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Japanese researchers have shown in mice that GlaxoSmithKline's marketed migraine drug Amerge naratriptan could be repurposed to treat spinal and bulbar muscular atrophy. Although the pharma is not saying if it will pursue the new indication for the serotonin (5-HT_{1D}) receptor agonist, the research group is already planning an investigator-led Phase II trial.

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Ember: warming up to brown fat

By Michael J. Haas, Senior Writer

A team led by Boston-area researchers has shown that inhibiting a cation channel dubbed TRPV4 induced white fat cells to behave like brown fat, thereby protecting mice from diet-induced obesity and insulin resistance.¹ **Ember Therapeutics Inc.** has options to in-license the findings as a part of a trio of new deals for brown fat-related targets.

Brown adipose tissue (BAT), or brown fat, has a high mitochondrial content that allows it to burn and dissipate chemical energy as heat more efficiently than white adipose and other tissues. Although human adults have only small deposits of brown fat compared with infants and rodents, a potential strategy for treating obesity and related metabolic conditions is inducing white adipose tissue to take on the mitochondrial and thermogenic properties of brown fat—an approach known as browning.

Peroxisome proliferation-activated receptor- γ coactivator 1 α (PPARGC1A; PGC-1 α) is a key player in oxidative metabolism and thermogenesis in multiple tissue types,² and a previous study by the Boston team found that exposure to cold and other factors upregulated PGC-1 α in brown fat and skeletal muscle.³

Thus, the researchers postulated that compounds that induced PGC-1 α expression—directly or indirectly—could help treat metabolic diseases.

The team screened small molecule libraries for compounds that upregulated Pgc-1 α in mouse white adipocytes and identified two hits that were known antagonists of transient receptor potential vanilloids (TRPVs), a subfamily of the transient receptor potential ion channels.

To determine if any of the six TRPVs known in humans and mice played a predominant role in activating Pgc-1 α , the team treated mouse white adipocytes with small hairpin RNAs against each of the four *Trpvs* targeted by the two hits—the other two *Trpvs* are not antagonized by these molecules. Knocking down *Trpv4* (transient receptor potential vanilloid 4; *VRL2*) resulted in the greatest upregulation of Pgc-1 α and other mitochondrial genes involved in thermogenesis.

In addition, *Trpv4*-deficient mice fed a high-fat diet gained less weight than wild-type controls on the same diet. The difference resulted from greater energy expenditure in the *Trpv4*-deficient models and not from changes in food intake, oxygen consumption or levels of physical activity.

The *Trpv4*-deficient models also had greater glucose tolerance and lower insulin resistance than controls.

In mouse models of diet-induced obesity, the TRPV4 antagonist

**EDITORIAL**

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GSK205 increased glucose tolerance and decreased insulin resistance compared with vehicle. The molecule did not produce weight loss, which the team attributed to poor pharmacokinetics. GSK205 is a research compound originally discovered by **GlaxoSmithKline plc**.

Additionally, because GSK205 is not orally available, it had to be given every day by intraperitoneal injection, team leader Bruce Spiegelman told *SciBX*. “The procedures involved put stress on the models and can cause them to lose weight anyway. So, although we did use proper controls in the experiment, we wouldn’t have looked for GSK205 to induce weight loss.”

Spiegelman is professor of cell biology and medicine at the **Dana-Farber Cancer Institute** and **Harvard Medical School**. He also is a cofounder of Ember and chairman of its scientific advisory board.

The team included researchers from **Boston Children’s Hospital, Duke University School of Medicine, Howard Hughes Medical Institute, Massachusetts General Hospital and Scripps Florida**.

Data were reported in *Cell*.

“All of the biology around these three targets indicates that inhibiting them browns fat and that all three are druggable.”

—Lou Tartaglia,
Ember Therapeutics Inc.

Broadening the brown

Ember, which did not fund any aspect of the *Cell* study, has secured an exclusive option from Dana-Farber to in-license the team’s findings. The company thinks TRPV4 is a good target for inducing white fat to behave like brown fat, said Lou Tartaglia, president and interim CEO of Ember and partner at **Third Rock Ventures**.

The TRPV4 deal is one of a trio that Ember announced last week as part of an IP land grab in the brown fat space. The other deals were options to in-license IP for two other brown fat-related targets from **Brigham and Women’s Hospital**—aldehyde dehydrogenase 1 family member A1 (ALDH1A1) and StAR-related lipid transfer domain containing 14 (STARD14; THEM1).

Studies in mouse models of obesity by separate teams at the institution showed that inhibiting *Aldh1a1* induced brown fat-like attributes in white adipose tissue to limit weight gain and improve glucose homeostasis^{4,5} and that inhibiting *Them1* increased fatty acid oxidation in brown fat to limit weight gain and induce resistance to diabetes, inflammation and hepatic steatosis.⁶

“All of the biology around these three targets indicates that inhibiting them browns fat and that all three are druggable,” Tartaglia said.

The deals “reflect our review of activity in the brown fat space over the last nine months and our thinking that these three targets are the best of recent findings,” he added.

He noted that blocking each target has a different mode of action in browning fat: inhibiting TRPV4 recruits brown fat by inducing brown fat-like gene expression and thermogenic properties in white fat; inhibiting ALDH1A1 activates brown fat—how is not clear—and also induces brown fat-like gene expression in white fat; and inhibiting THEM1 shunts fatty acid metabolism through brown fat.

Although these differences make it difficult to say which target might

be the best to treat metabolic disease, the differences also “open up a possibility that inhibitors of two or all three could have additive effects on weight loss” and metabolic disease, Tartaglia told *SciBX*.

Ember’s next step is to set up high throughput screens of small molecule libraries to identify lead inhibitors of the three targets and then develop the compounds to treat obesity and diabetes.

Given the *in vivo* results for GSK205 reported in the *Cell* paper, Tartaglia acknowledged that it is not yet clear whether TRPV4 inhibition could induce weight loss in already obese animals and thus potentially treat obesity in humans. “But we think the findings in the models of diet-induced obesity reflect the fact that the research compound GSK205 is far from optimal,” he said. “We are not even using it as a starting point. Instead, we expect our screening efforts to identify more potent compounds that will have a more robust effect on weight loss.”

Although the company’s main focus is on biologics that target brown fat, “we are also fleshing out our pipeline because brown fat is such a new field,” Tartaglia said. “It’s not yet known whether a biologic or small molecule will make the better compound for targeting brown fat. So we’re taking as broad an approach as possible to brown fat to thus identify the best pathway or target and type of therapeutic.”

Ember has variants of the hormone irisin in preclinical testing to treat obesity. Irisin is a secreted form of fibronectin type III domain containing 5 (FNDC5) that plays a role in regulating brown fat development.

The company also is conducting target-based *in vitro* screens and pathway-oriented cellular screens for lead compounds that activate PR domain containing 16 (PRDM16) and forkhead box C2 (FOXC2; MFH-1)

and biologics based on bone morphogenetic protein 7 (BMP7; OP-1).⁷ All three proteins play roles in regulating the development of brown fat.

Dana-Farber has filed a patent application covering the findings reported in *Cell*.

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COMPANIES AND INSTITUTIONS MENTIONED

Boston Children’s Hospital, Boston, Mass.
Brigham and Women’s Hospital, Boston, Mass.
Ember Therapeutics Inc., Boston, Mass.
Dana-Farber Cancer Institute, Boston, Mass.
Duke University School of Medicine, Durham, N.C.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
Howard Hughes Medical Institute, Chevy Chase, Md.
Massachusetts General Hospital, Boston, Mass.
Scripps Florida, Jupiter, Fla.
Third Rock Ventures, Boston, Mass.

