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B cell lymphoma and the microbiome

By Kai-Jye Lou, Senior Writer

A key challenge in mining the microbiome for therapeutic strategies has been to characterize the functional role of specific bacterial populations in the context of a disease. Now, University of California researchers have shown the gut microbiome is a key contributor to lymphoma risk and identified specific alterations to microbiome composition that could potentially attenuate this risk.¹

The UC researchers are sifting through a set of bacterial species to identify those that could be used as probiotics or targeted to alter disease phenotypes, and have founded **Microbio Pharma Inc.** to develop and commercialize resulting products.

For more than a decade, Robert Schiestl has been using lymphoma-prone, *ataxia telangiectasia mutated (Atm)* knockout mice to study mechanisms that drive carcinogenesis.

Schiestl is a professor in the departments of pathology and laboratory medicine, environmental health sciences, and radiation oncology at the **University of California, Los Angeles.**

Ataxia telangiectasia is an autosomal recessive neurodegenerative disorder caused by mutations in *ATM*, which has roles in cell cycle control and DNA repair. In addition to neuromuscular and immune system deficits, patients with the condition also have a high risk of developing hematological malignancies, and the majority of those cases are B cell lymphomas.²

Researchers from Schiestl's lab and others have found large disparities among different types of *Atm*-knockout mice in the time to lymphoma onset and median lifespan.³⁻⁵ The mechanistic underpinnings of these disparities were unclear.

After ruling out genetic diversity as the culprit, Schiestl's group sought to determine whether environmental factors such as housing conditions and diet could be responsible for the differences. In 2006, the group reported that *Atm*-knockout mice housed in sterile conditions had delayed lymphoma onset and much longer lifespans than those housed in nonsterile conditions.⁶

That result suggested the culprit could be microbial in origin.

In the current study, Schiestl's group sought to determine the specific

“This is a novel and important result that opens the way for more targeted and mechanistic studies to analyze the specific role of bacterial species and their mechanism of action.”

—Giorgio Trinchieri,
National Cancer Institute

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microbes responsible for the differences in disease latency and lifespan in the *Atm*-knockout mice.

In *Atm*-knockout mice from colonies housed under sterile conditions, genetic instability decreased and lymphoma latency and lifespans increased gradually from one generation to the next. Compared with *Atm*-knockout mice housed under nonsterile conditions, those housed under sterile conditions had less genetic instability and longer lymphoma latency and lifespans.

The researchers ruled out external microbial sources as the culprit because the benefits were transmissible in mice housed under sterile conditions. Thus, Schiestl looked at internal microbial sources—namely the gut microbiome.

Indeed, multiple recent studies have linked dysregulation of the gut microbiome to various cancers, including those outside the gastrointestinal system.^{7–11}

Analysis of fecal pellets showed the gut microbiome in *Atm*-knockout mice housed under sterile conditions had less diversity and different dominant bacterial species than the more conventional microbiome of those housed under nonsterile conditions.

To confirm microbiome differences were responsible, the researchers used the same parental mouse strain to establish two colonies of *Atm*-knockout mice—each with one of the distinct gut microbiome phenotypes. The two mouse colonies recapitulated the differences in genetic instability and lifespans seen in mice housed under sterile and nonsterile conditions.

Additional microbiome profiling of these two mouse colonies showed that one of the most prominent differences was increased abundance of *Lactobacillus johnsonii* in the restricted gut microbiome compared with the more diverse, conventional microbiome.

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In *Atm*-knockout mice harboring the more diverse microbiome, oral administration of *L. johnsonii* decreased multiple markers of lymphoma risk such as oxidative stress, DNA damage, systemic inflammation and micronucleus formation compared with saline.

Results were published in *Cancer Research* and included authors at the **University of California, Riverside**.

“The data, in a correlative way, link differences in the microbiota with systemic oxidation state, inflammation and genotoxicity,” said Giorgio Trinchieri, director of the cancer and inflammation program and chief of the laboratory of experimental immunology at the **National Cancer Institute**. “This is a novel and important result that opens the way for more targeted and mechanistic studies to analyze the specific role of bacterial species and their mechanism of action.”

Revealing relevant bacteria

Schiestl said the studies have yielded a repertoire of bacterial species that vary between the two gut microbiome profiles. His group now is evaluating how changing individual bacterial populations affects the disease phenotype in *Atm*-knockout mice.

“We are inoculating our mice with these bacterial strains one by one to see if and how we change the disease phenotype,” he told *SciBX*.

Schiestl said one group of gut bacteria that deserves extra scrutiny is *Helicobacter*. “In addition to *H. pylori*, which are already linked to intestinal inflammation and cancer, we

found five other *Helicobacter* species that are more prevalent in the conventional microbiomes than in the less diverse, restricted microbiomes,” he noted.

Because the current study only evaluated the effects of *L. johnsonii* supplementation on markers of lymphoma risk in the *Atm*-knockout mice, Schiestl said his group still needs to run studies to show the direct effect *L. johnsonii* supplementation has on lymphoma onset and lifespan.

Trinchieri wanted to see more comprehensive studies to elucidate the underlying mechanisms and to determine how much of the mouse data will translate into humans.

“Better understanding of the molecular mechanisms in the mouse system and analysis of the contribution of different bacterial species and their effector molecules should be the objective of future studies,” he told *SciBX*.

In terms of therapeutic strategies, Schiestl noted that oral supplementation with bacterial species identified as beneficial and development of compounds that selectively kill off bacterial species

identified as harmful are possible approaches but declined to provide details.

Compounds to selectively kill specific bacterial populations include narrow-spectrum antibiotics and bacteriophages. The latter can be freeze-dried and turned into pills without losing efficiency, and phage-based products such as **Intralytix Inc.**'s ListShield and SalmoFresh have ‘generally recognized as safe’ (GRAS) status from **FDA**.

ListShield is a blend of phages that target and kill specific pathogenic strains of *Listeria monocytogenes*. SalmoFresh is a blend of phages that target and kill *Salmonella enterica*. Intralytix markets both as products to decrease food contamination and prevent food-borne illnesses.

Schiestl said the group plans to develop probiotic products based on its research and commercialize them through Microbio Pharma.

Trinchieri agreed that supplementation strategies could temporarily alter the gut microbiome, but thinks permanent changes may be more difficult to achieve. Moreover, he cautioned that changing the gut microbiome, particularly by adding individual bacterial species, may alter the equilibrium of the commensal population and have effects that are difficult to predict.

The Regents of the University of California have multiple pending patents that cover the findings described in the *Cancer Research* paper. Schiestl said he should be contacted directly for potential partnership and/or investment opportunities.

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COMPANIES AND INSTITUTIONS MENTIONED

Intralytix Inc., Baltimore, Md.
Microbio Pharma Inc., Los Angeles, Calif.
National Cancer Institute, Bethesda, Md.
University of California, Los Angeles, Los Angeles, Calif.
University of California, Riverside, Riverside, Calif.
Food and Drug Administration, Silver Spring, Md.

“Better understanding of the molecular mechanisms in the mouse system and analysis of the contribution of different bacterial species and their effector molecules should be the objective of future studies.”

—**Giorgio Trinchieri, National Cancer Institute**

Translational tidbits

By Lev Osherovich, Senior Writer, C. Simone Fishburn, Senior Editor and Kai-Jye Lou, Senior Writer

Scripps' Sigma factor

Academic and industry researchers eager to use new tool compounds typically must reproduce synthetic schemes published in academic journals or wait months for reagent makers to list new compounds in their catalogs. To speed up the process, **The Scripps Research Institute** has partnered with **Sigma-Aldrich Corp.** to fast-track access to new research reagents from Scripps chemistry labs.

The deal gives the reagent maker exclusive, early access to tool compounds from six of the institute's chemistry labs. The agreement initially covers IP from labs led by professors Phil Baran, Jin-Quan Yu, Benjamin Cravatt, Carlos Barbas, Philip Dawson and K. Barry Sharpless.

The goal is to have commercial batches of the compounds available from Sigma-Aldrich as soon as a paper describing the compounds is published online.

"Today, when a paper gets published, the reagents aren't necessarily commercially available until 6 to 12 months later," said Amanda Halford, VP of academic research at Sigma-Aldrich. "We want to cut that timeline and make the reagents available exactly at the time of publication."

Table 1. Selected public-private partnerships for July 2013. Europe has had a busy month with public-private partnerships. Significant PPPs announced in July included the U.K.'s SynbiCITE synthetic biology innovation and knowledge center and France's Nano Innovation for Cancer (NICE) consortium to promote the development of nanomedicines. In the U.S., **Sigma-Aldrich Corp.** (NASDAQ:SIAL) announced it will provide undisclosed development funding and exclusively commercialize reagents from six labs at **The Scripps Research Institute**.

