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By Tracey Baas, Senior Editor

A European team has used the diabetes drug glibenclamide to block inflammation-induced neurodegeneration in mice.¹ The team plans to test the nonspecific inhibitor of the cationic channel TRPM4 in an investigator-led clinical trial in multiple sclerosis and is looking for pharmas to develop more specific antagonists of the target.

Transient receptor potential cation channel subfamily M member 4 (TRPM4) is a widely expressed Ca^{2+} -activated, voltage-dependent cation channel that depolarizes the plasma membrane by increasing sodium influx.

A group of German and Swiss researchers hypothesized that TRPM4 might be a key player in MS because disease-associated inflammation leads, in part, to elevated glutamate levels, which promote excitotoxic neurodegeneration by inducing Na^+ and Ca^{2+} influx.²

Indeed, the ion channels $\text{NaV}1.6$ (PN4; SCN8A), Na^+ - Ca^{2+} exchanger and acid-sensing ion channel-1 (ASIC1) are dysregulated in MS,³⁻⁵ but nothing was known about the role TRPM4 might play in the disease.

In *Trpm4* knockout mice with experimental autoimmune encephalomyelitis (EAE), compared with wild-type EAE mice, the team saw an overall decrease in disease severity—despite similar immune cell activation and infiltration.

Brain samples from both EAE wild-type mice and patients with MS showed that TRPM4 expression was greater within active demyelinating brain lesions than inactive lesions or tissue adjacent to active lesions.

The unanswered question was if—and how—*Trpm4* affected the way in which neurons responded to toxic insults.

In assays to monitor ion channel activity, wild-type murine hippocampal neurons showed higher current density and electrical capacitance than *Trpm4* knockout hippocampal neurons after receiving neurotoxic levels of glutamate. The lower levels of flowing current indicate that the *Trpm4*^{-/-} neurons are protected from the induction of excitotoxicity.

Further analysis of the wild-type neurons showed that the increase in electrical capacitance corresponded to swelling of the cell and a loss of cell integrity. Conversely, the *Trpm4* knockout neurons showed similar cell volumes and integrity in glutamate-treated and untreated conditions.

Axonal swellings occur in the brains of patients with MS⁶ and in the spinal cords of mice with EAE,^{7,8} suggesting TRPM4 may contribute to axonal injury and pathogenesis of MS.

To test the effects of pharmacological inhibition of the target, the team turned to glibenclamide, a generic sulfonylurea that blocks multiple ion channels, including TRPM4.⁹⁻¹¹

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In wild-type EAE mice, glibenclamide decreased axonal and neuronal degeneration and clinical disease scores compared with vehicle without affecting CNS immune responses. *In vitro* testing of wild-type mouse neurons showed that glibenclamide also inhibited glutamate-mediated cell swelling and excitotoxicity.

Results were published in *Nature Medicine*.

The team included researchers from the **University Medical Center Hamburg-Eppendorf, Geneva University Hospitals, the University of Geneva, Catholic University Leuven, Saarland University, the University of Goettingen and Heidelberg University.**

“No one had been paying attention to TRPM4 in MS, and targeting TRPM4 provides therapeutic benefit in a manner separate from the classical immune intervention that many groups are going after,” said Lawrence Steinman, professor of neurology and neurological sciences, pediatrics and genetics at **Stanford University School of Medicine.**

“I would like to see what happens when ion channel blockers to suppress axon and neuronal damage caused by glutamate-induced neurotoxicity are used in conjunction with immunomodulators,” added Steinman.

“I think focusing on a single drug with pleotropic effects is the best strategy” in MS, said Marc Simard, professor of neurosurgery, pathology and physiology at the **University of Maryland School of Medicine.** “Glibenclamide is such a drug.” Simard added that not only does glibenclamide block TRPM4 but also there is good evidence that it exerts anti-inflammatory effects, reducing neutrophil infiltration.

“I think the work opens new perspectives on the role of the ion channel in MS pathology, and I believe in the efficacy of glibenclamide,” added Pierre Launay, who pioneered the use of glibenclamide to target TRPM4 and is a research director at the **Institut National de la Santé et**

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de la Recherche Médicale (INSERM). “The team will have to be diligent in monitoring possible physiopathology in multiple organs since this channel has a broad regulatory effect.”

Into the clinic

“We want to start an investigator-led trial of glibenclamide in MS but will need to secure financing first,” said Manuel Friese, leader of the German/Swiss team and group leader of an Emmy Noether Research Group at the Center for Molecular Neurobiology Hamburg at the University Medical Center Hamburg-Eppendorf.

Glibenclamide is the second drug the group has repurposed for MS. In 2011, the team showed that the hypertension drug amiloride blocked ASIC1 and staved off inflammation-induced neurodegeneration.⁴

An investigator-led trial in patients with primary-progressive MS (PPMS) has further shown that amiloride may exert neuroprotective effects. The findings will be published in the near future in *Brain*.