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Leukemia team building

By Chris Cain, Senior Writer

The **Leukemia & Lymphoma Society** has announced its first research partnership with a large biopharma company—a four-year, multimillion-dollar deal with **Celgene Corp.** to solicit and fund proposals from academics and smaller biotechs. The not-for-profit organization expects the deal's framework to serve as a template for future collaborations and is in talks with additional big biotech and pharma companies.

In its first year, the partnership will support up to 10 projects that explore basic disease mechanisms underlying hematological

malignancies and up to 2 product development programs for advanced preclinical or early stage clinical candidates. Celgene will provide all research funding and will have right of first negotiation on any IP resulting from the projects.

“Over the last five years we’ve been partnering with biotech companies in earnest through the Therapy Acceleration Program, where we look for small companies that have assets that might be useful in treating blood cancers. What we hadn’t had were partnerships with big pharma or big biotech,” said Louis DeGennaro, EVP and chief mission officer of the Leukemia & Lymphoma Society (LLS).

Through the Therapy Acceleration Program (TAP), LLS funds the development of preclinical or early clinical assets discovered by academics or small biotechs. In return, recipients agree to pursue the funded project for a prescribed period of time and LLS is eligible to receive a fixed-multiple ROI that is fulfilled through a small royalty on

Table 1. Programs on TAP. The **Leukemia & Lymphoma Society** (LLS) has partnered with academic institutions or biotech companies to fund the development of at least 14 therapeutics in preclinical through Phase III development via its Therapy Acceleration Program (TAP).

Source: *BCIQ: BioCentury Online Intelligence; Leukemia & Lymphoma Society*

| Partner | Year | Compound name | Description | Indication | Clinical status | LLS commitment |
|---|------|----------------|---|---------------------------------------|-----------------|----------------|
| University Health Network/BioTheryX Inc. ^A | 2008 | Ciclopirox | Repurposed small molecule antifungal | Hematological malignancies | Phase I | Undisclosed |
| Celgene Corp. ^B | 2010 | CC-292 | Small molecule Bruton's tyrosine kinase (Btk) inhibitor | B cell malignancies | Phase Ib | \$3.2 M |
| Onconova Therapeutics Inc./Baxter International Inc. (NYSE:BAX) | 2010 | Rigosertib | Small molecule phosphoinositide 3-kinase (PI3K) and polo-like kinase 1 (PLK1; STPK13) inhibitor | Myelodysplastic syndrome (MDS) | Phase III | \$12.5 M |
| Shape Pharmaceuticals Inc. | 2010 | SHP-141 | Topical histone deacetylase (HDAC) inhibitor | Cutaneous T cell lymphoma (CTCL) | Phase I | \$3.3 M |
| University of Colorado Denver | 2011 | Not applicable | Combination of cyclosporin A and tyrosine kinase inhibitor | Drug-resistant leukemia | Phase I | Undisclosed |
| Acetylon Pharmaceuticals Inc. ^C | 2011 | ACY-1215 | Small molecule HDAC6 inhibitor | Multiple myeloma (MM) | Phase I | \$5.6 M |
| Memorial Sloan-Kettering Cancer Center | 2011 | MSK-777 | Small molecule inhibitor of cell division cycle 7-related protein kinase (CDC7) | Acute leukemias | Preclinical | Undisclosed |
| University of Florida ^D | 2011 | Oxi4503 | Combretastatin A1 diphosphate (CA1P) tubulin inhibitor | Acute myelogenous leukemia (AML)/MDS | Phase I | Undisclosed |
| Not applicable | 2011 | RI-BPI | Retro-inverso B cell CLL lymphoma 6 (BCL6) peptide inhibitor | Diffuse large B cell lymphoma (DLBCL) | Preclinical | Undisclosed |
| Curis Inc. | 2011 | CUDC-907 | Small molecule dual PI3K and HDAC inhibitor | B cell lymphoma and MM | Preclinical | \$4 M |
| University of Michigan Medical School | 2012 | Undisclosed | Small molecules that block the interaction of myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX) with multiple endocrine neoplasia I (MEN1; menin) | MLL | Preclinical | Undisclosed |
| The Johns Hopkins University School of Medicine | 2012 | PD-0332991 | Small molecule inhibitor of cyclin dependent kinase 4 (CDK4) and CDK6 | Acute leukemias/ MDS | Phase I | Undisclosed |
| Celator Pharmaceuticals Inc. | 2012 | CPX-351 | Liposomal formulation of cytarabine and daunorubicin | Secondary AML | Phase III | \$5 M |
| Constellation Pharmaceuticals Inc. | 2012 | Undisclosed | Small molecule inhibitor of the bromodomain and extra terminal domain (BET) family of bromodomain-containing proteins | Hematological malignancies | Preclinical | \$7.5 M |

^ALLS has a \$4.5 M equity investment in BioTheryX. ^BProgram was known as AVL-292 prior to the purchase of Avila Therapeutics Inc. by Celgene in March 2012. Avila is now Celgene Avilomics. ^CAcetylon has received investment from Celgene. ^DOxi4503 is under development by **OxiGene Inc.** (NASDAQ:OXGN) for additional oncology indications.

net sales if a product makes it to market.

TAP currently supports 14 programs (see Table 1, “Programs on TAP”).

DeGennaro said a new program was needed to complement TAP and enable LLS to coordinate with biopharma companies to cofund external research projects. “We needed a new framework onto which we could build a partnership that would ensure that our mission was being fulfilled while at the same time ensuring that the pharma would get something out of the collaboration,” he said.

Thus, the organization created the Targets, Leads and Candidates Program (TLCP) to support research via two distinct funding mechanisms: one tailored to early stage research into mechanisms of disease and one tailored to advancing preclinical or Phase I drug candidates.

Early and late

Celgene is the first participant in TLCP. The majority of the projects funded by the partners will explore basic science questions, such as identifying pathways and mechanisms that underlie the development of hematological malignancies. To narrow down research topics, Celgene and LLS will first form a joint steering committee tasked with identifying specific focus areas.

LLS then will issue a call for proposals from academic investigators, which will be peer reviewed in a process handled solely by the foundation. Applications that pass muster will be reviewed by the steering committee for final approval. DeGennaro said this selection and peer-review process is the key contribution LLS makes to the partnership.

“We have a well-established, proven infrastructure to identify high-quality research and have been doing this for 50 years. Our research grant funding has touched the discovery and development of every therapy used to treat blood cancers. What Celgene and other big companies can expect to get is access to that infrastructure and peer-review process and industry-quality project management by the LLS research team,” he said.

Celgene spokesperson Greg Geissman said infrastructure indeed was

“Over the last five years we’ve been partnering with biotech companies in earnest through the Therapy Acceleration Program, where we look for small companies that have assets that might be useful in treating blood cancers. What we hadn’t had were partnerships with big pharma or big biotech.”

—*Louis DeGennaro,*
Leukemia & Lymphoma Society

a driver of the company’s partnering decision. “We believe that LLS has a particular strength in its network and ability to identify promising early stage, foundational research at academic centers,” he said.

DeGennaro said retaining internal control over the review process was essential to the structure of the partnership. “While the joint steering committee has the final go/no-go decision, the LLS vetting and peer-review process is intact. These are the rules that we felt we had to play by. At the end of the day it must be our internal review processes that judge what is worthy of funding,” he said.

Unlike other academic project grants funded by LLS, the TLCP projects will have

specific timelines, milestones and deliverables, with progress overseen by the foundation’s staff.