Source: *Biocentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
Agilent Technologies Inc. (NYSE:A); GlaxoSmithKline plc (LSE:GSK; NYSE:GSK); Hockley International Ltd. ; Lisk and Jones Consultants Ltd. ; Microsoft Corp. (NASDAQ:MSFT); New-Food Innovation Ltd. ; Oil Plus Ltd. ; Oxitec Ltd. ; Pulse Medical Technologies Ltd. ; Royal Dutch Shell (NYSE:RDS-A); Suterra LLC ; Syngenta AG (SIX:SYNN; NYSE:SYT); Visbion Ltd.	Bangor University ; Biotechnology and Biological Sciences Research Council (BBSRC) ; Cardiff University ; Engineering and Physical Sciences Research Council (EPSRC) ; Imperial College London ; Newcastle University ; Queen's University of Belfast ; Royal College of Art ; Swansea University ; U.K. Technology Strategy Board ; University College London ; University of Birmingham ; University of Bristol ; University of Cambridge ; University of Edinburgh ; University of Glasgow ; University of Oxford ; University of Sheffield	Other	£5 million (\$7.6 million) received plus £5 million over next two years; another £14 million (\$21.2 million) promised by industry partners	SynbiCITE innovation and knowledge center to translate synthetic biology research into applications
BioAlliance Pharma S.A. (Euronext:BIO); DBI S.A.S. ; Nanobiotix S.A. (Euronext:NANO)	Institut Galien Paris-Sud ; CEA-Leti	Cancer	€9 million (\$11.7 million)	Nano Innovation for Cancer (NICE) five-member consortium to build a platform to accelerate the development and industrialization of nanomedicine in France
AB Science S.A. (Euronext:AB); Skuldtech	Brain and Spine Institute (ICM) ; French Alternative Energies and Atomic Energy Commission (CEA) ; Institut National de la Santé et de la Recherche Médicale (INSERM) ; Imagine Foundation	Neurology	€8.6 million (\$11.3 million)	Role of Mast Cells in Neurology (ROMANE) consortium to develop AB Science's masitinib (AB1010) to treat Alzheimer's disease (AD)
BioNTech AG ; immatics biotechnologies GmbH ; BCN Peptides	Association for Cancer Immunotherapy ; Beatson West of Scotland Cancer Centre ; Eberhard Karls University of Tuebingen ; Herlev Hospital ; Leiden University Medical Centre ; University of Pittsburgh ; University Hospital of Geneva ; Heidelberg University Hospital ; University of Southampton ; Technion-Israel Institute of Technology ; Vall d'Hebron University Hospital	Cancer	€6 million (\$7.8 million)	Glioma Actively Personalized Vaccine Consortium (GAPVAC) to develop a new class of therapeutic cancer vaccines for brain cancer with grant funding from EU's Seventh Framework Program (FP7)
Imaxio S.A. ; Preclin Biosystems AG	European Vaccine Initiative ; University of Oxford	Infectious	€5.5 million (\$7.2 million)	Bellerophon Project to develop a vaccine against <i>Staphylococcus aureus</i> with grant funding from EU FP7
AstraZeneca plc	Cancer Research UK ; University of Cambridge	Cancer	Unavailable	Two-year collaboration comprised of three projects to research tumor mutations and therapies in various cancers

(Continues on p. 5)

Table 1. Selected public-private partnerships for July 2013. (continued)

Companies	Institutions	Business area	Disclosed value	Purpose
AstraZeneca plc	Tufts University	Neurology	Undisclosed	Collaboration to research discovery-level compounds and validate targets for various brain diseases and disorders, including AD, Parkinson's disease (PD) and autism spectrum disorders
FIT Biotech Oyj Plc	Catholic University of Leuven (KU Leuven)	Cancer; Infectious	Undisclosed	Collaboration to develop immunotherapies based on FIT Biotech's gene transport unit (GTU) technology for transient <i>in vivo</i> expression of mAbs
Ipsen Group (Euronext:IPN; Pink:IPSEY);	Harvard University	Neurology	Undisclosed	Harvard University to discover and develop engineered recombinant botulinum toxins to treat neurological diseases with funding from Ipsen
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151)	La Jolla Institute for Allergy & Immunology	Autoimmune; inflammation	Undisclosed	Collaboration to research and develop therapies for inflammatory and autoimmune indications
NeoStem Inc.(NYSE-M:NBS)	University of California, San Francisco	Endocrine/metabolic; inflammation; transplantation	Undisclosed	Collaboration to develop human T _{reg} cells to treat type 1 diabetes, steroid-resistant asthma and organ-transplant rejection
Pharming Group N.V. (Euronext:PHARM)	China State Institute of Pharmaceutical Industry	Hematology; inflammation	Undisclosed	Collaboration to develop, manufacture and commercialize recombinant human proteins using Pharming's GMP-compliant platform
Sigma-Aldrich Corp.	The Scripps Research Institute	Supply/service	Undisclosed	Sigma-Aldrich to provide development funding and exclusively commercialize reagents from six labs at Scripps
UCB Group (Euronext:UCB)	Lieber Institute for Brain Development	Neurology	Undisclosed	Collaboration to discover compounds to treat cognitive impairment

Scott Forrest, VP of business development at Scripps, said the deal builds on previous collaborations between individual Scripps researchers and Sigma-Aldrich and gives the reagent maker broad and early access to composition of matter IP.

"Traditionally, a tech transfer office signs a series of one-off reagent deals, but this is time and labor intensive," said Forrest. "We were highly interested in finding a reagent partner of choice" to replace the individual deals covering specific reagents.

Under the deal, key compounds in peer-reviewed papers from the six labs will be assigned Sigma-Aldrich catalog numbers at the time of publication. Papers will include hyperlinks to Sigma-Aldrich's ordering website.

It takes up to half a year to scale up and synthesize commercial quantities of most research reagents, but Halford said the deal's early-access terms will give the company sufficient lead time to deliver the compounds by the publication date.

"To scale up the synthesis, we need to work out the process

development," said Halford. "The goal is to do this as quickly as possible so there is no delay in the publication."

Financial terms were not disclosed.

The agreement does not give Sigma-Aldrich access to IP for therapeutic candidates and covers only tool compounds and reagent platforms that do not have direct biomedical applications.

"This agreement is focused on reagents that are used in the discovery process," said Halford, adding that the deal has already given the company "a pipeline covering chemical-biology probes and click chemistry from the Sharpless laboratory."

Click chemistry is a modular approach to small molecule design that was originally developed in the early 2000s by Sharpless and other chemists.

Forrest and Halford said the deal was inspired by the success of Sigma-Aldrich's series of zinc-based difluoromethylation compounds from Baran's lab.¹ Those compounds, which came on the market last year, have been widely adopted in medicinal chemistry laboratories

in academia and industry as an easy way to fluoridate pharmaceutical leads.

Diagnosing patent rulings

A common sentiment expressed at last month's [Technology Transfer Summit of North America](#) was that a new patent law and multiple U.S. Supreme Court rulings have collectively altered the way technology transfer organizations (TTOs) approach patenting university inventions. The most profound effects are on diagnostic-based discoveries.

As of mid-March, new patent filings are subject to the Leahy-Smith America Invents Act (AIA), which switches patent priority from 'first to invent' to 'first to file', meaning rights will no longer relate to who made the discovery but to who was the first inventor to file the patent.^{2,3}

"First to file rewards people for paperwork, not for early hard work," said a TTO employee who spoke at the meeting under the Summit's [condition of anonymity](#).

She said that because the new law places a premium on filing as soon as possible, TTOs will need to make the financial and manpower commitment to filing patents before researchers may have had the chance to characterize the invention thoroughly. As a result, TTOs may end up spending their already limited resources on preliminary discoveries that later prove to have little value.

However, even under the first-to-invent system, smaller academic institutions, similarly to smaller biotechs, were at a disadvantage because their budgets are more limited than those of large universities and pharma. Furthermore, many TTOs were already operating under a first-to-file strategy to comply with European patent law.

TTOs are grappling in particular with the patent eligibility of methods claims for molecular diagnostics under Section 101 of the AIA. Much like biotechs in the space, TTOs have been left twisting in the wind by Supreme Court rulings that have essentially punted on the issue of the threshold of patent eligibility under that section.⁴⁻⁶

TTO representatives had mixed views on the ramifications of the recent Supreme Court ruling, in *Association for Molecular Pathology v. Myriad Genetics Inc.*, that found isolated DNA sequences were products of nature and could not be patented.

Some TTOs saw *Myriad* as an extra obstacle for diagnostic patents that leaves the picture still murky because the ruling did not settle on a definition of what is a product of nature and what is a true invention. Others said the ruling provided clarity for the field by providing a line of demarcation between existing genes, which are unpatentable, and artificial constructs of those genes or information about the behavior of a panel of genes, both of which remain patentable.

"Today, when a paper gets published, the reagents aren't necessarily commercially available until six to 12 months later. We want to cut that timeline and make the reagents available exactly at the time of publication."