“In PPMS patients, we observed a significant decrease in normalized annual rate of whole-brain volume during the treatment phase compared to the pretreatment phase,” said Lars Fugger, professor of clinical

neurosciences at **The Weatherall Institute of Molecular Medicine at University of Oxford**. “Consistent with this decrease, we showed that changes in diffusion indices of tissue damage within major, clinically relevant white matter and deep grey matter structures was also significantly decreased during the treatment phase.”

The researchers now are enrolling patients with MS who have optic neuritis in a Phase IIb trial of amiloride. The study is organized and coordinated by Fugger and Matt Craner, clinical lead of the MS Clinical Trials Unit at the **University of Oxford**.

“I think the work opens new perspectives on the role of the ion channel in MS pathology, and I believe in the efficacy of glibenclamide. The team will have to be diligent in monitoring possible physiopathology in multiple organs since this channel has a broad regulatory effect.”

—*Pierre Launay,*
Institut National de la Santé et de la Recherche Médicale

The German/Swiss team also is exploring the use of glibenclamide in other animal models of disease in which glutamate excitotoxicity is important for pathogenesis, such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and stroke. Friese declined to give further details.

A patent application has been filed by University Medical Center Hamburg-Eppendorf for the use of TRPM4 inhibitors to treat MS. The work is not licensed, but the university is looking for pharmaceutical companies to develop specific inhibitors for TRPM4.

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REFERENCES

- Schattling, B. *et al. Nat. Med.*; published online Nov. 18, 2012; doi:10.1038/nm.3015
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- Lau, A. & Tymianski, M. *Pflugers Arch.* **460**, 525–542 (2010)
- Craner, M.J. *et al. Proc. Natl. Acad. Sci. USA* **101**, 8168–8173 (2004)
- Friese, M.A. *et al. Nat. Med.* **13**, 1483–1489 (2007)
- Vergo, S. *et al. Brain* **134**, 571–584 (2011)
- Fisher, E. *et al. Ann. Neurol.* **62**, 219–228 (2007)
- Nikić, I. *et al. Nat. Med.* **17**, 495–499 (2011)
- Stirling, D.P. & Stys, P.K. *Trends Mol. Med.* **16**, 160–170 (2010)
- Demion, M. *et al. Cardiovasc. Res.* **73**, 531–538 (2007)
- Becerra, A. *et al. Cardiovasc. Res.* **91**, 677–684 (2011)
- Chen, M. *et al. J. Neurosci.* **23**, 8568–8577 (2003)

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Genomics in the Big Apple

By *Tim Fulmer, Senior Writer*

The **New York Genome Center** launched its translational research unit last week with the appointment of Robert Darnell as president and scientific director of the center. With the sequencing service side of the center already up and running, Darnell will oversee the development of specific internal research projects as well as the hiring of researchers to fill out the unit.

Late last year, 11 New York City–area medical centers along with industry partners **Roche** and **Illumina Inc.** launched the New York Genome Center (NYGC) as a large-scale genome-sequencing facility for translational research.

The basic mission of NYGC is to offer next-generation genome sequencing, bioinformatics services and data storage to researchers worldwide and to set up an in-house translational research center staffed by researchers drawn from local universities and medical institutions.

Darnell will remain professor of cancer biology at **The Rockefeller University**, one of the founding institutions of NYGC. The other founding institutions include **Cold Spring Harbor Laboratory**, **Columbia University**, **Cornell University**, the **Memorial Sloan-Kettering Cancer Center**, the **Mount Sinai Medical Center**, **New York–Presbyterian Hospital**, **New York University**, the **North Shore–LIJ Health System**, **The Jackson Laboratory** and the **State University of New York at Stony Brook**. The in-house research center will be located in a permanent facility now being built in Manhattan.

Darnell's research is focused on paraneoplastic neurological disorders (PNDs), which arise when a cancer patient's antitumor response triggers an autoimmune attack on healthy neurological tissue. The protein antigens shared by the tumor and healthy neurons bind and regulate RNA. He has developed methods to generate a genomewide picture of RNA expression and regulation.

Darnell said joining NYGC will allow him and other researchers “to overcome the rate-limiting step of handling and making sense of massive genomics data sets collected across many labs and patient groups.”

He added, “NYGC exists to break down traditional research silos. It will bring together clinicians, genomics researchers, computational modelers and mathematicians under one roof, allowing them to pool, analyze, mine and interpret genomics data in new ways.”

“NYGC exists to break down traditional research silos. It will bring together clinicians, genomics researchers, computational modelers and mathematicians under one roof, allowing them to pool, analyze, mine and interpret genomics data in new ways.”

—*Robert Darnell,
New York Genome Center*

NYGC plans to hire at least six principal investigators in the next five years, Executive Director Nancy Kelley told *SciBX*.

A key goal of the center's research will be to generate new IP covering therapeutics and diagnostics that are made available for licensing, said Kelley. She declined to provide additional details.

“We are recruiting scientists in the general areas of genomics research, clinical biology, bioinformatics and computational biology,” Darnell said. “We anticipate having a mix of established and junior researchers on our staff, and researchers will be given the option of maintaining a joint appointment with NYGC and their home academic institution.”