TLCP will not operate in a vacuum, and to fund preclinical or early clinical-stage research the program will leverage the existing infrastructure used to identify projects eligible for the TAP program. LLS staff members will vet candidate projects as is currently done for TAP, and projects then will be presented to the joint steering committee, which will decide whether to adopt them as Celgene-funded projects.

Although the amount of research funding being provided by Celgene is undisclosed, DeGennaro said that projects will be funded over multiple years with annual budgets of between \$200,000 and \$1 million, depending on the type of research and stage of development.

The partners hope to identify research areas of joint interest and issue the first call for proposals before year end.

DeGennaro said LLS is in discussions with potential biopharma partners to set up additional independent collaborations using the TLCP framework.

With additional reporting from Sydney Blankers, Research Analyst.

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COMPANIES AND INSTITUTIONS MENTIONED

Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Leukemia & Lymphoma Society, White Plains, N.Y.

Closing time for HCV protease

By Kai-Jye Lou, Staff Writer

Astex Pharmaceuticals Inc. has used its fragment-based drug discovery platform to identify a new allosteric binding site on the full-length HCV NS3/4A protein and thinks compounds that bind the site can inhibit the protein's helicase activity in addition to its proteolytic activity.¹ The result could be molecules with better efficacy than existing HCV drugs that target the protease active site.

The full-length HCV NS3/4A protein consists of a protease domain linked to a helicase domain. According to Astex president, director and cofounder Harren Jhoti, R&D efforts to target the NS3/4A complex have previously focused on compounds that target the active site of the protein's protease domain due to screening limitations—it is more technically challenging to express and crystallize the full-length protein than individual domains for screening purposes.

Celia Schiffer, a professor of biochemistry and molecular pharmacology and director of the Center for AIDS Research at the

University of Massachusetts Medical School, noted that another reason the HCV field has focused on developing compounds against the individual domains of the NS3/4A protein stems from the view that the protein's helicase and protease functions are essentially independent of one another.

Despite not working with the full protein, efforts to inhibit the HCV NS3/4A protease active site have borne fruit—notably the approvals of Victrelis boceprevir from **Merck & Co. Inc.** and Incivek telaprevir from **Vertex Pharmaceuticals Inc.** in May of last year.

There are at least 10 HCV NS3/4A protease inhibitors in various stages of clinical development, including three in Phase III trials.

Jhoti said compounds that target the same site on the HCV protein are likely to be affected by the same resistance mutations. Thus, rather than joining an already crowded space by pursuing compounds against the protease active site, the Astex team sought to identify alternative sites on the NS3/4A protein that could be targeted to inhibit its function.

The group generated crystals of the full-length NS3/4A protein and used X-ray-based crystallographic screening against a library of chemical fragments to identify compounds that bound to the target.

The crystal structures of the full-length protein in complex with screening hits revealed a new binding pocket at the interface of the protein's helicase and protease domains. The fragment screening hits had

Figure 1. Targeting the full-length HCV NS3/4A protein complex.

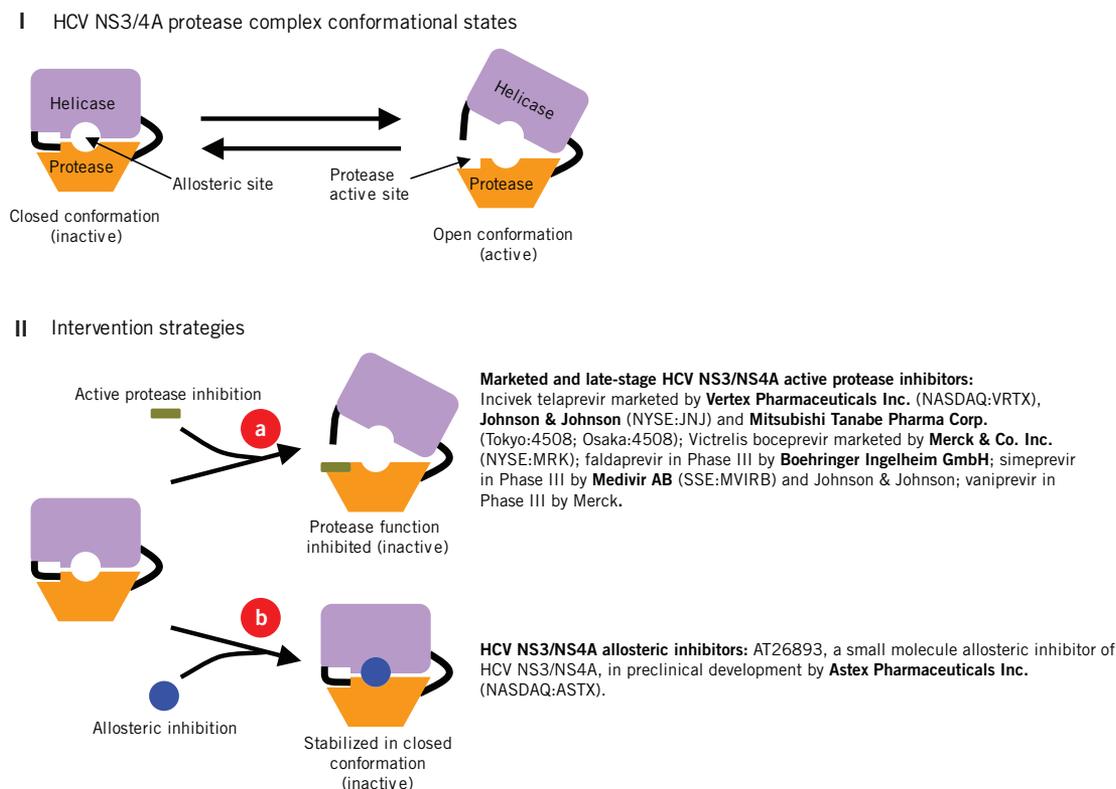
Researchers at **Astex Pharmaceuticals Inc.** have identified a new binding pocket on the full-length HCV NS3/4A protein complex that could be targeted to treat HCV infection. The full-length protein consists of a helicase domain linked to a protease domain.

[I] The complex switches between an active, open conformation and an inactive, closed conformation. In the closed conformation, the C-terminus of the helicase domain occupies the protease active site.

[II] Direct inhibition of the protease active site is the primary strategy

drug developers have pursued to inhibit the complex. There are already at least 2 such drugs marketed to treat HCV infection and at least another 10 in clinical trials. Targeting this site inhibits the complex's proteolytic activity [II(a)].

The newly identified allosteric site is present when the full-length NS3/4A protein complex is in its closed conformation. Compounds that target the site stabilize the complex in this inactive conformation [II(b)]. Unlike inhibitors against the protease active site, compounds that target the allosteric site also have the potential to inhibit the complex's helicase activity in addition to its proteolytic activity.



weak inhibitory activity but showed ligand efficiencies that suggested they could be optimized into potent compounds.

Ligand efficiency is a measure of how well a small molecule binds to a protein, regardless of its size. In fragment-based screening, it is used as a criterion to select chemical fragments that could be good candidates for further optimization.²

Structure-based optimization of a screening hit yielded a chemical probe that inhibited the full length NS3/4A protein with an IC₅₀ of <10 nM. In cell-based replicon assays, the optimized probe showed antiviral activity with an EC₅₀ of 8.3 nM.

Data from a series of *in vitro* biophysical assays suggested compounds binding to the newly identified pocket allosterically inhibit the function of the NS3/4A protein by stabilizing it in an inactive conformation (see Figure 1, “Targeting the full-length HCV NS3/4A protein complex”).

Results were published in *Nature Chemical Biology*.