**—Amanda Halford,
Sigma-Aldrich Corp.**

Although the ruling placed a limit on what could be patented, this clarity helps TTOs advise researchers on whether their genetics-based research is likely to be patentable and have commercial potential.

PPP roundup

Europe had a busy July with public-private partnerships (see [Table 1](#), "Selected public-private partnerships for July 2013"). Significant PPPs announced in July included the U.K.'s SynbiCITE synthetic biology innovation and knowledge center and France's Nano Innovation for Cancer consortium to promote the development of nanomedicines.

The U.K.'s **Engineering and Physical Sciences Research Council**, **Biotechnology and Biological Sciences Research Council** and **Technology Strategy Board** provided £10 million (\$15.2 million) in funding to launch SynbiCITE to translate synthetic biology into application.

The center will receive £5 million (\$7.6 million) in funding over the next two years. It will involve researchers from 17 universities and academic institutions across the U.K., as well as 13 partners from industry.

In France, **BioAlliance Pharma S.A.** is leading the Nano Innovation for Cancer. The five-member consortium received about €9 million (\$11.7 million) in funding through

the Strategic Industrial Innovation program of **bpifrance** (formerly OSEO).

The consortium's goal is to build a platform to accelerate the development and commercialization of nanomedicine in France.

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COMPANIES AND INSTITUTIONS MENTIONED

BioAlliance Pharma S.A. (Euronext:BIO), Paris, France
Biotechnology and Biological Sciences Research Council, Swindon, U.K.
bpifrance, Maisons-Alfort, France
Engineering and Physical Sciences Research Council, Swindon, U.K.
Myriad Genetics Inc. (NASDAQ:MYGN), Salt Lake City, Utah
Prometheus Laboratories Inc., San Diego, Calif.
The Scripps Research Institute, La Jolla, Calif.
Sigma-Aldrich Corp. (NASDAQ:SIAL), St. Louis, Mo.
Technology Strategy Board, Swindon, U.K.

IL-17 inhibitors: good news, bad news

By Michael J. Haas, Senior Writer

New partnerships and release of Phase III data highlight a flurry of activity this summer around the autoimmune target IL-17A. Now, emerging research suggests companies developing inhibitors of IL-17A signaling have both a repurposing opportunity and a new safety concern to navigate.

Findings by the **Genentech Inc.** unit of **Roche** suggest IL-17A inhibitors could treat cancers that are resistant to VEGF inhibitors.¹ However, an academic team from Sweden and the U.S. reported that blocking IL-17A can destabilize atherosclerotic plaques and thus increase the risk of cardiovascular events.²

IL-17A is a member of the IL-17 family of proinflammatory cytokines, which have roles in allergy and autoimmune diseases. Another member of the family, IL-17F, shares about 50% homology with IL-17A and is involved in airway inflammation in asthma. IL-17A and IL-17F function by binding a heteromeric complex that includes IL-17 receptor (IL17R; IL17RA) and IL-17 receptor C (IL17RC).

Multiple preclinical studies have shown that IL-17 cytokines and Th17 cells—a type of T helper cell that produces the cytokines—in the tumor microenvironment can promote tumor growth or stimulate antitumor immunity, depending on the cancer type and model studied.³ Moreover,

the role of IL-17 cytokines in mediating tumor resistance to cancer therapies—such as anti-angiogenics that inhibit signaling between VEGF and VEGF receptor—has been poorly understood.

The Genentech team set out to study the mechanisms by which tumors develop the resistance that blunts the effectiveness of anti-angiogenics. The group started by generating two mouse models—one from a lymphoma cell line that is resistant to VEGF inhibition and the other from a lymphoma cell line that is sensitive to VEGF inhibition.

Levels of IL-17a were higher in the resistant tumors than in the sensitive tumors.

In models with the resistant lymphomas, co-treatment with mouse antibodies against IL-17a and Vegf decreased tumor growth compared with the anti-Vegf antibody alone.

Similarly, in models of murine lung and colon cancers, antibodies against IL-17a and Vegf reduced tumor growth compared with the anti-Vegf antibody alone. The team chose those malignancies because tumor infiltration of Th17 cells is associated with poor prognosis in patients with lung and colorectal cancers.

Next, in models with resistant lymphomas treated with the anti-Vegf antibody, deficiency in *Il17rc* decreased tumor growth compared with normal *Il17rc* expression.

Finally, the team injected normal mice with either the VEGF inhibitor-sensitive lymphoma cell line or the same cell line modified to overexpress IL-17a. The anti-Vegf antibody decreased tumor growth in mice injected with the unmodified cells more so than in those receiving the IL-17a-overexpressing cells.

Table 1. Opportunities and obstacles for IL-17 inhibitors. Studies by two independent teams suggest inhibitors of IL-17A signaling could help treat cancers that are resistant to VEGF inhibitors but could also destabilize atherosclerotic plaques and thus increase the risk of cardiovascular events. The findings therefore present a repurposing opportunity and a safety caveat to companies developing inhibitors of members of the IL-17 family or IL-17 receptor (IL17R; IL17RA) to treat autoimmune and inflammatory indications.

Source: BCIQ: BioCentury Online Intelligence

Company	Compound	Target(s) ^a	Type	Status
Amgen Inc. (NASDAQ:AMGN)/ AstraZeneca plc (LSE:AZN; NYSE:AZN)	Brodalumab (AMG 827)	IL17R	Antibody	Phase III to treat psoriasis; Phase II to treat psoriatic arthritis and asthma
Eli Lilly and Co. (NYSE:LLY)	Ixekizumab (LY2439821)	IL-17A	Antibody	Phase III to treat psoriasis and psoriatic arthritis; Phase II to treat rheumatoid arthritis (RA)
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151)	KHK4827	IL17R	Antibody	Phase III to treat psoriasis
Novartis AG (NYSE:NVS; SIX:NOVN)	Secukinumab (AIN457)	IL-17A	Antibody	Phase III to treat ankylosing spondylitis, psoriasis, psoriatic arthritis and RA; Phase II to treat multiple sclerosis
4SC AG (Xetra:VSC)	Vidofludimus (4SC-101)	IL-17 expression and dihydroorotate dehydrogenase (DHODH)	Small molecule	Phase II to treat inflammatory bowel disease
NovImmune S.A./Genentech Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY)	NI-1401 (RG7624; MCAF5352A)	IL-17A and IL-17F	Antibody	Phase I to treat autoimmune diseases
AnaptysBio Inc.	ANB004	IL-17	Antibody	Preclinical to treat autoimmune and inflammatory diseases
Covagen AG	COVA322	IL-17A and tumor necrosis factor (TNF)	Protein	Preclinical to treat inflammatory diseases
Ensemble Therapeutics Corp./Novartis AG	E-036041	IL-17A	Macrocycle	Preclinical to treat arthritis
Pieris AG	PRS-190	IL-17 and IL-23	Protein	Preclinical to treat autoimmune diseases

^aUnless noted, the specific form of IL-17 (A, B, C, D E and/or F) inhibited by the compound is undisclosed.

Taken together, the findings show IL-17A has a role in tumor resistance to VEGF inhibitors and that blocking IL-17A signaling could re-sensitize some types of tumors to those inhibitors, the team wrote in its *Nature Medicine* paper.

Napoleone Ferrara led the team while he was a fellow at Genentech. He now is a professor of pathology at the **University of California, San Diego**.

Roche, Genentech and **Chugai Pharmaceutical Co. Ltd.** market Avastin bevacizumab, a humanized mAb against VEGF, to treat breast, brain, colorectal and renal cancers, non-small cell lung cancer (NSCLC), neurofibromatosis and solid tumors.

Genentech, Roche and **NovImmune S.A.** are co-developing an antibody against IL-17A and IL-17F to treat autoimmune diseases (see **Table 1, Opportunities and obstacles for IL-17 inhibitors**).

Problems with plaque

The Swedish-U.S. researchers wanted to know how signaling between transforming growth factor β 1 (TGF β 1) and mothers against decapentaplegic homolog 7 (MADH7; SMAD7) affected subpopulations of T cells in atherosclerosis, but they discovered a role for IL-17A instead.

The team found *Smad7*-deficient mouse models of atherosclerosis developed plaques with larger, more fibrous caps than wild-type controls. The deficient mice also had higher numbers of Th17 cells in draining lymph nodes and higher levels of Il-6—which can trigger Th17 differentiation—in the plaques.

These results led the team to hypothesize that IL-17A produced by Th17 cells promoted the

development of fibrous caps on the plaques.

Indeed, in the *Smad7*-deficient models a murine anti-IL-17a antibody decreased the size of fibrous caps on the plaques compared with a nonspecific murine control antibody.

In cultured human vascular smooth muscle cells, IL-17A increased levels of fibrous collagen compared with no treatment. Furthermore, the team's transcriptome analysis of 132 human atherosclerotic plaques identified positive associations between levels of IL-17A, fibrous collagen and a marker of smooth muscle cells.