Over the next few months, NYGC will make announcements regarding specific research projects to be carried out in the center. “Cancer, neurological diseases and immunology will be three areas of focus,” said Darnell. He declined to provide additional details.

NYGC is part of a larger push to make the greater New York City area into a biopharma research hub.

Earlier this year, Laurie Glimcher told *SciBX*, “New York City has the potential to be a major player in this area.”¹ At that time, Glimcher had just been hired as dean of **Weill Cornell Medical College**. Prior to that, she was a professor at **Harvard Medical School**.

Weill Cornell, Rockefeller University and Memorial Sloan-Kettering have a tri-institutional alliance and over the past 3 years have together founded 14 biopharma

companies. More than half of those are based in New York City.¹

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REFERENCES

1. Kotz, J. *SciBX* 5(2); doi:10.1038/scibx.2012.31

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Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
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Thinking outside the amyloid box

By Lev Osherovich, Senior Writer

Two European groups have proposed strategies for treating Alzheimer's disease that are focused on hitting intermediate protein fragments and enzymatic steps in the pathway that produces β -amyloid.^{1,2} A team at **Institut National de la Santé et de la Recherche Médicale** and the **University of Nice Sophia Antipolis** thinks the goal should be reducing levels of C99, a protein fragment that is a precursor of β -amyloid. A team at **Catholic University Leuven** expects that hitting a newly identified cofactor of γ -secretase can yield the same effect as eliminating C99 and β -amyloid while potentially acting more selectively on the β -amyloid pathway than γ -secretase inhibitors.

AD is thought to be driven by the accumulation of β -amyloid ($A\beta$), a toxic fragment of amyloid precursor protein (APP). Thus, blocking $A\beta$ production has been a prime approach to treating AD.

Toward this goal, academic and industry researchers have spent decades working out the enzymatic steps that lead to the conversion of APP into $A\beta$ ³ (see Figure 1, "APP processing in AD"). In the two most critical steps of the pathway, full-length APP is first cut by β -site APP-cleaving enzyme 1 (BACE1) to yield the C99 fragment, which is then cut a second time by γ -secretase, a multisubunit proteolytic complex, to yield $A\beta$.

Initially, researchers deemed γ -secretase the most therapeutically tractable target in this pathway. However, safety problems cratered multiple clinical trials of first-generation γ -secretase compounds. mAbs that directly hit $A\beta$, such as **Johnson & Johnson** and **Pfizer Inc.**'s bapineuzumab and **Eli Lilly and Co.**'s solanezumab, avoided the safety issues associated with blocking γ -secretase but nonetheless failed in Phase III trials for lack of efficacy.

Now, a team at the University of Nice Sophia Antipolis branch of Institut National de la Santé et de la Recherche Médicale (INSERM) has mouse data showing that accumulation of C99, which previous work has suggested could play a role in AD disease progression, is actually made worse by γ -secretase inhibitors.

The INSERM team's findings help build a case for treating AD by preventing C99 accumulation rather than focusing exclusively on $A\beta$.

Meanwhile, a group at Catholic University Leuven thinks hitting a specific subunit of γ -secretase could reduce levels of both APP fragments. The team found that γ -secretase converts C99 into $A\beta$ through an intracellular cofactor, arrestin $\beta 2$ (ARRB2), and a cell surface protein called G protein-coupled receptor 3 (GPR3), and they found that blocking the GPR3-ARRB2 pathway alters the activity of γ -secretase in a way that lowers levels of both C99 and $A\beta$.

C99 problems

Previous work by other researchers showed that C99 overexpression was highly toxic to cultured neurons, suggesting the APP cleavage intermediate could contribute to AD pathology independently of $A\beta$.⁴

The INSERM team, led by Research Director Frédéric Checler, used an antibody that detects C99 to show that the protein fragment accumulated inside the hippocampal neurons of aging mice. The buildup occurred prior to the accumulation of extracellular $A\beta$ deposits, which are a hallmark of AD pathology.

C99 accumulation also occurred in a different mouse model of AD in which there was relatively little extracellular $A\beta$. Thus, Checler thinks the accumulation of intracellular C99 is an early marker of AD pathology.

"We have found a new phenotype in these mice that is linked with what is seen in AD patients. C99 is present in older mice and correlates with the onset of symptoms" more closely than $A\beta$ deposits, said Checler.

The team then showed that ELND006, a discontinued γ -secretase inhibitor from **Elan Corp. plc**, increased levels of C99 compared with vehicle. Checler thinks this finding could help explain why two other discontinued γ -secretase inhibitors, Lilly's semagacestat and **Bristol-Myers Squibb Co.**'s avagacestat, appeared to worsen rather than relieve AD symptoms in respective Phase III and Phase II trials.⁵

The findings were published in *The Journal of Neuroscience*.

Bart De Strooper, professor of human genetics at Catholic University Leuven, said Checler's study "does a very careful analysis of the transgenic mice, showing that C99 is accumulating at a very early stage."