“They have discovered potent HCV NS3/4A inhibitors that simultaneously interact with both the protease and the helicase domains,” said Schiffer, who also is co-director of the Institute for Drug Resistance at the University of Massachusetts Medical Center. “I think having small, reasonably bioavailable inhibitors that interact with conserved regions of both domains could be a very useful strategy for the various genotypes of HCV and may be a strategy for other flaviviruses as well.”

However, Schiffer wanted to see additional experimental data to prove that the inhibitors are acting via the described allosteric mechanism.

“It would also be very interesting to know if these inhibitors impact the helicase activity at all,” she added.

Known target, new strategy

Astex has selected a lead preclinical candidate, AT26893, which exploits the allosteric inhibitory mechanism against the full-length HCV NS3/4A protein. The company hopes to start Phase I testing in mid-2013.

“The goal of our HCV program is to find and develop molecules that will have superior physicochemical properties compared to protease active site inhibitors,” said Jhoti, corresponding author on the paper. “What we were trying to do in this study is determine whether our fragment-based screening approach could discover compounds that bind to a site on the NS3/4A protein that’s different from the one protease active site inhibitors bind to.”

It is too early to know how Astex’s allosteric inhibitor will compare with marketed and clinical-stage NS3/4A protease inhibitors. Nevertheless, Jhoti said the company’s molecule could have improved efficacy, better safety and lower risk of cross-resistance based on the compound’s hypothesized mechanism and some unpublished preliminary preclinical data.

“Our compound appears to stabilize the NS3/4A protein in its closed, inactive conformation and thus could have the ability to inhibit both the helicase and protease enzymatic functions of the protein,” he told *SciBX*. “Because of this, there is a possibility that the antiviral effect of our compound could be more pronounced than current protease active site

inhibitors, which only inhibit the protein’s protease function. However, we still need to confirm these potential advantages in experimental assays.”

Moreover, telaprevir and boceprevir, as well as many protease inhibitors marketed to treat HIV infection, are known to inhibit cytochrome P450 3A4 (CYP3A4).^{3,4} The enzyme is involved in the metabolism of many known drugs, including the protease inhibitors themselves.

Because Astex’s AT26893 comes from a different chemical class, Jhoti thinks it should avoid many of the bioavailability, toxicity and drug-interaction issues caused by off-target inhibition of cytochrome P450 (p450) isoenzymes. He added that this could translate

into more consistent efficacy and tolerability profiles between patients.

Finally, Jhoti said the resistance profile of the company’s allosteric inhibitor should be very different from that of active site inhibitors.

In addition to the potential therapeutic advantages, Astex expects that avoiding compounds that bind to the protease active site of the NS3/4A protein will give the company greater operating freedom in designing and optimizing lead candidates from screening hits.

“Many companies already have compounds that target the NS3/4A protease active site, and both the chemical space and IP space have become very crowded,” Jhoti told *SciBX*. “Because we are going after a different binding site on the protein, we get to work in a different chemical space that’s also relatively unconstrained by existing IP.”

He said the paper also demonstrates that the company’s fragment-based platform could be used to discover leads that modulate the activity of disease-relevant proteins via allosteric sites. Astex plans to publish data soon related to pyruvate kinase M2 isozyme (PKM2) and also plans to report on efforts to target a protein-protein interaction involving X-linked inhibitor of apoptosis (XIAP). Both proteins are linked to cancer.

Astex has filed composition-of-matter patents covering its allosteric inhibitors of the full-length NS3/4A protein. The compounds are available for licensing.

Jhoti noted that the company also is interested in forming collaborations and/or partnerships to help advance its HCV program.

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COMPANIES AND INSTITUTIONS MENTIONED

Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
University of Massachusetts Medical School, Worcester, Mass.
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Cambridge, Mass.

Repurposing naratriptan

By Lauren Martz, Staff Writer

Japanese researchers have shown in mice that **GlaxoSmithKline plc's** marketed migraine drug Amerge naratriptan could be repurposed to treat spinal and bulbar muscular atrophy.¹ The pharma is not saying if it will pursue the new indication for the serotonin (5-HT_{1D}) receptor agonist, but the academics who did the work are planning an investigator-led Phase II trial.

Spinal and bulbar muscular atrophy (SBMA) involves degeneration of lower motor neurons in the spinal cord and brainstem of males. The degeneration causes progressive weakness and atrophy of facial, limb and bulbar muscles. The disease is caused by CAG glutamine repeats within the *androgen receptor (AR)* gene, which causes pathogenic AR accumulation in the nucleus of motor neurons.

There are no approved treatments for SBMA. Previous efforts to treat the disease have included strategies to eliminate the pathogenic AR accumulation such as treatment with the luteinizing hormone–releasing hormone (LHRH) analog leuporelin. In 2010, however, Masahisa Katsuno and colleagues reported that leuporelin failed to improve swallowing and muscle function in an investigator-led Phase II trial.²

Takeda Pharmaceutical Co. Ltd. markets Leuplin leuporelin acetate to treat prostate cancer.

“Accumulation of abnormal protein is the primary molecular event as well as a substantial therapeutic target for neurodegenerative diseases. However, drugs that inhibit abnormal protein deposits, such as antibodies to β -amyloid and antiandrogens for SBMA, show limited effects in clinical trials. This may suggest that various molecular events downstream of abnormal protein aggregation overwhelm the neuroprotection by such interventions,” said Katsuno, who is an associate professor of neurology at the **Nagoya University Graduate School of Medicine**.

Thus, Katsuno and colleagues wanted to probe the downstream effects of pathogenic AR accumulation on gene expression in motor neurons. The team, which also included researchers from **The University of Tokyo**, used a transgenic mouse model of SBMA in which the mice expressed human AR with pathogenic CAG repeats. Microarray analysis revealed 124 deregulated genes in the SBMA mice, whereas there were no deregulated genes in animals expressing wild-type human AR or in wild-type mice.

Of the identified genes, the group focused on *calcitonin gene-related peptide (CGRP)* for two reasons: it was significantly upregulated in the SBMA mice and previous studies suggested its expression was restricted to the lower motor neurons in the spinal cord—the parts of the CNS affected by SBMA.

In human neuroblastoma cells expressing pathogenic AR, knockdown or pharmacological inhibition of CGRP protected against toxicity and

cell death compared with no knockdown or inhibition. Mechanistically, upregulated CGRP activated the neurotoxic c-Jun N-terminal kinase (JNK) pathway in motor neurons.

Previous studies have shown that CGRP is overexpressed in other neurological conditions including migraine, and marketed serotonin (5-HT_{1B}) receptor and 5-HT_{1D} agonists suppress CGRP secretion and neurological symptoms in patients with migraine. Therefore, Katsuno's group set out to determine whether the migraine therapeutics also could help treat SBMA.

In human neuroblastoma cells expressing pathogenic AR, naratriptan and other 5-HT_{1D} agonists restored cell viability and decreased damage compared with vehicle control.

In male mice expressing human pathogenic AR, naratriptan increased grip strength, body weight and life span compared with vehicle control. The effects were comparable to those seen with *Cgrp* knockout.

Results were published in *Nature Medicine*.

Repurposing serotonin receptor agonists

Katsuno told *SciBX* that the next step is to perform an investigator-led Phase II trial of naratriptan.

Maria Pennuto, group leader in the Department of Neuroscience and Brain Technologies at the **Italian Institute of Technology**, said it is worth testing naratriptan in SBMA but noted that “naratriptan's use is associated with side effects such as dizziness, nausea and other symptoms, which calls for caution in the use of this drug for the treatment of a chronic disease.”

“This treatment has to be continued for the entire life of an individual. It might be possible that a chronic treatment reveals unsuspected side effects or that the already known side effects may become intolerable by the patients,” added Angelo Poletti, professor of applied biology in the Department of Pharmacological and Biomolecular Sciences at the **University of Milan**.