The findings collectively suggest IL-17A secreted by Th17 cells promotes the production of collagen by vascular smooth muscle cells in atherosclerotic plaques, leading to the formation of fibrous caps on those plaques, the team wrote in *Science Translational Medicine*.

Because cap size is crucial to plaque stability, IL-17A inhibitors could potentially destabilize atherosclerotic plaques and thus increase the risk of stroke and other cardiovascular events, team co-leader Göran Hansson told *SciBX*.

To assess the extent of this risk, “it will be important to analyze

cardiovascular events in patients treated with IL-17 inhibitors,” he said. “We hope to do this in collaboration with our colleagues in the relevant academic disciplines and perhaps also with pharma companies.”

Hansson is a professor of experimental cardiovascular research at the **Karolinska Institute**. Richard Flavell, chair of immunobiology at the **Yale School of Medicine** and an investigator at the **Howard Hughes Medical Institute**, co-led the team, which included researchers from **Umeå University**.

Moving along IL-17

In addition to monitoring the cardiovascular health of patients receiving IL-17 inhibitors, the Swedish-U.S. team wants to use its findings to develop therapies that could stabilize atherosclerotic plaques and thus reduce the risk of cardiovascular events in patients who have severe atherosclerosis.

However, “because IL-17 receptors are expressed on many cell types throughout the body, targeting IL-17 or IL-17 receptors directly could be hazardous,” said Anton Gisterå, first author on the team's paper and a Ph.D. student in Hansson's research group.

Thus, according to Gisterå, the group is investigating specific plaque-related molecules in the blood-vessel walls that could be targeted to mimic the effect of IL-17A on plaque stability.

He said the findings reported in *Science Translational Medicine* are unpatented.

According to Genentech spokesperson Nadine Pinell, the company has not yet determined whether it will conduct additional studies of IL-17A's role in VEGF inhibitor-resistant cancers.

Pinell declined to disclose the IP status of the *Nature Medicine* findings.

Haas, M.J. *SciBX* 6(31); doi:10.1038/scibx.2013.814
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COMPANIES AND INSTITUTIONS MENTIONED

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Howard Hughes Medical Institute, Chevy Chase, Md.
Karolinska Institute, Stockholm, Sweden
NovImmune S.A., Plan-les-Quates, Switzerland
Roche, (SIX:ROG; OTCQX: RHHBY), Basel, Switzerland
Umeå University, Umeå, Sweden
University of California, San Diego, La Jolla, Calif.
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“It will be important to analyze cardiovascular events in patients treated with IL-17 inhibitors. We hope to do this in collaboration with our colleagues in the relevant academic disciplines and perhaps also with pharma companies.”

—Göran Hansson,
Karolinska Institute

Chromosome shutdown

By Tracey Baas, Senior Editor

A new technique to shut down chromosome 21 provides the clearest window yet into the cellular pathologies that underlie Down syndrome.¹ The findings will reshape how the condition is modeled and, in the longer term, could point to new disease targets or even a strategy to remove the extra chromosome.

Down syndrome occurs when an individual has three rather than two copies of chromosome 21, and it is the leading genetic cause of intellectual disabilities. Other Down syndrome health issues include congenital heart defects, early onset Alzheimer's disease (AD), premature aging and some forms of leukemia.

The cellular pathologies of trisomy 21 are likely to come from elevations in gene products, which could be tied to a protein-encoding gene directly or to a non-protein-encoding gene with a regulatory function.²

Efforts to correlate which genetic changes lead to which cellular pathology have been imprecise because researchers have had to compare disomic with trisomic cells from different humans. Thus, genetic polymorphisms and differences in patient age and medical history, as well as in cell culture conditions, have confounded such comparisons.³⁻⁷

Polymorphisms in the natural genetic background of the individual are speculated to have an important role in the variability of phenotypic severity seen in Down syndrome.

To eliminate individual variation due to genetic polymorphisms or make an isogenic comparison, a team from the **University of Massachusetts Medical School** and **Sangamo BioSciences Inc.** developed a technique to compare the same person's cells with and without trisomy 21.

In induced pluripotent stem (iPS) cells derived from a patient with Down syndrome, the researchers used Sangamo's zinc-finger nucleases to insert inducible *X inactive specific transcript* (non-protein-encoding) (*XIST*) into chromosome 21.

Normally, *XIST* produces a very large piece of noncoding RNA that shuts down one of the X chromosomes, triggering condensation of the chromatin to form an inactive Barr body.

In the iPS cells, induction of the newly inserted transgene resulted in expression of *XIST* noncoding RNA that coated chromosome 21 and triggered chromosome inactivation.

The researchers used fluorescence *in situ* hybridization (FISH), genome-wide expression profiling and methylomics to confirm the inactivation of chromosome 21.

iPS cells with induced *XIST* expression and chromosome 21 inactivation developed into neural rosettes, a signature of neural progenitor cells. In the cells that lacked induced *XIST* expression, however, neural rosette formation was delayed.

By using iPS cells from the same patient, the researchers were able to observe and compare the kinetics of neural differentiation associated with trisomy 21 without the confounding variability that occurs in comparisons of iPS cell lines from a trisomic individual and a disomic individual.

Results were published in *Nature*.

Breaking down trisomy 21

Next steps could include using the isogenic model to pinpoint specific genes or pathways that contribute to the underlying pathologies associated with Down syndrome, such as early AD or leukemia.

"Despite much progress in understanding Down syndrome, no human gene has yet been conclusively linked to causing a specific trisomy 21 phenotype," said André Mégarbané, professor of molecular biology and cytogenetics at **Saint Joseph University**.

He thinks the new system "could provide candidate genes associated with the syndrome that could be tested in mouse models for Down syndrome, evaluated at different stages of development and hopefully targeted with different therapeutic medicines."

Jeannie Lee, professor of genetics and pathology at **Harvard Medical School**, agreed the method could provide a useful system for understanding

the pathology of Down syndrome. "The work is an exciting proof of concept that *XIST* can be used to inactivate chromosome 21 and balance chromosome 21 gene products in trisomic cells," she said. In 1996, Lee used transgenic analysis to show that coating of autosomes by *XIST* RNA resulted in silencing of that autosome. At the time, she was working in the laboratory of Rudolf Jaenisch, professor of biology at the **Massachusetts Institute of Technology**.

But David Russell noted that two active chromosomes 21 plus one inactive chromosome 21 might not necessarily represent disomy. "The *XIST* method shuts down the chromosome, but the chromosome is still there. Although many of the genes are probably shut down, some genes could still leak through to complicate comparison of the cells," he said. Russell is professor of medicine at the **University of Washington School of Medicine**.

Late last year, his team inserted *TKNEO*—a fusion gene encoding resistance to thymidine kinase and neomycin—into iPS cells derived from individuals with Down syndrome.⁸ When selecting against *TKNEO*, spontaneous loss of chromosome 21 occurred through a natural cellular selection process, and iPS cells trisomic for chromosome 21 became disomic.

"Our system might be a little cleaner because the *TKNEO* method completely removes one chromosome 21," Russell told *SciBX*.

Regardless of approach, Russell said that differentiating iPS cells into somatic cell types complicates comparison between trisomic and disomic cells.

"We have differentiated iPS cells into neuronal and other cell types and have noticed it is very tricky to get consistent differentiation," he said. "There is a lot of clone to clone variation. So when comparing an iPS-derived trisomic neuronal cell to an iPS-derived disomic neuronal cell, you may be highlighting cell culture properties rather than pathology differences."

"The work is an exciting proof of concept that *XIST* can be used to inactivate chromosome 21 and provide isogenic cells with and without trisomy 21."

**—Jeannie Lee,
Harvard Medical School**

The upshot, he said, is that researchers need “to establish reproducible and robust phenotypes in order to make those comparisons.”

The long road to chromosomal therapy

Although the general media jumped on the idea that chromosomal therapy could be used to shut down the extra chromosome in blood cells to prevent leukemia, the actual near-term applications of the *XIST* approach include using the model to discover genes and pathways relevant to the pathologies associated with Down syndrome that could be candidates for drug targeting.

“Developing *XIST*-corrected patient cells in a cell-based therapy is going to be a long, tough road,” said Lee. “People will be interested in producing *XIST*-corrected neuronal cells, but brain tissue is an especially difficult one in which to attempt cell-based therapy.”

Lee also said the production of *XIST*-corrected blood cells to protect individuals with Down syndrome from developing leukemia is likely to be unwieldy.

“Bone-marrow transplantation and chemotherapy are established procedures for treating leukemia and may still be the easier treatment,” said Lee.

Mégarbané agreed. “Down syndrome patients have a tendency to develop pre-leukemia and are monitored closely. As soon as pre-leukemia is detected, treatments are started, which are very effective,” he said.