De Strooper, who discovered γ -secretase, said the findings provide potential explanations for "the problems with broad-spectrum γ -secretase inhibitors, since one of the consequences of these compounds is the accumulation of C99."

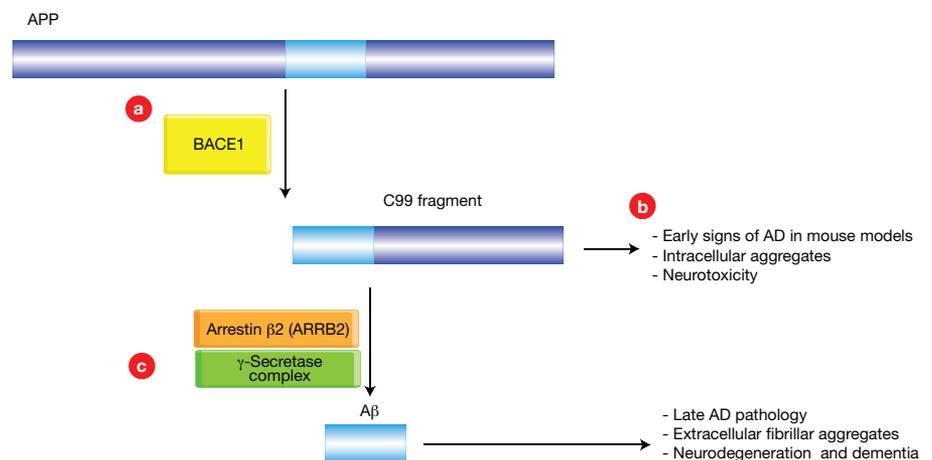


Figure 1. APP processing in AD. In early Alzheimer's disease pathogenesis, amyloid precursor protein (APP) is processed by a series of proteases to yield several neurotoxic protein fragments. First, APP is cut by β -site APP-cleaving enzyme 1 (BACE1) [a] to yield a fragment called C99 [b], which is subsequently cut by the γ -secretase complex [c] to yield β -amyloid ($A\beta$).

Lauritzen *et al.* have provided *in vivo* evidence in a mouse model of AD that suggests intracellular C99 accumulation contributes to early AD pathology. Thathiah *et al.* have shown that arrestin $\beta 2$ (ARRB2) acts as a γ -secretase cofactor that specifically regulates the processing of C99.

Human touch

The big question is whether C99 plays a role in human disease, but answering this is technically challenging.

Because Checler's anti-C99 mAbs are immunohistochemical probes that cannot be used *in vivo*, it is not possible to use them to scan the brains of early stage AD patients for C99 accumulation.

An alternative approach is to pharmacologically block production of C99 with BACE1 inhibitors. But such compounds would also prevent A β production, making it difficult to unravel which aspects of AD arise from intracellular C99 vs. extracellular A β .

"The best way to investigate this in patients is to try to detect C99 postmortem, but at best this would be correlative," said De Strooper.

Virginia Lee, director of the Center for Neurodegenerative Disease Research and professor of pathology and laboratory medicine at the **Perelman School of Medicine at the University of Pennsylvania**, wanted

to see more evidence of C99 accumulation in human tissue. She cautioned that Checler's studies were done in mice that overexpress APP. At more physiological levels of APP expression, she said the conversion of APP into C99 and then A β may work differently.

"We don't yet know the biological significance of C99 accumulation," said Lee. "In models

that overexpress APP, C99 may be important, but you don't know what it's like in wild-type animals and humans."

To resolve this question, Lee recommended developing selective anti-C99 mAbs and using them in additional immunohistochemistry studies in a variety of mouse models of AD and in human tissue.

Checler said he is collaborating with an undisclosed company to identify and characterize next-generation antibodies against C99.

Gamma world

Meanwhile, De Strooper's team is identifying proteins that interact with γ -secretase and could be targeted with safer compounds than the failed broad-spectrum inhibitors.

In 2009, De Strooper and researchers at **Galapagos N.V.** reported that an orphan GPCR called GPR3 plays an essential role in γ -secretase activity.⁶

Now, De Strooper has found that ARRB2 is required for GPR3's effects on γ -secretase.

In cell culture, mutations in GPR3 disrupted the receptor's ability to bind ARRB2 and also prevented γ -secretase from converting C99 into A β . The finding suggests ARRB2 transmits a signal from GPR3 to γ -secretase that governs the enzyme's activity.

Indeed, overexpression of ARRB2 increased production of A β and small interfering RNA knockdown of ARRB2 decreased A β levels compared with what was seen using vector controls.

Arrb2 knockout mice with AD had lower γ -secretase activity and A β levels than wild-type controls. Finally, the brains of patients with AD had higher levels of ARRB2 than brains from age-matched healthy controls.

Altogether, the findings suggest ARRB2 facilitates γ -secretase activity on C99 by coupling the enzyme to GPR3 at the cell surface.