Katsuno countered that the side effects of naratriptan can be attenuated with symptomatic therapies such as treatments for nausea and hypertension. However, patients experiencing angina would need to discontinue naratriptan.

Andrew Cato, group leader at **Karlsruhe Institute of Technology's** Institute of Toxicology and Genetics, was less sanguine about the repurposing opportunity. “Compared with leuporelin, naratriptan only had a marginal effect in protecting against neurodegeneration in the mouse experiments. It is therefore debatable whether it would have a major impact on the treatment of patients,” he said.

Nobuyuki Nukina, head of the Structural Neuropathology Lab at the **RIKEN Brain Science Institute**, suggested that a combination of naratriptan with other candidates could generate the best efficacy.

Pennuto agreed. “It may be worth it to design a study in which combination therapy is also considered, for instance, naratriptan together with leuporelin or other drugs to decrease androgen levels in the serum,” she said.

Katsuno told *SciBX* that his team is running another trial of leuporelin for SBMA. “If we can prove that leuporelin suppresses

“If we can prove that leuporelin suppresses disease progression of SBMA, we want to test the combination of this hormonal therapy with naratriptan.”

**—Masahisa Katsuno,
Nagoya University Graduate School
of Medicine**

disease progression of SBMA, we want to test the combination of this hormonal therapy with naratriptan,” he said.

He added, “Since the results of the previous trial were not conclusive, we are now conducting an additional Phase II trial of leuprorelin that mainly focuses on the SBMA patients whose disease duration is less than 10 years.”

Polyglutamine diseases

Despite his reservations, Cato did say that naratriptan’s mechanism could apply to neurodegeneration that occurs in other polyglutamine diseases such as amyotrophic lateral sclerosis (ALS).

Indeed, Pennuto wanted to know whether the pathway is upregulated in Huntington’s disease (HD) and spinocerebellar ataxias caused by polyglutamine expansion.

She cautioned that the modification of *CGPR* transcription in SBMA is specifically caused by the polyglutamine repeats within *AR*. Because other diseases have different affected genes, it remains to be determined whether the same strategy would be efficacious.

Katsuno said the microarray-based strategy used to identify *CGPR* as a target is applicable to HD and other polyglutamine disorders.

He told *SciBX* that **Nagoya University** has filed a patent application

covering the findings in the paper and that the licensing status is undisclosed.

GlaxoSmithKline declined to comment on the findings.

Martz, L. *SciBX* 5(40); doi:10.1038/scibx.2012.1048

Published online Oct. 11, 2012

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2. Katsuno, M. *et al. Lancet Neurol.* **9**, 875–884 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

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Italian Institute of Technology, Genoa, Italy
Karlsruhe Institute of Technology, Karlsruhe, Germany
Nagoya University, Nagoya, Japan
Nagoya University Graduate School of Medicine, Nagoya, Japan
RIKEN Brain Science Institute, Saitama, Japan
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
University of Milan, Milan, Italy
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This week in therapeutics

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

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|--|---|---|--|--|
| Cancer | | | | |
| Cancer | Pyruvate kinase M2 isozyme (PKM2) | <p>Cell culture and mouse studies suggest PKM2 activators could help treat cancer. In a lung cancer cell line grown under hypoxic conditions, PKM2 activators altered glucose metabolism plus other metabolic pathways and decreased cell proliferation compared with vehicle. In xenograft mice with the lung cancer cell line, the PKM2 activator increased the tumor latency period and decreased tumor size compared with vehicle. Next steps include evaluating PKM2 activators in mice with established tumors.</p> <p>Agios Pharmaceuticals Inc. has a discovery-stage program targeting PKM2 in cancer.</p> <p>Dynamix Pharmaceuticals Ltd's PKM2 activator, DNX-3000, is in preclinical development for cancer.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1049 Published online Oct. 11, 2012</p> | Composition of matter patented; available for licensing from NIH | <p>Anastasiou, D. <i>et al. Nat. Chem. Biol.</i>; published online Aug. 26, 2012; doi:10.1038/nchembio.1060</p> <p>Contact: Matthew G. Vander Heiden, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: mvh@mit.edu</p> |
| Cardiovascular disease | | | | |
| Blood clots | Anoctamin 6 (ANO6; TMEM16F) | <p>Mouse and cell culture studies suggest inhibiting TMEM16F could help prevent thrombosis. In mice, knocking out <i>Tmem16f</i> increased bleeding time compared with no knockout and prevented chemical-induced thrombus formation. Studies in human and amphibian cell lines showed that TMEM16F forms a Ca²⁺-activated, nonselective cation channel needed for lipid scrambling, a process that regulates membrane phospholipid composition, in platelets during coagulation. Next steps could include screening for and evaluating compounds that inhibit TMEM16F.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1050 Published online Oct. 11, 2012</p> | Patent and licensing status unavailable | <p>Yang, H. <i>et al. Cell</i>; published online Sept. 28, 2012; doi:10.1016/j.cell.2012.07.036</p> <p>Contact: Lily Yeh Jan, University of California, San Francisco, Calif. e-mail: lily.jan@ucsf.edu</p> |
| Endocrine/metabolic disease | | | | |
| α -Antitrypsin (AAT) deficiency | α -Antitrypsin (AAT; A ₁ AT; SERPINA1); histone deacetylase 7 (HDAC7) | <p><i>In vitro</i> studies suggest suberoylanilide hydroxamic acid (SAHA) could help treat AAT deficiency. The Z-variant of AAT deficiency is the most severe form of the condition, which involves defective folding, trafficking and secretion of AAT from the endoplasmic reticulum. In human cell lines expressing Z-AAT, HDAC inhibitors including SAHA increased AAT trafficking from the endoplasmic reticulum compared with vehicle. In these cells, small interfering RNA knockdown of HDAC7 increased AAT stability and trafficking compared with silencing of other HDACs. Next steps could include testing SAHA in animal models of AAT deficiency. At least six companies have therapeutics to treat AAT deficiency in development stages ranging from preclinical to marketed. Merck & Co. Inc. markets Zolinza SAHA to treat cutaneous T cell lymphoma (CTCL).</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1051 Published online Oct. 11, 2012</p> | Patent and licensing status unavailable | <p>Bouchecareilh, M. <i>et al. J. Biol. Chem.</i>; published online Sept. 20, 2012; doi:10.1074/jbc.M112.404707</p> <p>Contact: William E. Balch, The Scripps Research Institute, La Jolla, Calif. e-mail: webalch@scripps.edu</p> |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|---|--|--|--|---|
| Diabetes; obesity | Transient receptor potential vanilloid 4 (TRPV4; VRL2) | A study in cell culture and in mice suggests antagonizing TRPV4 could help treat obesity and type 2 diabetes. In mice fed a high-fat diet, <i>Trpv4</i> knockout increased energy expenditure and glucose tolerance and decreased weight gain and insulin resistance compared with no knockout. In mouse models of diet-induced obesity, a TRPV4 antagonist increased glucose tolerance and decreased insulin sensitivity compared with vehicle. Next steps at Ember Therapeutics Inc. include running a screen to identify lead TRPV4 antagonists (<i>see Ember: warming up to brown fat, page 1</i>). | Patent application filed; licensed to Ember Therapeutics | Ye, L. <i>et al. Cell</i> ; published online Sept. 28, 2012; doi:10.1016/j.cell.2012.08.034 Contact: Bruce M. Spiegelman, Dana-Farber Cancer Institute, Boston, Mass. e-mail: bruce_spiegelman@dfci.harvard.edu |
| SciBX 5(40); doi:10.1038/scibx.2012.1052 Published online Oct. 11, 2012 | | | | |
| Hematology | | | | |
| Hemophilia | Factor IX; factor Xa | <i>In vitro</i> and monkey studies identified a bifunctional antibody targeting factor IX and factor Xa that could help treat hemophilia A. In human factor VIII-deficient plasma, an antibody that bound factor IX and factor Xa induced coagulation. In a monkey model of hemophilia A, the same antibody had high subcutaneous bioavailability and a long half-life and decreased bleeding compared with no treatment. Next steps include clinical testing. At least 10 companies have therapeutics targeting factor VIII to treat hemophilia in development stages ranging from clinical to marketed. | Findings patented; licensing status undisclosed | Kitazawa, T. <i>et al. Nat. Med.</i> ; published online Sept. 30, 2012; doi:10.1038/nm.2942 Contact: Takehisa Kitazawa, Fuji-Gotemba Research Laboratories, Shizuoka, Japan e-mail: kitazawatkh@chugai-pharm.co.jp |
| SciBX 5(40); doi:10.1038/scibx.2012.1053 Published online Oct. 11, 2012 | | | | |
| Infectious disease | | | | |
| Gram-positive bacterial infection | GTP pyrophosphokinase (relA) | <i>In vitro</i> studies identified an inhibitor of relA that could help treat Gram-positive bacterial infections. relA synthesizes (p)ppGpp, which is required for a bacterial starvation survival mechanism called the stringent response. In enzymatic assays, a 2'-deoxyguanosine-based analog of (p)ppGpp, dubbed Relacin, inhibited relA and prevented synthesis of (p)ppGpp from <i>Escherichia coli</i> and <i>Deinococcus radiodurans</i> . In spore-forming <i>Bacillus subtilis</i> cells, the analog also decreased (p)ppGpp production, cell viability and sporulation compared with no treatment. Next steps include determining the effects of Relacin on eukaryotic cells and examining antibiotic activity in animal models. | Patent application filed; unlicensed | Wexselblatt, E. <i>et al. PLoS Pathog.</i> ; published online Sept. 20, 2012; doi:10.1371/journal.ppat.1002925 Contact: Sigal Ben-Yehuda, The Hebrew University of Jerusalem, Jerusalem, Israel e-mail: sigalb@ekmd.huji.ac.il |
| SciBX 5(40); doi:10.1038/scibx.2012.1054 Published online Oct. 11, 2012 | | | | |
| HCV | HCV NS3/4A protein complex | Fragment-based screening using crystals of the HCV NS3/4A holoenzyme identified inhibitors of an allosteric site that could help treat HCV infection. Structure-guided optimization of a lead fragment against an allosteric site on the HCV NS3/4A holoenzyme yielded a compound that inhibited the enzyme with an IC ₅₀ under 10 nM. In a cell-based assay, the optimized compound showed antiviral activity with an EC ₅₀ of 8.3 nM. IND-enabling studies of an optimized molecule that binds the same site are ongoing. Astex Pharmaceuticals Inc.'s lead HCV NS3/4A protease inhibitor, which is the optimized molecule, is in preclinical development to treat HCV infection. Vertex Pharmaceuticals Inc. markets Incivek telaprevir, a small molecule HCV NS3/4A protease inhibitor, to treat HCV infection. Merck & Co. Inc. markets Victrelis boceprevir, a small molecule HCV NS3/4A protease inhibitor, for the same indication. At least six other companies have inhibitors of the HCV NS3/4A protease in Phase III testing or earlier to treat HCV infection (<i>see Closing time for HCV protease, page 6</i>). | Patent applications filed covering composition of matter; available for licensing and partnering | Saalau-Bethell, S.M. <i>et al. Nat. Chem. Biol.</i> ; published online Sept. 30, 2012; doi:10.1038/nchembio.1081 Contact: Harren Jhoti, Astex Pharmaceuticals Inc., Cambridge, U.K. e-mail: jhoti@stx.com |
| SciBX 5(40); doi:10.1038/scibx.2012.1055 Published online Oct. 11, 2012 | | | | |