“The real challenge of using *XIST* for chromosomal therapy is going to be delivery,” said Mitchell Guttman, assistant professor of biology and biological engineering at the **California Institute of Technology**. “You may be able to deliver *XIST* into patient cells *ex vivo*, but delivering it *in vivo* will be a major challenge. First, you’ll need to deliver *XIST* into cells of the embryo, and second, you will likely need to hit every cell to achieve success.”

Guttman added, “Using it to treat a developmental disorder, like Down syndrome, would require targeting all cells during early development, but doing that is still quite impractical and currently hard to imagine.”

Mégarbané was more sanguine and thinks some pathologies of Down syndrome could eventually be amenable to chromosomal therapy. He

also said targeting all cells was not an absolute requirement. In some individuals with Down syndrome, not all cells have three copies of chromosome 21.

“It is hypothesized that the presence of cells with a normal number of chromosomes may result in a less severe presentation of Down syndrome [symptoms] such as impaired cognitive ability,” Mégarbané said. “So even if only a percentage of cells could be corrected, that might be enough to benefit the patient.”

One might want to attempt chromosome therapy during early embryonic development, for example, to prevent heart defects, which occur in about 50% of children with Down syndrome, he said.

Jeanne Lawrence, professor of cell and developmental biology and pediatrics at the University of Massachusetts Medical School and lead investigator of the *Nature* study, could not be reached for comment. The patent and licensing status of the work is unavailable.

Baas, T. *SciBX* 6(31); doi:10.1038/scibx.2013.815
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University of Massachusetts Medical School, Worcester, Mass.
Saint Joseph University, Beirut, Lebanon
University of Washington School of Medicine, Seattle, Wash.

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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)	Not applicable	<p>Mouse studies identified a combination of 17 <i>Clostridia</i> strains (17-mix) that could help treat inflammatory bowel disease. In germ-free mice, inoculation with human fecal samples led to identification of 17 <i>Clostridia</i> strains that increased the population of colonic T_{reg} cells compared with no inoculation. In a mouse model of allergic diarrhea, 17-mix reduced the occurrence and severity of diarrhea compared with vehicle. In a mouse model of colitis, 17-mix decreased colon shortening and normalized colonic histology compared with vehicle. Next steps include testing 17-mix in other preclinical models of inflammatory bowel disease. Vedanta Biosciences Inc. has 17-mix in preclinical development to treat inflammatory bowel disease.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.816 Published online Aug. 15, 2013</p>	<p>Patented by University of Tokyo; licensed to Vedanta Biosciences Inc.</p>	<p>Atarashi, K. <i>et al. Nature</i>; published online July 10, 2013; doi:10.1038/nature12331 Contact: Kenya Honda, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan e-mail: kenya@rcai.riken.jp</p>
Multiple sclerosis (MS)	Notch	<p>Cell culture and mouse studies suggest the tocopherol derivative TFA-12 could help promote remyelination in MS. In primary cell culture, TFA-12 suppressed astroglial and microglial activation and promoted the differentiation of precursor cells into oligodendrocytes with myelin-like sheaths. In mice with experimental autoimmune encephalomyelitis or lysolecithin-induced demyelination, TFA-12 reduced demyelination and enhanced remyelination. Next steps include further evaluation of TFA-12 in models of MS and in human oligodendrocytes.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.817 Published online Aug. 15, 2013</p>	<p>Patent application filed covering the use of TFA derivatives as inhibitors of Notch signaling; licensing status unavailable</p>	<p>Blanchard, B. <i>et al. J. Neurosci.</i>; published July 10, 2013; doi:10.1523/JNEUROSCI.0774-13.2013 Contact: Brahim Nait Oumesmar, Pierre and Marie Curie University, Paris, France e-mail: brahim.nait_oumesmar@upmc.fr</p>
Cancer				
B cell lymphoma	Unknown	<p>Mouse studies suggest <i>Lactobacillus johnsonii</i> supplementation could help prevent ataxia-telangiectasia-associated B cell lymphomas. In a mouse model of ataxia telangiectasia, mice from a colony with late lymphoma onset and longer lifespans had higher amounts of <i>L. johnsonii</i> in the gut than did mice from a colony with early lymphoma onset and shorter lifespans. In mice with earlier lymphoma onset, oral administration of <i>L. johnsonii</i> decreased markers of lymphoma risk such as systemic micronucleus formation, inflammation and DNA damage compared with saline administration. Next steps include identifying additional bacterial strains that could be used to reduce lymphoma incidence and progression in the mouse model. Corresponding author Robert Schiestl has founded Microbio Pharma Inc. to commercialize the findings (<i>see B cell lymphoma and the microbiome, page 1</i>).</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.818 Published online Aug. 15, 2013</p>	<p>Covered by two pending patents; licensing details available from corresponding authors</p>	<p>Yamamoto, M.L. <i>et al. Cancer Res.</i>; published online July 15, 2013; doi:10.1158/0008-5472.CAN-13-0022 Contact: Robert H. Schiestl, University of California, Los Angeles, Calif. e-mail: rschiestl@mednet.ucla.edu Contact: James Borneman, University of California, Riverside, Calif. e-mail: borneman@ucr.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Polo-like kinase 4 (PLK4; STK18)	<i>In vitro</i> and mouse studies identified small molecule PLK4 inhibitors that could help treat breast cancer. Computational modeling, chemical synthesis and <i>in vitro</i> testing of (indazolyl)methylene indolinone analogs identified several lead compounds as selective, nanomolar inhibitors of PLK4. In multiple human breast cancer cell lines, one lead compound inhibited growth at low nanomolar IC ₅₀ values. In mice with xenograft breast tumors, the lead compound decreased tumor growth compared with vehicle. Ongoing work includes IND-enabling studies of an optimized PLK4 inhibitor and planning of a Phase I trial of that inhibitor to treat solid tumors. SciBX 6(31); doi:10.1038/scibx.2013.819 Published online Aug. 15, 2013	Patented by the University Health Network; available for licensing or partnering	Laufer, R. <i>et al. J. Med. Chem.</i> ; published online July 6, 2013; doi:10.1021/jm400380m Contact: Henry W. Pauls, The Campbell Family Cancer Research Institute at the Princess Margaret Cancer Centre, Toronto, Ontario, Canada e-mail: hpauls@uhnresearch.ca
Cancer	Keratinocyte growth factor receptor (KGFR; FGFR2; CD332); tumor protein p63 (TP63; p63)	Cell culture and mouse studies suggest inhibiting FGFR2 could help treat squamous cell carcinoma (SCC). In a newly developed mouse model of chemically induced SCC, p63-mediated induction of FGFR2 signaling was increased in tumors compared with normal skin, and the small molecule FGFR antagonist AZD4547 arrested tumor development and improved progression-free survival (PFS) compared with vehicle. Next steps include the identification of biomarkers to predict response to FGFR2-directed therapy in SCC. AstraZeneca plc's AZD4547 is in Phase II testing to treat various cancers. At least five companies have FGFR inhibitors in Phase II or earlier development to treat various cancers. SciBX 6(31); doi:10.1038/scibx.2013.820 Published online Aug. 15, 2013	Unpatented; licensing not applicable	Ramsey, M.R. <i>et al. J. Clin. Invest.</i> ; published online July 8, 2013; doi:10.1172/JCI68899 Contact: Leif W. Ellisen, Massachusetts General Hospital Cancer Center, Boston, Mass. e-mail: ellisen@helix.mgh.harvard.edu
Colorectal cancer	Cystathionine β-synthase (CBS)	<i>In vitro</i> and mouse studies suggest inhibiting CBS could help treat colorectal cancer. In a human colon cancer cell line, small hairpin RNA-mediated knockdown of CBS or a CBS inhibitor decreased proliferation, migration and invasion compared with control shRNA or vehicle. In mice bearing human cell line-derived or patient-derived colon tumors, a CBS inhibitor decreased tumor growth and tumor blood vessel density compared with vehicle. Future studies could include determining whether CBS is overexpressed in other solid tumor types. SciBX 6(31); doi:10.1038/scibx.2013.821 Published online Aug. 15, 2013	Patented by The University of Texas Medical Branch; licensing status undisclosed	Szabo, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 8, 2013; doi:10.1073/pnas.1306241110 Contact: Mark R. Hellmich, The University of Texas Medical Branch, Galveston, Texas e-mail: mhellmic@utmb.edu Contact: Csaba Szabo, same affiliation as above e-mail: szabocsaba@aol.com
Liver cancer	Core 1 synthase glycoprotein-N-acetyl galactosamine 3-β-galactosyltransferase 1 (C1GALT1)	Human tissue and mouse studies suggest inhibiting C1GALT1 could help treat hepatocellular carcinoma (HCC). In patient samples, C1GALT1 was higher in HCC tissues than in adjacent normal tissues. In HCC patients, high C1GALT1 expression in tumor tissue was associated with more advanced tumor stage, increased metastasis and decreased survival compared with low C1GALT1 expression. In a mouse xenograft model of human HCC, small hairpin RNA-mediated knockdown of C1GALT1 decreased tumor growth compared with control shRNA. Next steps could include developing and evaluating pharmacological inhibitors of C1GALT1. SciBX 6(31); doi:10.1038/scibx.2013.822 Published online Aug. 15, 2013	Patent and licensing status unavailable	Wu, Y.-M. <i>et al. Cancer Res.</i> ; published online July 5, 2013; doi:10.1158/0008-5472.CAN-13-0869 Contact: Min-Chuan Huang, National Taiwan University College of Medicine, Taipei, Taiwan e-mail: mchuang@ntu.edu.tw