De Strooper's team also found that knocking down ARRB2 in cell culture lowered both C99 and A β levels, suggesting that blocking the GPR3-ARRB2 pathway works differently than inhibiting γ -secretase outright, which Checler's team found to prevent A β production at the cost of increasing C99 levels. Although the exact mechanistic details are not known, decreasing ARRB2 levels led to increased proteasomal degradation of C99.

Moreover, knocking down ARRB2 did not interfere with γ -secretase's ability to cleave other substrates besides C99, suggesting that ARRB2 is a fairly AD-specific target.

Results were published in *Nature Medicine*.

De Strooper thinks the findings will help focus screening efforts for GPR3-binding compounds that specifically antagonize ARRB2 activity. De Strooper said a prior collaboration with Galapagos to identify such compounds has ended, and he is now working with a different, undisclosed company. A spokesperson for Galapagos said that the company retains patents and a discovery-stage screening program targeting GPR3 in AD.

De Strooper said that although γ -secretase inhibitors have failed in the clinic, his findings are proof of principle that modulating γ -secretase activity can reduce both C99 and A β levels without compromising the enzyme's other functions.

"There is a way to affect γ -secretase activity without causing C99 accumulation," said De Strooper. "The message is that we shouldn't give up on γ -secretase."

The results from Checler's team are not patented. De Strooper has filed a patent on modulating ARRB2 to treat AD. That patent is not available for licensing.

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REFERENCES

- Lauritzen, I. *et al. J. Neurosci.*; published online Nov. 14, 2012; doi:10.1523/JNEUROSCI.2775-12.2012
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- Jin, L.-W. *et al. J. Mol. Neurosci.* 19, 57–61 (2002)
- Osherovich, L. *BioCentury* 19(44), A8; Oct. 24, 2011
- Thathiah, A. *et al. Science* 323, 946–951 (2009)

COMPANIES AND INSTITUTIONS MENTIONED

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"There is a way to affect γ -secretase activity without causing C99 accumulation. The message is that we shouldn't give up on γ -secretase."

—Bart De Strooper,
Catholic University Leuven

Micromanaging tolerance

By Kai-Jye Lou, Staff Writer

Researchers at **Northwestern University** and the **Myelin Repair Foundation** have simplified an autologous cell-based strategy for promoting antigen-specific tolerance by replacing splenic leukocytes with synthetic microparticles as the antigen carrier.¹ The groups are planning to first develop the therapy and establish clinical proof of concept in autoimmune indications for which the key antigen is known before moving forward in multiple sclerosis.

Apoptotic splenic leukocytes coupled to peptide antigens induce antigen-specific immune tolerance in T cell-mediated autoimmune diseases such as MS.²⁻⁴ Indeed, in a Phase I trial in patients with new-onset relapsing-remitting MS (RRMS), researchers showed that infusion of such cells induced tolerance against the coupled myelin peptide antigens and did not cause significant adverse effects.

The trial was sponsored by the Myelin Repair Foundation (MRF) and the German government.

Despite the positive initial results, the MRF and Northwestern researchers wanted to simplify the approach and make it more amenable for commercialization as an off-the-shelf therapy. The cell therapy involves isolating patient leukocytes via leukapheresis, coupling the cells to peptide autoantigens via ethylene carbodiimide chemistry, rendering the cells apoptotic and then infusing the cells back into the patient.

“In the clinical trial, we found that we could infuse patients with up to three billion such cells without causing significant adverse effects and promote tolerance toward multiple myelin-associated antigens,” said Stephen Miller, a professor and director of the Interdepartmental Immunobiology Center at Northwestern. “However, producing these cells is a very complex and expensive process.”

Thus, the team sought to develop an alternative synthetic vehicle that could mimic the antigen-carrying role of the apoptotic splenic leukocytes and promote tolerance without the complexities associated with autologous cell therapies. The group settled on inert, negatively-charged carboxylated microparticles.

“We have shown that nanoparticles with certain surface properties can be anti-inflammatory but, more importantly, also home to the same place in the spleen as the dying, peptide-coupled cells,” said Daniel Getts, a visiting research professor at Northwestern. “As such, we figured that we could use inert nanoparticles that the body potentially perceives as dying cells to deliver antigens and induce tolerance.”

As proof of concept, the researchers used ethylene carbodiimide chemistry to attach an encephalitis-inducing peptide antigen to negatively charged poly(lactide-co-glycolide) (PLG) microparticles.

In a mouse model of experimental autoimmune encephalomyelitis (EAE), a single i.v. infusion of the peptide-linked microparticles induced tolerance to the attached peptide antigen and decreased symptom severity compared with infusion of microparticles linked to a control peptide.

The tolerogenic effects persisted for the duration of the mouse studies and depended on a scavenger receptor called macrophage

receptor with collagenous structure (MARCO; SCARA2). The peptide-linked microparticles had no effect in mice lacking the receptor.

The peptide-linked microparticles work by homing to the splenic marginal zone, where they are taken up by MARCO-expressing macrophages. This in turn leads to a long-term T cell-mediated tolerogenic response specific to the peptide antigen.