This week in therapeutics (continued)

| Indication | Target/marker/ pathway | Summary | Licensing status | Publication and contact information |
|---|--|---|---|---|
| Musculoskeletal disease | | | | |
| Spinal muscular atrophy | Calcitonin gene- related peptide (CGRP) | <i>In vitro</i> and mouse studies suggest reducing CGRP expression could help treat spinal and bulbar muscular atrophy (SBMA). In human neuroblastoma cells and motor neurons expressing disease-causing glutamine CAG repeats in <i>androgen receptor</i> , small interfering RNA against or inhibition of CGRP decreased cytotoxicity and increased cell viability compared with control siRNA or no inhibition. In a mouse model of SBMA, reduction of <i>Cgrp</i> expression, using the serotonin (5-HT _{1D}) receptor agonist Amerge naratriptan, increased motor function and lifespan compared with vehicle control. Next steps include Phase II trials of Amerge in the indication. GlaxoSmithKline plc markets Amerge to treat migraine. At least four companies have antibodies or antagonists targeting the CGRP receptor in clinical and preclinical testing to treat migraine (see <i>Repurposing naratriptan</i> , page 8). | Patent application filed; unavailable for licensing | Minamiyama, M. <i>et al. Nat. Med.</i> ; published online Sept. 30, 2012; doi:10.1038/nm.2932 Contact: Gen Sobue, Nagoya University, Nagoya, Japan e-mail: sobueg@med.nagoya-u.ac.jp Contact: Masahisa Katsuno, same affiliation as above e-mail: ka2no@med.nagoya-u.ac.jp |
| Neurology | | | | |
| Alzheimer's disease (AD) | β -Site APP-cleaving enzyme 1 (BACE1); β -amyloid 40 | Rodent studies suggest fused bicyclic iminopyrimidinone-based BACE1 inhibitors could help treat neurodegenerative diseases such as AD. <i>In vitro</i> , a lead member of the series inhibited BACE1 with a K_i of 4 nM. In a rat model of AD, oral treatment with the lead inhibitor decreased plasma, cerebrospinal fluid and brain levels of β -amyloid 40 compared with vehicle treatment. Next steps include studies to move a lead analog from the series toward clinical development. MK-8931, a BACE1 inhibitor from Merck & Co. Inc., is in Phase I testing to treat AD. At least six other companies have BACE1 inhibitors in Phase I development or earlier to treat AD. | Patented; unavailable for licensing | Mandal, M. <i>et al. J. Med. Chem.</i> ; published online Sept. 18, 2012; doi:10.1021/jm301039c Contact: Mihirbaran Mandal, Merck Research Laboratories, Kenilworth, N.J. e-mail: mihirbaran.mandal@merck.com |
| Alzheimer's disease (AD) | Epidermal growth factor receptor (EGFR) | <i>Drosophila</i> and mouse studies suggest EGFR inhibitors could help treat AD. In transgenic flies expressing human β -amyloid 42, the EGFR inhibitors Iressa and Tarceva prevented memory loss as effectively as the approved AD drug memantine. In a transgenic mouse model of AD, Iressa decreased memory loss compared with vehicle. In both a mouse and fly behavioral screen of 2,000 synthetic compounds that modulate protein kinase activities, 3 compounds prevented memory loss and inhibited β -amyloid 42-mediated Egfr activity. Next steps include identifying more compounds for preclinical screening. Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd. and Roche market Tarceva erlotinib to treat pancreatic cancer and non-small cell lung cancer (NSCLC). AstraZeneca plc's Iressa is in Phase III testing to treat head and neck cancer. | Patent application filed; available for licensing | Wang, L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 27, 2012; doi:10.1073/pnas.1208011109 Contact: Yi Zhong, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. e-mail: zhongyi@cshl.edu |
| SciBX 5(40); doi:10.1038/scibx.2012.1056 Published online Oct. 11, 2012 | | | | |
| SciBX 5(40); doi:10.1038/scibx.2012.1057 Published online Oct. 11, 2012 | | | | |
| SciBX 5(40); doi:10.1038/scibx.2012.1058 Published online Oct. 11, 2012 | | | | |