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Liver cancer	DNA	<i>In vitro</i> and mouse studies suggest a new class of metal hydrides could help treat cancer. In a human liver cancer cell line, a lead DNA-binding aryltrinitro iridium hydride complex decreased proliferation and increased apoptosis with >20-fold higher potency than cisplatin. In mice with murine liver tumors, the lead complex decreased tumor growth with potency comparable to cisplatin without inducing weight loss or other markers of toxicity. Ongoing studies include synthesizing and testing other metal hydride complexes in human cancer cell lines. SciBX 6(31); doi:10.1038/scibx.2013.823 Published online Aug. 15, 2013	Patented by Sinocompound Catalysts Co. Ltd.; available for licensing or partnering	Song, X., <i>et al.</i> , <i>J. Med. Chem.</i> ; published online July 11, 2013; doi:10.1021/jm4004973 Contact: Jing Zhao, Nanjing University, Nanjing, China e-mail: jingzhao@nju.edu.cn
Lung cancer	Notch 3 (NOTCH3)	Cell culture and mouse studies suggest inhibiting NOTCH3 could help treat lung cancer by eliminating tumor-propagating cells (TPCs). In mice engrafted with TPCs expressing three propagation markers including <i>Notch3</i> , tumor burdens were elevated and survival was reduced compared with mice engrafted with cells not expressing these markers. In mice with TPCs, cisplatin increased the proportion of TPCs in tumors compared with vehicle, suggesting TPCs could be resistant to chemotherapy. In xenograft mouse models of lung cancer, small hairpin RNA-mediated knockdown of <i>Notch3</i> decreased tumor burden compared with no knockdown. Next steps include understanding the molecular basis for cisplatin resistance. OncoMed Pharmaceuticals Inc.'s OMP-59R5, an antibody to NOTCH3, is in Phase II or earlier testing to treat various cancers. At least four companies have NOTCH inhibitors in Phase I testing to treat cancer. SciBX 6(31); doi:10.1038/scibx.2013.824 Published online Aug. 15, 2013	Patent and licensing status undisclosed	Zheng, Y. <i>et al.</i> <i>Cancer Cell</i> ; published online June 8, 2013; doi:10.1016/j.ccr.2013.05.021 Contact: E. Alejandro Sweet-Cordero, Stanford University School of Medicine, Stanford, Calif. e-mail: ascor@stanford.edu Contact: Erica L. Jackson, Genentech Inc., South San Francisco, Calif. e-mail: jackson.eric@gene.com
Lymphoma	IL-17A; IL-17 receptor C (IL17RC); VEGF	Mouse studies suggest IL-17A inhibitors could help treat VEGF inhibitor-resistant cancers. In mouse models of murine lymphoma, IL-17a levels were higher in VEGF inhibitor-resistant tumors than in VEGF inhibitor-sensitive tumors. In mice with resistant lymphomas treated with anti-Vegf antibody, <i>Il17rc</i> deficiency or co-treatment with an anti-IL-17a antibody decreased tumor growth compared with intact <i>Il17rc</i> or no co-treatment. Future studies could include testing IL-17A inhibitors in models bearing VEGF inhibitor-resistant xenograft tumors. At least eight companies have antibodies against IL-17A or IL-17 receptor (IL17R; IL17RA) in Phase I through Phase III testing to treat multiple autoimmune and/or inflammatory indications (<i>see IL-17 inhibitors: good news, bad news, page 7</i>). SciBX 6(31); doi:10.1038/scibx.2013.825 Published online Aug. 15, 2013	Patent and licensing status undisclosed	Chung, A.S. <i>et al.</i> <i>Nat. Med.</i> ; published online Aug. 4, 2013; doi:10.1038/nm.3291 Contact: Napoleone Ferrara, University of California San Diego, La Jolla, Calif. e-mail: nferrara@ucsd.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Atherosclerosis	IL-17	<p>Studies in patient samples, human cell culture and mice suggest upregulation of IL-17 signaling could help reduce the risk of cardiovascular events. In 132 human atherosclerotic plaques, transcriptome analysis identified a correlation between levels of IL-17, fibrous collagen and a marker of smooth muscle cells. In cultured human vascular smooth muscle cells, IL-17 increased abundance of fibrous collagen compared with no treatment. In a mouse model of atherosclerosis, an anti-IL-17 antibody decreased the size of fibrous caps and stability of atherosclerotic plaques compared with a nonspecific antibody. Planned work includes investigation of other molecules in the IL-17 signaling pathway as potential therapeutic targets to help stabilize atherosclerotic plaques.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.826 Published online Aug. 15, 2013</p>	Unpatented; unlicensed; available for partnering	<p>Gisterå, A. <i>et al. Sci. Transl. Med.</i>; published online July 31, 2013; doi:10.1126/scitranslmed.3006133 Contact: Göran K. Hansson, Karolinska Institute, Stockholm, Sweden e-mail: goran.hansson@ki.se Contact: Richard A. Flavell, Yale School of Medicine, New Haven, Conn. e-mail: richard.flavell@yale.edu</p>
Endocrine/metabolic disease				
Obesity; metabolic syndrome	Complement component 1q subcomponent (C1Q); complement component 1q subcomponent A chain (C1QA)	<p>Mouse studies suggest inhibiting C1Q signaling could help prevent obesity-associated metabolic impairments and metabolic syndrome. In women who were obese and in mice fed a high-fat diet, complement-factor activation in adipose tissue was increased compared with lean controls. In mice, <i>C1qa</i> deficiency prevented high-fat diet-induced impairments in glucose homeostasis and decreased both hepatic steatosis and insulin resistance compared with no <i>C1qa</i> deficiency. Next steps could include developing C1QA-specific inhibitors and evaluating them in obesity models.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.827 Published online Aug. 15, 2013</p>	Patent and licensing status unavailable	<p>Hillian, A.D. <i>et al. J. Biol. Chem.</i>; published online June 20, 2013; doi:10.1074/jbc.M113.465674 Contact: Laura Nagy, Cleveland Clinic Cleveland, Ohio e-mail: nagyL3@ccf.org</p>
Gastrointestinal disease				
Pancreatitis	Calcium release-activated calcium channel (CRAC)	<p>Cell culture studies suggest antagonizing CRAC could help treat acute pancreatitis. In a pancreatic acinar cell model of acute pancreatitis, a discontinued small molecule CRAC inhibitor research reagent from GlaxoSmithKline plc prevented excess calcium influx and necrosis. Next steps include genetic and pharmacological studies in mice to validate CRAC inhibition in a model of alcohol-induced pancreatitis. Synta Pharmaceuticals Corp. and CalciMedica Inc. each have CRAC inhibitors in preclinical development for psoriasis, rheumatoid arthritis (RA), inflammatory bowel disease and other autoimmune and inflammatory indications.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.828 Published online Aug. 15, 2013</p>	Not patented; licensing status not applicable	<p>Gerasimenko, J.V. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 22, 2013; doi:10.1073/pnas.1300910110 Contact: Ole H. Petersen, Cardiff University, Cardiff, U.K. e-mail: petersenoh@cardiff.ac.uk Contact: Oleg V. Gerasimenko, same affiliation as above e-mail: gerasimenkoov@cardiff.ac.uk Contact: Pawel E. Ferdek, same affiliation as above e-mail: ferdekpe@cardiff.ac.uk</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Huntington's disease (HD)	Histone deacetylase 3 (HDAC3); huntingtin (HTT)	Cell culture studies suggest HDAC3 inhibitors could help treat HD. In rat and mouse neurons expressing mutant HTT, <i>Hdac3</i> deficiency increased survival compared with normal <i>Hdac3</i> expression. Ongoing work includes generating <i>Hdac3</i> -deficient mouse models of HD and testing RG2833, an HDAC3 inhibitor from Repligen Corp., in cell culture models of HD. RG2833 is in Phase I testing to treat ataxia. SciBX 6(31); doi:10.1038/scibx.2013.829 Published online Aug. 15, 2013	Unpatented; unlicensed	Bardai F.H. <i>et al. J. Neurosci.</i> ; published online July 17, 2013; doi:10.1523/JNEUROSCI.5831-12.2013 Contact: Santosh R. D'Mello, University of Texas at Dallas, Richardson, Texas e-mail: dmello@utdallas.edu
Huntington's disease (HD)	Jumonji/ARID domain containing protein 1C (KDM5C; JARID1C)	Studies in patient samples, cultured cells and flies suggest inhibiting JARID1C could help to treat HD. In brain tissue from HD patients, trimethylation of histone H3 at lysine 4 (H3K4) was decreased on genes that were expressed at lower levels compared with tissues from healthy individuals. In cultured mouse neurons expressing mutant Huntingtin (<i>Htt</i>), shRNA knockdown of the H3K4 demethylase-encoding <i>Kdm5c</i> increased the expression of these target genes compared with control shRNA. In a fly model of HD, insects lacking one copy of a gene encoding an H3K4 demethylase had a less severe disease phenotype compared with flies carrying both copies of the gene. Next steps could include identifying downstream genes regulated by JARID1C that contribute to HD pathology. SciBX 6(31); doi:10.1038/scibx.2013.830 Published online Aug. 15, 2013	Patent and licensing status unavailable	Vashishtha, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 19, 2013; doi:10.1073/pnas.1311323110 Contact: Leslie M. Thompson, University of California, Irvine, Calif. e-mail: lmthomps@uci.edu Contact: Ernest Fraenkel, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: fraenkel-admin@mit.edu Contact: David E. Housman, same affiliation as above e-mail: dhousman@mit.edu
Huntington's disease (HD)	NMDA receptor NR3A subtype (GRIN3A; NR3A); huntingtin (HTT)	Patient and mouse studies suggest inhibiting GRIN3A could help to prevent or delay HD progression. In patients with HD and in a mouse model of HD, synaptic expression of GRIN3A was increased compared with healthy individuals or mice. In the HD mouse model, <i>Grin3a</i> knockout decreased motor and cognitive dysfunction compared with no knockout and prevented striatal atrophy and synaptic disconnection. In a rat corticostriatal slice model, transfection of mutant HTT plus <i>Grin3a</i> led to decreased survival of spiny neurons compared with transfection of mutant HTT alone. Next steps include testing the protective effects of small interfering RNA-mediated knockdown of <i>Grin3a</i> in mouse models of HD after onset of disease pathology. SciBX 6(31); doi:10.1038/scibx.2013.831 Published online Aug. 15, 2013	Not patented, licensing status not applicable	Marco, S. <i>et al. Nat. Med.</i> ; published online July 14, 2013; doi:10.1038/nm.3246 Contact: Isabel Pérez-Otaño, Center for Applied Medical Research at the University of Navarra, Pamplona, Spain e-mail: otano@unav.es
Neurology	Adenosine A _{2A} receptor (ADORA _{2A}); ecto-5'-nucleotidase (NT5E; NT; CD73)	Mouse studies suggest inhibiting CD73 could help to improve memory by regulating adenosine signaling in the brain through ADORA _{2A} . In mice, Cd73-derived adenosine was required for the activation and function of Adora _{2a} in the striatum. <i>Cd73</i> -knockout mice showed better performance in memory tasks compared with wild-type controls. Next steps could include identifying and evaluating CD73-specific inhibitors in mouse models. SciBX 6(31); doi:10.1038/scibx.2013.832 Published online Aug. 15, 2013	Patent and licensing status unavailable	Augusto, E. <i>et al. J. Neurosci.</i> ; published online July 10, 2013; doi:10.1523/JNEUROSCI.5817-12.2013 Contact: Rodrigo A. Cunha, University of Coimbra, Coimbra, Portugal e-mail: cunharod@gmail.com Contact: Jiang-Fan Chen, Boston University, Boston, Mass. e-mail: chenjf@bu.edu

