrast between the two populations during fluorescence imaging. Apoptotic macrophages are associated with vulnerable atherosclerotic plaques. In rats, the nanoparticles also decreased total cholesterol and triglyceride levels compared with vehicle, which suggests a potential therapeutic benefit. Next steps include testing the nanoparticles in animal models for atherosclerosis.</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.561 Published online June 6, 2013</p>	Patented; available for licensing	<p>Marrache, S. & Dhar, S. <i>Proc. Natl. Acad. Sci. USA</i>; published online May 13, 2013; doi:10.1073/pnas.1301929110 Contact: Shanta Dhar, The University of Georgia, Athens, Ga. e-mail: shanta@uga.edu</p>
Instrumentation			
Poly(carboxybetaine methacrylate) (PCBMA), zwitterionic hydrogels to coat implantable devices	<p>Mouse studies identified PCBMA hydrogels that could be applied to implantable devices to prevent foreign body reactions. Foreign body reactions cause encapsulation of implanted devices in collagen capsules. In mice, collagen density around implanted PCBMA hydrogels was only 30%–40%, whereas around clinically available poly(2-hydroxyethyl methacrylate) (PHEMA) it was higher than 90% and accompanied by increased inflammation. Next steps could include testing the zwitterionic hydrogels as device coatings.</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.562 Published online June 6, 2013</p>	Patent and licensing status unavailable	<p>Zhang, L. <i>et al. Nat. Biotechnol.</i>; published online March 12, 2013; doi:10.1038/nbt.2580 Contact: Shaoyi Jiang, University of Washington, Seattle, Wash. e-mail: sjiang@uw.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
<i>G-CSF receptor (CSF3R; CD114)</i> mutations to guide diagnosis and treatment of atypical chronic myelogenous leukemia (aCML) and chronic neutrophilic leukemia (CNL)	<p>Patient sample studies suggest mutations in <i>CD114</i> could help diagnose aCML and CNL and guide treatment decisions for the diseases. Activating mutations in <i>CD114</i> were found in 16 of 27 patients with CNL or aCML, which is defined as <i>BCR-ABL tyrosine kinase</i>-negative CML. In patient samples, those with <i>CD114</i> truncation mutations were sensitive to Sprycel dasatinib, whereas those with <i>CD114</i> membrane proximal mutations were sensitive to Jakafi ruxolitinib. In one patient with CNL who had <i>CD114</i> membrane proximal mutations, Jakafi normalized platelet counts and decreased white blood cell and neutrophil counts. Next steps include clinical trials to evaluate the drugs in patients who have <i>CD114</i> mutations.</p> <p>Incyte Corp. and Novartis AG market Jakafi, a Janus kinase-1 (JAK-1) and JAK-2 inhibitor, to treat myeloproliferative disorder. Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel, a small molecule inhibitor of BCR-ABL tyrosine kinase and Src, to treat acute lymphoblastic leukemia (ALL) and CML.</p> <p>SciBX 6(22); doi:10.1038/scibx.2013.563 Published online June 6, 2013</p>	Patent application filed; available for licensing	<p>Maxson, J.E. <i>et al. N. Engl. J. Med.</i>; published online May 9, 2013; doi:10.1056/NEJMoa1214514</p> <p>Contact: Jeffrey W. Tyner, Oregon Health & Science University, Portland, Ore. e-mail: tynerj@ohsu.edu</p>

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