This week in therapeutics (continued)

| Indication | Target/marker/ pathway | Summary | Licensing status | Publication and contact information |
|---|-------------------------------|---|--|--|
| Amyotrophic lateral sclerosis (ALS); Parkinson's disease (PD) | Superoxide dismutase 1 (SOD1) | <p>Mouse and worm studies suggest a new class of carbazoles could help treat ALS and PD. Previous work identified a lead aminopropylcarbazole that prevented apoptosis of hippocampal neurons in newborn mice. In a mutant <i>SOD1</i> mouse model of ALS, an optimized aminopropylcarbazole increased survival of spinal motor neurons, delayed disease onset and decreased loss of motor function compared with vehicle. In mouse and <i>Caenorhabditis elegans</i> models of chemically induced PD, the optimized carbazole increased survival of dopaminergic neurons compared with vehicle. Ongoing work in collaboration with 2M BioTech L.P. includes testing the aminopropylcarbazoles in models of traumatic brain injury and peripheral nerve injury.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1059 Published online Oct. 11, 2012</p> | Patented by The University of Texas System and 2M Biotech; available for licensing or partnering | <p>De Jesús-Cortés, H. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 1, 2012; doi:10.1073/pnas.1213956109</p> <p>Tesla, R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 1, 2012; doi:10.1073/pnas.1213960109</p> <p>Contact: Andrew A. Pieper, University of Iowa Carver College of Medicine, Iowa City, Iowa e-mail: andrew-pieper@uiowa.edu</p> <p>Contact: Steven L. McKnight, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: steven.mcknight@utsouthwestern.edu</p> <p>Contact: Joseph M. Ready, same affiliation as above e-mail: joseph.ready@utsouthwestern.edu</p> |
| Stroke | Not applicable | <p>Rat studies suggest ceria nanoparticles could help treat stroke. In rats, i.v. injection of nanoparticles incorporating cerium ions after induction of ischemic stroke decreased infarct volume compared with saline injection. Next steps include determining the therapeutic window for ceria nanoparticle-mediated protection against stroke in rats and evaluating efficacy and toxicity in large animals.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1060 Published online Oct. 11, 2012</p> | Patent application filed; available for licensing | <p>Kim, C.K. <i>et al. Angew. Chem. Int. Ed.</i>; published online Sept. 11, 2012; doi:10.1002/anie.201203780</p> <p>Contact: Taeghwan Hyeon, Seoul National University, Seoul, South Korea e-mail: thyeon@snu.ac.kr</p> <p>Contact: Seung-Hoon Lee, same affiliation as above e-mail: sb0516@snu.ac.kr</p> |

This week in techniques

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

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

| Approach | Summary | Licensing status | Publication and contact information |
|--|---|--|--|
| Assays & screens | | | |
| NMR of hyperpolarized fluorine to characterize ligand-protein interactions | Hyperpolarized fluorine could improve the sensitivity of fluorine-based NMR for characterizing ligand-protein interactions. Samples were rapidly injected into an aliquot of hyperpolarized fluorine and analyzed by NMR. The use of hyperpolarized fluorine enabled generation of readable NMR spectra even when ligand and protein concentrations differed by up to six orders of magnitude, which enabled the calculation of K_d values. Next steps include using hyperpolarized fluorine in drug discovery efforts. | Unpatented; licensing status not applicable | Lee, Y. <i>et al. J. Am. Chem. Soc.</i> ; published online Sept. 28, 2012; doi:10.1021/ja308437h Contact: Christian Hilty, Texas A&M University, College Station, Texas e-mail: chilty@chem.tamu.edu |
| Chemistry | | | |
| Vascular catheters modified with polysulfobetaine to prevent thrombus formation and microbial attachment | Polysulfobetaine surface modification of vascular catheters could help prevent catheter-associated thrombosis and infection. Nonleaching polysulfobetaine was attached to the inner surface of commercially available, peripherally inserted central catheters. In a canine model of thrombosis, the polysulfobetaine-modified catheter showed a 99% decrease in thrombus formation compared with an unmodified catheter. The modified catheter also showed 97%–99.9% lower adhesion of 5 tested microbes and 97% less biofilm formation with <i>Staphylococcus aureus</i> than the unmodified catheter. The Semprus BioSciences Corp. unit of Teleflex Inc. markets the polysulfobetaine-modified catheter in the EU, and the product is under FDA review. | Covered by multiple issued and pending patents; licensing status undisclosed | Smith, R.S. <i>et al. Sci. Transl. Med.</i> ; published online Sept. 26, 2012; doi:10.1126/scitranslmed.3004120 Contact: Christopher Loose, Semprus BioSciences Corp., Cambridge, Mass. e-mail: chris.loose@semprusbio.com |
| Disease models | | | |
| Mice with mesodermal inactivation of <i>Pten</i> (<i>Mmac1</i> ; <i>Tep1</i>) as models for alveolar capillary dysplasia (ACD) | Mice with mesodermal inactivation of <i>Pten</i> could help identify new treatments for ACD, a congenitally lethal condition characterized by disordered pulmonary vascular development. Analysis of lung tissue samples from newborns who died from ACD showed decreased <i>PTEN</i> and increased <i>protein kinase B</i> (<i>PKB</i> ; <i>PKBA</i> ; <i>AKT</i> ; <i>AKT1</i>) expression compared with newborns who died from other causes. Mice with pulmonary mesodermal-specific <i>Pten</i> inactivation had defects in lung development and failure in blood oxygenation and died at birth. Next steps include validating the model using samples isolated from infants affect by ACD. | Unpatented; licensing status not applicable | Tiozzo, C. <i>et al. J. Clin. Invest.</i> ; published online Oct. 1, 2012; doi:10.1172/JCI61334 Contact: Parviz Minoo, University of Southern California, Los Angeles, Calif. e-mail: minoo@usc.edu |
| Drug delivery | | | |
| β -Galactosidase-responsive prodrugs of chemotherapeutics targeted to cancer surface receptors | <i>In vitro</i> and mouse studies suggest tumor-penetrating, β -galactosidase-responsive prodrugs could help treat cancers. A monomethyl auristatin E (MMAE) prodrug that is activated by the β -galactosidase found inside cells was designed to include a ligand targeting the cancer-specific folate receptor. Cancer cells expressing the folate receptor took up the prodrug and showed cytotoxicity, whereas cells lacking the receptor did not. In mice with folate receptor-expressing tumor xenografts, the MMAE prodrug caused near-complete tumor elimination without weight loss. Next steps include additional preclinical studies of the prodrugs. | Patent application filed; available for licensing | Legigan, T. <i>et al. Angew. Chem. Int. Ed.</i> ; published online Sept. 20, 2012; doi:10.1002/anie.201204935 Contact: Sébastien Papot, University of Poitiers, Poitiers, France e-mail: sebastien.papot@univ-poitiers.fr |