Results were published in *Nature Biotechnology*. Getts is a colead author on the paper and Miller is a co-corresponding author.

“These inert microparticles could be formulated for use in a specific indication and then stored in a bottle on a shelf,” said Jay Tung, chief research officer at MRF. “The microparticles are also easier to manufacture and characterize than a cell therapy and would thus have a more straightforward route for seeking FDA approval.”

He added that the preclinical data have been independently validated by a CRO.

Miller said his group and the MRF are moving forward with the PLG microparticles. PLG is a biodegradable, FDA-approved polymer that is used in medical sutures and is amenable to GMP manufacturing in large quantities. Moreover, PLG also is immunologically inert, so the particles themselves should not trigger or exacerbate an immune response.

“These peptide-linked microparticles appear to have a robust therapeutic effect in the preclinical models, and the tolerogenic response appears to be antigen specific, which is a good thing,” said Howard Weiner, director of the Partners Multiple Sclerosis Center and co-director of the Center for Neurologic Diseases at **Brigham and Women’s Hospital**. “None of the currently marketed drugs for multiple sclerosis works in an antigen-specific manner.”

Weiner also said the persistent tolerogenic effect seen in the mouse models suggests the microparticles would not need to be dosed chronically.

Lawrence Steinman, professor of neurology and neurological sciences, pediatrics and genetics at the Beckman Center for Molecular and Genetic Medicine at the **Stanford University School of Medicine**, said immunomodulatory drugs for MS work by depleting T cells and/or B cells and that chronic treatment with these immune cell-depleting therapies can have significant side effects, such as increased risk of infection.

He noted that antigen-specific strategies have the potential to trigger or exacerbate an autoimmune response and that future studies will need to monitor for such effects.

Antigen ambiguity

MRF and Northwestern now want to establish clinical proof of concept for the microparticle therapy in another autoimmune-related indication before attempting to develop it in MS.

“These inert microparticles could be formulated for use in a specific indication and then stored in a bottle on a shelf. The microparticles are also easier to manufacture and characterize than a cell therapy and would thus have a more straightforward route for seeking FDA approval.”

— Jay Tung,
Myelin Repair Foundation

Steinman said it all comes down to picking the relevant antigens.

“Diseases such as relapsing-remitting MS and secondary MS are going to be problematic because we still don’t have a clear idea as to what the causal antigens are,” he told *SciBX*. “Instead, I think that one should first try to develop these microparticles in autoimmune diseases where the causal antigens are known and no effective treatments are available. This is where the probability of success is going to be the highest.”

He cited diseases such as neuromyelitis optica and myasthenia gravis. The former is caused by an autoimmune response against aquaporin 4 (AQP4) and the latter by an autoimmune response against nicotinic acetylcholine receptors (nAChRs).

Getts and Miller agreed that it may be easier to first develop the microparticles in an indication other than MS.

“What we don’t want to have happen in clinical trials is to find out that the microparticles are ineffective because we didn’t target the correct antigens,” said Miller. “We want to first select a disease indication where we know the exact antigen to target.”

Miller’s group is also trying to show preclinical proof of principle in additional immune-mediated conditions, including type 1 diabetes, allergic airway disease and transplant rejection. He also said that the microparticles could be used as an adjunct to prevent an immune response against recombinant protein therapies for hemophilia.

Other possibilities, added Getts, include celiac disease and peanut allergy. “These are conditions where we have a reasonable handle on the precise antigens involved and can target them with great accuracy,” he told *SciBX*.

Tung said MRF is in discussions to partner or out-license the technology for various indications. He said the foundation does plan to develop the microparticles for MS but acknowledged that it will be

difficult to move forward in the indication until the manufacturing and analytical components of the therapy are better understood.

“MS is our primary mission, but it makes more sense to first demonstrate that the technology works in humans in a simpler system before tackling a problem as complex as MS,” said Tung. “The beauty of this technology is that techniques that work out in simpler therapeutic areas will be applicable to MS.”

MRF also plans to run additional studies to further characterize the microparticles and optimize their properties. He said the plan is to carry out such studies with an industry partner.

Tung said the microparticle technology is at least three years from an IND submission.

Northwestern and the MRF have pending patents covering the microparticles and their use for induction of antigen-specific tolerance. MRF has exclusive rights to license this technology in all therapeutic areas.

Lou, K.-J. *SciBX* 5(47); doi:10.1038/scibx.2012.1226

Published online Dec. 6, 2012

REFERENCES

1. Getts, D.R. *et al. Nat. Biotechnol.*; published online Nov. 18, 2012; doi:10.1038/nbt.2434
Contact: Stephen D. Miller, Northwestern University, Evanston, Illinois
e-mail: s-d-miller@northwestern.edu
2. Vanderlugt, C.L. *et al. J. Immunol.* **164**, 670–678 (2000)
3. Turley, D.M. & Miller, S.D. *J. Immunol.* **178**, 2212–2220 (2007)
4. Getts, D.R. *et al. J. Immunol.* **187**, 2405–2417 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

Brigham and Women’s Hospital, Boston, Mass.