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Human plasmablast enrichment to identify broadly neutralizing influenza A antibodies with high frequency	<p>A strategy to enrich human plasmablasts could be used to identify broadly neutralizing influenza A antibodies with high frequency. Peripheral blood mononuclear cells (PBMCs) from human donors vaccinated against influenza A virus were treated with an influenza A virus hemagglutinin antigen premix and transplanted into the spleens of immunodeficient mice to allow for rapid expansion and differentiation into human plasmablasts. Isolated plasmablasts bound influenza A virus variants with 150-fold higher frequency than did plasmablasts derived from untreated PBMCs. In 950 enriched plasmablasts, two broadly neutralizing mAbs were identified through the screening of only 840 cloned antibodies, whereas the previously described, broadly neutralizing mAb F16 was identified through analysis of about 104,000 cultured human plasma cells. Next steps could include testing the antibodies in humans.</p> <p>F16 is being developed by Humabs BioMed S.A., which has licensed the product to an undisclosed pharma.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.833 Published online Aug. 15, 2013</p>	Patent and licensing status undisclosed	<p>Nakamura, G. <i>et al. Cell Host Microbe</i>; published online July 17, 2013; doi:10.1016/j.chom.2013.06.004</p> <p>Contact: Lee R. Swem, Genentech, South San Francisco, Calif. e-mail: leers@gene.com</p> <p>Contact: Mercedesz Balazs, same affiliation as above e-mail: mercedesz.balazs@gmail.com</p>
<i>In situ</i> RNA sequencing in fixed cells and tissues	<p><i>In situ</i> RNA sequencing could help reveal genetic heterogeneity in complex samples for clinical diagnostics. In fresh-frozen cells or tissues, single-cell RNA sequence information was derived from sequencing by ligation after padlock probing and rolling-circle amplification. Control <i>in situ</i> experiments on the human β-actin transcript showed an average accuracy of 98.6%. In sections of frozen tissue from breast cancer biopsies, 39 probes, including 21 from a prognostic gene panel, were combined in a single multiplex reaction, and the results were validated by comparison to published RNA-sequencing data.</p> <p>Next steps could include optimization of the workflow for handling large numbers of samples and comparison of this method directly with bulk expression profiling for prognostic evaluation.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.834 Published online Aug. 15, 2013</p>	Patent and licensing status undisclosed	<p>Ke, R. <i>et al. Nat. Methods</i>; published online July 14, 2013; doi:10.1038/nmeth.2563</p> <p>Contact: Mats Nilsson, Stockholm University, Stockholm, Sweden e-mail: mats.nilsson@scilifelab.se</p> <p>Contact: Carolina Wählby, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: carolina@broadinstitute.org</p>
Inner-ear hair cell cultures generated from embryonic stem cells (ESCs) as a screening platform for otology drugs	<p>Inner-ear cell cultures generated from ESCs could help identify drug compounds that are ototoxic or promote inner-ear hair cell differentiation and regeneration. In serum-free 3D cultures of mouse ESCs, sequential treatment with cocktails of human proteins and small molecule inhibitors induced differentiation into inner-ear sensory epithelial cells. Electrophysiological, genetic and morphological analyses classified the cells as type II vestibular hair cells, which aid in sensing head position and movement. Ongoing studies include generating cochlear hair cells from mouse ESCs and functional hair cell types from human ESCs.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.835 Published online Aug. 15, 2013</p>	Patent application filed by the Indiana University School of Medicine; unavailable for licensing	<p>Koehler, K.R. <i>et al. Nature</i>; published online July 10, 2013; doi:10.1038/nature12298</p> <p>Contact: Eri Hashino, Indiana University, Indianapolis, Ind. e-mail: ehashino@iupui.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Dominant negative-disrupted in schizophrenia 1 (DISC1) mouse models of prefrontal cortex dysfunction	Mice expressing a dominant negative form of DISC1 (DN-DISC1) could help model cognitive disorders. In models of adaptive behavior, DN-DISC1 mice showed decreased ability to modify responses or alter expectations compared with wild-type mice. In behavioral motivation models, DN-DISC1 mice showed decreased effort for reward and decreased interaction with unknown mice compared with wild-type mice. Next steps include using DN-DISC1 mice in discovery programs for neuropsychiatric and neurological disorders. SciBX 6(31); doi:10.1038/scibx.2013.836 Published online Aug. 15, 2013	Unpatented; licensing status not applicable	Johnson, A.W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 9, 2013; doi:10.1073/pnas.1307925110 Contact: Michela Gallagher, The Johns Hopkins University, Baltimore, Md. e-mail: michela@jhu.edu Contact: Akira Sawa, affiliation as above e-mail: asawa1@jhmi.edu
Genetic duplication mouse model for a hypomyelinating disorder	Mice with an engineered genomic duplication at the proteolipid protein 1 (Plp1) locus could be useful for studying the hypomyelinating disorder Pelizaeus–Merzbacher disease (PMD). The mice showed decreases in speed, movement fluidity and gait abnormalities compared with wild-type mice. In these mice, levels of Plp1 and other myelin proteins were decreased compared with that of wild-type controls. The mice recapitulated markers of PMD in humans, such as progressive loss of myelin followed by axonal loss. Next steps include using the model to evaluate therapeutic candidates. SciBX 6(31); doi:10.1038/scibx.2013.837 Published online Aug. 15, 2013	Unpatented; model to be submitted to Mutant Mouse Regional Resource Centers for distribution	Clark, K. <i>et al. J. Neurosci.</i> ; published online July 17, 2013; doi:10.1523/JNEUROSCI.1336-13.2013 Contact: Grace Hobson, Alfred I. duPont Hospital for Children, Wilmington, Del. e-mail: ghobson@nemours.org
<i>In vitro</i> liver platform to model malaria infection	A hepatocyte culture model could be used to model liver-stage infection with <i>Plasmodium falciparum</i> or <i>Plasmodium vivax</i> . Previously, hepatocytes and supportive stromal cells were co-cultured to generate an <i>in vitro</i> liver model that was stable for 4–6 weeks and compatible with medium-throughput screens. In the current model, cryopreserved human hepatocytes combined with cryopreserved <i>P. falciparum</i> and <i>P. vivax</i> samples were conducive to liver-stage growth of the parasites. This system was adapted to 96-well format to enable the screening and identification of antimalarial compounds. Next steps could include using the model to screen for antimalarial compounds. SciBX 6(31); doi:10.1038/scibx.2013.838 Published online Aug. 15, 2013	Patent and licensing status unavailable	March, S. <i>et al. Cell Host Microbe</i> ; published online July 18, 2013; doi:10.1016/j.chom.2013.06.005 Contact: Sangeeta N. Bhatia, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: sbhatia@mit.edu