This week in techniques (continued)

| Approach | Summary | Licensing status | Publication and contact information |
|--|---|---|--|
| Drug platforms | | | |
| Cell or tissue transplantation to restore organ functions | <p>Mouse studies suggest transplantation of cells into lymph nodes could rescue organ function. In a mouse model of lethal metabolic liver failure, transplantation of allogeneic hepatocytes to lymph nodes led to engraftment, which rescued the animals from liver failure. In athymic nude mice, transplantation of minced thymus tissue to lymph nodes led to engraftment, production of T cells that were present in the peripheral blood and immune responses against tumor cell transplants. In a mouse model of diabetes, transplantation of islets to lymph nodes led to engraftment and production of C-peptide and glucagon, and it restored blood glucose levels to those of normal mice. Next steps include testing the method in swine.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1065 Published online Oct. 11, 2012</p> | Patent application filed; available for licensing | <p>Komori, J. <i>et al. Nat. Biotechnol.</i>; published online Sept. 23, 2012; doi:10.1038/nbt.2379</p> <p>Contact: Eric Lagasse, University of Pittsburgh School of Medicine, Pittsburgh, Pa. e-mail: lagasse@pitt.edu</p> |
| Imaging | | | |
| Functionalized multiwalled carbon nanotubes as contrast agents for ultrasound imaging | <p>Functionalized multiwalled carbon nanotubes could be used as contrast agents to enhance ultrasound imaging. Multiwalled carbon nanotubes were oxidized and then modified by adding azomethine ylides to make them biocompatible. In <i>ex vivo</i> studies using pig livers and hearts, injection of the carbon nanotubes increased ultrasound imaging contrast 20-fold compared with water. In pig studies, delivery of the carbon nanotubes to the bladder increased ultrasound imaging contrast compared with no treatment. Next steps could include evaluating the safety and pharmacokinetics of the carbon nanotubes.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1066 Published online Oct. 11, 2012</p> | Patent and licensing status unavailable | <p>Delogu, L.G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 24, 2012; doi:10.1073/pnas.1208312109</p> <p>Contact: Alberto Bianco, Institute of Molecular and Cellular Biology, Strasbourg, France e-mail: a.bianco@ibmc-cnrs.unistra.fr</p> <p>Contact: Lucia Gemma Delogu, University of Sassari, Sassari, Italy e-mail: lgdelogu@uniss.it</p> |
| Markers | | | |
| <i>Fibroblast growth factor receptor 1 (FGFR1; CD331), FGFR2 and fibroblast growth factor 19 (FGF19)</i> amplification may help predict sensitivity to FGFR inhibitors in cancer | <p><i>FGFR1</i>, <i>FGFR2</i> and <i>FGF19</i> amplification may help predict sensitivity to FGFR inhibitors. In breast, lung and osteosarcoma cell lines and primary human osteosarcoma samples, <i>FGFR1</i> amplification was associated with sensitivity to the pan-FGFR inhibitor NVP-BGJ398. In breast, gastric and esophageal cancer cells and in gastric cancer xenografts in rats, <i>FGFR2</i> amplification was associated with sensitivity to the compound. In liver cancer cell lines, <i>FGF19</i> amplification was associated with NVP-BGJ398 sensitivity when <i>klotho-β (KLB)</i> was expressed. Ongoing work includes clinical trials with NVP-BGJ398 to treat patients with cancer bearing genetic alterations in FGFRs. NVP-BGJ398 is currently in Phase I trials to treat cancer.</p> <p>At least seven different companies have FGFR inhibitors in development, ranging from preclinical to Phase III trials, to treat various cancers.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1067 Published online Oct. 11, 2012</p> | Patent application filed for compound; unlicensed | <p>Guagnano, V. <i>et al. Cancer Discov.</i>; published online Sept. 20, 2012; doi:10.1158/2159-8290.CD-12-0210</p> <p>Contact: Diana Graus Porta, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: diana.graus_porta@novartis.com</p> |
| <i>Fibroblast growth factor receptor 4 (FGFR4; CD334)</i> SNP as a response marker for pancreatic neuroendocrine tumors | <p>A SNP in <i>FGFR4</i> could be used as a marker to predict pancreatic neuroendocrine tumor progression and response to mammalian target of rapamycin (mTOR; FRAP; RAFT1) inhibitors. In 71 patients with pancreatic neuroendocrine tumors, a polymorphism in <i>FGFR4</i> substituting an arginine for glycine at codon 388 was associated with larger, more aggressive and more invasive tumors. In mice with human pancreatic neuroendocrine tumors, the mTOR inhibitor Afinitor everolimus delayed growth and progression of tumors expressing <i>FGFR4</i> G388 but not tumors expressing <i>FGFR4</i> R388. Next steps could include developing an assay to screen patients for the <i>FGFR4</i> SNP.</p> <p>Novartis AG markets Afinitor to treat multiple cancers and to prevent transplant rejection.</p> <p>SciBX 5(40); doi:10.1038/scibx.2012.1068 Published online Oct. 11, 2012</p> | Patent and licensing status unavailable | <p>Serra, S. <i>et al. Cancer Res.</i>; published online Sept. 17, 2012; doi:10.1158/0008-5472.CAN-12-2102</p> <p>Contact: Sylvia L. Asa, University Health Network, Toronto, Ontario, Canada e-mail: sylvia.asa@uhn.ca</p> |

This week in techniques (continued)

| Approach | Summary | Licensing status | Publication and contact information |
|--|---|---|---|
| Mutations in <i>v-ski sarcoma viral oncogene homolog (SKI)</i> as the cause of Shprintzen-Goldberg syndrome (SGS) with aortic aneurysm | Genetic studies suggest mutations in <i>SKI</i> cause SGS with aortic aneurysm, a connective tissue disorder with unknown etiology. In 10 patients with SGS, whole-exome and Sanger sequencing identified mutations in <i>SKI</i> , which is a repressor of transforming growth factor- β (TGFB; TGF β) signaling. In zebrafish, morpholino-mediated knockdown of <i>SKI</i> paralogs recapitulated the SGS phenotype seen in humans. Next steps could include validating the results in a larger patient cohort and developing an assay to detect <i>SKI</i> mutations. SciBX 5(40); doi:10.1038/scibx.2012.1069 Published online Oct. 11, 2012 | Patent and licensing status unavailable | Doyle, A.J. <i>et al. Nat. Genet.</i> ; published online Sept. 30, 2012; doi:10.1038/ng.2421 Contact: Harry C. Dietz, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: hdietz@jhmi.edu |
| RNA profiling to determine prognosis in multiple sclerosis (MS) | Studies of patient samples identified a transcriptional signature that could help determine MS prognosis. Microarray data were generated for peripheral blood mononuclear cells (PBMCs) isolated from 363 patients with MS who were previously untreated or who had received interferon- β (IFNB; IFN- β) or Copaxone glatiramer acetate. Unsupervised computational clustering of the subgroup of 141 previously untreated patients identified 2 distinct gene expression signatures that were correlated with significantly different rates of disease activity (Cox proportional hazard ratio 0.6; $p=0.0077$). Next steps include performing transcriptional analysis of subsets of purified blood cells. Copaxone glatiramer acetate is marketed by Teva Pharmaceutical Industries Ltd. to treat MS. Biogen Idec Inc. markets Avonex interferon beta-1a, Bayer AG markets Betaseron interferon beta-1b and the Merck Serono S.A. division of Merck KGaA and Pfizer Inc. market Rebif interferon beta-1a to treat MS. SciBX 5(40); doi:10.1038/scibx.2012.1070 Published online Oct. 11, 2012 | Unpatented; licensing status not applicable | Ottoboni, L. <i>et al. Sci. Transl. Med.</i> ; published online Sept. 26, 2012; doi:10.1126/scitranslmed.3004186 Contact: Philip L. De Jager, Brigham and Women's Hospital, Boston, Mass. e-mail: pdejager@rics.bwh.harvard.edu |

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