Myelin Repair Foundation, Saratoga, Calif.

Northwestern University, Chicago, Ill.

Stanford University School of Medicine, Stanford, Calif.

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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				
Multiple sclerosis (MS)	Prostate-specific membrane antigen (PSMA; FOLH1; GCPII)	Human and mouse studies suggest inhibiting GCPII could help treat cognitive impairments associated with MS. In newly diagnosed patients with relapsing-remitting MS, magnetic resonance spectroscopy of brains showed that low levels of N-acetylaspartylglutamate (NAAG) correlated with cognitive dysfunction. In mice with experimental autoimmune encephalomyelitis (EAE), increasing levels of NAAG with a GCPII inhibitor did not affect physical disease symptoms but increased cognitive functions, including memory and learning, compared with vehicle control. Next steps include identifying new GCPII inhibitors or delivery vehicles.	Patent application filed; available for licensing	Rahn, K.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 19, 2012; doi:10.1073/pnas.1209934109 Contact: Adam I. Kaplin, The Johns Hopkins University, Baltimore, Md. e-mail: akaplin@jhmi.edu Contact: Barbara S. Slusher, same affiliation as above e-mail: bslusher@jhmi.edu
SciBX 5(47); doi:10.1038/scibx.2012.1227 Published online Dec. 6, 2012				
Multiple sclerosis (MS)	Transient receptor potential cation channel subfamily M member 4 (TRPM4)	Patient sample and mouse studies suggest inhibiting TRPM4 could help treat MS. In mice with experimental autoimmune encephalomyelitis (EAE), <i>Trpm4</i> knockout or <i>Trpm4</i> inhibition with glibenclamide decreased overall disease severity but led to similar immune cell activation and infiltration compared with normal <i>Trpm4</i> expression or no inhibition. In brain samples from EAE mice and patients with MS, TRPM4 expression was greater within active demyelinating brain lesions than inactive lesions or tissue adjacent to active lesions. Next steps include further developing inhibitors of TRPM4. Glibenclamide is a generic sulfonylurea approved to treat type 2 diabetes (<i>see A current affair in MS, page 1</i>).	Patent application filed; unlicensed	Schattling, B. <i>et al. Nat. Med.</i> ; published online Nov. 18, 2012; doi:10.1038/nm.3015 Contact: Manuel A. Friese, University Medical Center Hamburg-Eppendorf, Hamburg, Germany e-mail: manuel.friese@zmh.uni-hamburg.de
SciBX 5(47); doi:10.1038/scibx.2012.1228 Published online Dec. 6, 2012				
Cancer				
Breast cancer	Not applicable	An <i>in vitro</i> study identified a small molecule inhibitor of breast cancer stem cell growth that could help treat the disease. A high throughput screen of about 300,000 small molecules was conducted in a cellular model of breast cancer stem cells (CSCs) in which <i>E-cadherin</i> (<i>CDH1</i> ; <i>CD324</i>) was knocked down in human mammary epithelial cells to induce an epithelial-to-mesenchymal transition. Screening and optimization identified a lead compound, ML239, which inhibited two distinct breast CSC-like cell lines with IC_{50} values of 0.1 μ M and 1.2 μ M. Ongoing work has identified two additional classes of small molecules that inhibit breast CSC proliferation, and next steps include further characterizing the mechanism of action of these molecules.	Patent application filed; licensed to Verastem Inc.	Carmody, L.C. <i>et al. J. Biomol. Screen.</i> ; published online Aug. 30, 2012; doi:10.1177/1087057112458317 Contact: Leigh C. Carmody, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: lcarmody@broadinstitute.org
SciBX 5(47); doi:10.1038/scibx.2012.1229 Published online Dec. 6, 2012				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Glycogen liver phosphorylase (PYGL)	<p>A study in mice suggests inhibiting PYGL could help treat hypoxic tumors. In human glioblastoma, breast and colon cancer cell lines, hypoxia increased expression of <i>PYGL</i> compared with no hypoxia. In a xenograft mouse model of human glioblastoma, the antiangiogenic drug Avastin bevacizumab led to hypoxia and increased expression of glycogen metabolism genes compared with saline. In the same model, glioblastoma cells with stable knockdown of <i>PYGL</i> led to tumors that were about 10% as large as tumors in mice with glioblastoma cells expressing <i>PYGL</i>. Next steps include testing the effects of knocking down <i>PYGL</i> in combination with antiangiogenic therapies in mouse models of cancer.</p> <p>Avastin is marketed by Roche's Genentech Inc. unit to treat brain and breast cancer.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1230 Published online Dec. 6, 2012</p>	Unpatented; licensing status not applicable	<p>Favaro, E. <i>et al. Cell Metab.</i>; published online Nov. 21, 2012; doi:10.1016/j.cmet.2012.10.017 Contact: Adrian L. Harris, University of Oxford, Oxford, U.K. e-mail: adrian.harris@oncology.ox.ac.uk</p>