Mouse model of neonatal intracranial hemorrhage	A mouse model of neonatal intracranial hemorrhage could be useful for developing therapies for the condition. In mice engineered to conditionally express VEGF in the brain, induction of VEGF during late embryonic development led to germinal matrix hemorrhage and intraventricular hemorrhage, two common forms of neonatal hemorrhage. In the mouse model, glucocorticoid treatment decreased VEGF-induced hemorrhage compared with no treatment. Next steps include exploring the therapeutic potential of antagonizing downstream effectors of VEGF signaling. SciBX 6(31); doi:10.1038/scibx.2013.839 Published online Aug. 15, 2013	Patent and licensing status not applicable	Yang, D. <i>et al. Sci. Transl. Med.</i> ; published online July 10, 2013; doi:10.1126/scitranslmed.3005794 Contact: Chia-Yi Kuan, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio e-mail: alex.kuan@emory.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Blood vessels formed from induced pluripotent stem (iPS) cell-derived endothelial and mesenchymal stem cells	<p>Mouse studies suggest that iPS cell-derived endothelial cells could regenerate vasculature to help treat cardiovascular diseases. In immunocompromised mice, implantation of human iPS cell-derived endothelial cells and mesenchymal progenitor cells resulted in the formation of functional and durable blood vessels. Blood vessels also could be formed from iPS cells generated from patients with type 1 diabetes. Next steps include developing a safe protocol for iPS cell generation and studying the human host response to the cells.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.840 Published online Aug. 15, 2013</p>	Patent application filed; licensing status unavailable	<p>Samuel, R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 16, 2013; doi:10.1073/pnas.1310675110 Contact: Rakesh K. Jain, Massachusetts General Hospital, Boston, Mass. e-mail: jain@steele.mgh.harvard.edu Contact: Dai Fukumura, same affiliation as above e-mail: dai@steele.mgh.harvard.edu</p>
Crystal structures of sirtuin 1 (SIRT1), SIRT2 and SIRT3 bound to inhibitors	<p>Crystal structures of sirtuins bound to inhibitors could guide the development of compounds directed against specific sirtuins. Crystal structures of a SIRT1 inhibitor bound to SIRT1, SIRT3 or a bacterial Sirt2 showed the compound co-occupied a conserved pocket alongside the enzyme's catalytic product, thereby preventing product release. The co-crystal structures also showed no structural differences between the conserved pockets of the three sirtuins that could account for their differing binding affinities for the inhibitor. Crystal structures of a SIRT3 inhibitor bound to SIRT3 showed the compound simultaneously occupied the acetyllysine binding site and the conserved pocket. Ongoing work includes using the structural data to develop specific inhibitors of SIRT3.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.841 Published online Aug. 15, 2013</p>	Unpatented; unlicensed; available for partnering	<p>Gertz, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 9, 2013; doi:10.1073/pnas.1303628110 Nguyen, G.T.T. <i>et al. Acta Crystallogr. D. Biol. Crystallogr.</i>; published online July 17, 2013; doi:10.1107/S0907444913015448 Contact: Clemens Steegborn, University of Bayreuth, Bayreuth, Germany e-mail: clemens.steegborn@uni-bayreuth.de</p>
Direct reprogramming of fibroblasts into induced hepatic stem cells (iHSCs) for liver regeneration	<p>iHSCs derived directly from fibroblasts could help treat liver diseases. In culture, iHSCs generated from mouse embryonic fibroblasts by expression of the HNF1 homeobox B (Hnf1b) and forkhead box A3 (Foxa3) transcription factors were capable of self-renewal and differentiation into both hepatocytes and cholangiocytes. In a mouse model of liver failure, intrasplenic transplantation of the iHSCs improved liver function and survival compared with transplantation of mouse embryonic fibroblasts. Next steps could include translating the method to human cells.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.842 Published online Aug. 15, 2013</p>	Patent and licensing status unavailable	<p>Yu, B. <i>et al. Cell Stem Cell</i>; published online July 18, 2013; doi:10.1016/j.stem.2013.06.017 Contact: Yi-Ping Hu, Second Military Medical University, Shanghai, China e-mail: ypu@smmu.edu.cn Contact: Xin Wang, Inner Mongolia University, Huhhot, China e-mail: wangxin_cn@imu.edu.cn</p>
Generation of transplantable, vascularized liver buds from induced pluripotent stem (iPS) cells	<p>Human vascularized liver buds grown in culture could be used to regenerate human livers and model liver disease. Liver endoderm cells generated from human iPS cells were co-cultured with human endothelial cells and mesenchymal stem cells to form vascularized liver buds. In mice, implanted liver buds integrated with the host vasculature, matured and performed human liver-specific metabolic reactions. In mice with chemically induced liver failure, transplanted liver buds prolonged survival compared with transplanted hepatocytes. Next steps include scaling up the process to establish larger tissue segments and testing functionality in larger animal models.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.843 Published online Aug. 15, 2013</p>	Patent application filed; available for licensing through Yokohama City University	<p>Takebe, T. <i>et al. Nature</i>; published online July 3, 2013; doi:10.1038/nature12271 Contact: Takanori Takebe, Yokohama City University, Yokohama, Japan e-mail: ttakebe@yokohama-cu.ac.jp Contact: Hideki Taniguchi, same affiliation as above e-mail: rtanigu@yokohama-cu.ac.jp</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Single-dose RepliVax vaccine to prevent tick-borne encephalitis (TBE)	<p>A single-cycle virus vaccine platform, RepliVax, could help generate vaccines to protect against TBE. The single-cycle virus vaccine (RepliVax-TBE) was constructed using a West Nile virus backbone with deletion of the capsid gene and insertion of TBE virus envelope genes. In outbred mice, intraperitoneal immunization with RepliVax-TBE induced a protective immune response and increased survival against a lethal challenge with a TBE-related virus compared with mock immunization. In nonhuman primates, a single dose of RepliVax-TBE protected from challenge with a TBE-related virus and induced more durable immune responses compared with an inactivated human TBE virus vaccine. Next steps include evaluating the breadth of protection conferred by RepliVax-TBE against circulating wild-type TBE strains representing three major genotypes.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.844 Published online Aug. 15, 2013</p>	Patented by Sanofi Pasteur; licensing status undisclosed	<p>Rumyantsev, A.A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 15, 2013; doi:10.1073/pnas.1306245110 Contact: Konstantin V. Pugachev, Sanofi Pasteur, Discovery US, Cambridge, Mass. e-mail: konstantin.pugachev@sanofipasteur.com</p>
Synthetic vascular networks derived from human pluripotent stem cells	<p><i>In vitro</i> and mouse studies suggest patient-specific synthetic vascular networks could be used for vascular regeneration. <i>In vitro</i>, early vasculature cells derived from human pluripotent stem cells matured into endothelial cells and pericytes and organized into a vascular network on a synthetic matrix. In mice, subcutaneously implanted synthetic vascular networks integrated with the existing vasculature and carried blood. Next steps include testing the strategy in large animal models.</p> <p>SciBX 6(31); doi:10.1038/scibx.2013.845 Published online Aug. 15, 2013</p>	Patent application filed and optioned to an undisclosed startup; unavailable for licensing	<p>Kusuma, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 15, 2013; doi:10.1073/pnas.1306562110 Contact: Sharon Gerecht, Johns Hopkins University, Baltimore, Md. e-mail: gerecht@jhu.edu</p>

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