Cancer	Histone deacetylase 8 (HDAC8)	<p><i>In vitro</i> studies identified an HDAC8-selective inhibitor that could help treat cancer. <i>In vitro</i> screening identified a hydroxamate-based molecule that inhibited HDAC8 with an IC_{50} of 70 nM and showed selectivity over other HDAC isoforms. In a panel of human T cell lymphoma and neuroblastoma cell lines, the inhibitor blocked proliferation at low- to mid-micromolar concentrations. Next steps include testing the HDAC8-selective inhibitors in mouse xenograft models of cancer.</p> <p>Pharmacyclics Inc. has the HDAC8 inhibitor PCI-34051 in preclinical development for various cancers. TeraDiscoveries Inc. has the HDAC8 inhibitor TA-H8 in preclinical development for T cell lymphoma.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1231 Published online Dec. 6, 2012</p>	Patent application filed; available for licensing	<p>Suzuki, T. <i>et al. J. Med. Chem.</i>; published online Nov. 1, 2012; doi:10.1021/jm300837y Contact: Naoki Miyata, Nagoya City University, Aichi, Japan e-mail: miyata-n@phar.nagoya-cu.ac.jp Contact: Takayoshi Suzuki, Kyoto Prefectural University of Medicine, Kyoto, Japan e-mail: suzukit@koto.kpu-m.ac.jp</p>
Cancer	Protein kinase B (PKB; PKBA; AKT; AKT1)	<p><i>In vitro</i> studies suggest identifying the type of AKT1 mutations in patients with cancer could help guide treatment decisions. In a mouse lymphoid cell line, expression of Akt1 with mutations in the pleckstrin homology (PH)-kinase domain (KD) led to constitutive Akt1 activation, whereas expression of wild-type Akt1 did not. <i>In vitro</i>, allosteric AKT1 inhibitors showed lower efficacy for AKT1 with PH-KD mutations than for wild-type AKT1 or AKT1 with other activating mutations. In the same assay, ATP-site inhibitors were effective at blocking AKT1 with PH-KD mutations. Next steps could include determining how various mutations in AKT1 affect tumor responsiveness to various AKT1 inhibitors.</p> <p>At least 11 companies have AKT1 inhibitors in clinical and preclinical development to treat cancer.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1232 Published online Dec. 6, 2012</p>	Patent and licensing status undisclosed	<p>Parikh, C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 7, 2012; doi:10.1073/pnas.1204384109 Contact: Somasekar Seshagiri, Genentech Inc., South San Francisco, Calif. e-mail: sekar@gene.com</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Non-small cell lung cancer (NSCLC)	Transforming growth factor- β receptor II (TGF β -RII; TGFBR2); mediator complex subunit 12 (MED12)	<i>In vitro</i> studies suggest inhibiting TGFBR2 could help prevent resistance to targeted therapies in lung cancer. In NSCLC cells with activating mutations in <i>anaplastic lymphoma kinase (ALK)</i> or <i>epidermal growth factor receptor (EGFR)</i> , knockdown of MED12, a transcriptional complex component mutated in some cancers, caused resistance to ALK and EGFR inhibitors and upregulated TGFBR2. In the <i>MED12</i> ^{-/-} NSCLC cells, a TGFBR2 inhibitor plus ALK or EGFR inhibitors sensitized the cells to therapy and synergistically inhibited cell growth. Next steps could include testing TGFBR2 inhibitors in animal models. SciBX 5(47); doi:10.1038/scibx.2012.1233 Published online Dec. 6, 2012	Patent and licensing status unavailable	Huang, S. <i>et al. Cell</i> ; published online Nov. 21, 2012; doi:10.1016/j.cell.2012.10.035 Contact: René Bernards, The Netherlands Cancer Institute, Amsterdam, the Netherlands e-mail: r.bernards@nki.nl
Cardiovascular disease				
Hyperlipidemia	Angiopoietin-like 8 (ANGPTL8); ANGPTL3	<i>In vitro</i> and mouse studies suggest inhibiting activation of ANGPTL8 or ANGPTL3 could help treat hyperlipidemia. Cleavage of ANGPTL3 activates the protein and is necessary for ANGPTL3-mediated inhibition of lipases, which break down lipids. In cultured hepatocytes, coexpression of ANGPTL3 and ANGPTL8 led to cleavage of ANGPTL3, whereas expression of ANGPTL3 alone did not. In mice with liver-specific overexpression of Angptl8, knocking out <i>Angptl3</i> led to lower hyperlipidemia than that in wild-type controls. Next steps could include identifying ANGPTL8 inhibitors. SciBX 5(47); doi:10.1038/scibx.2012.1234 Published online Dec. 6, 2012	Patent and licensing status unavailable	Quagliarini, F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 12, 2012; doi:10.1073/pnas.1217552109 Contact: Helen H. Hobbs, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: helen.hobbs@utsouthwestern.edu Contact: Jonathan C. Cohen, same affiliation as above e-mail: jonathan.cohen@utsouthwestern.edu
Gastrointestinal disease				
Pancreatitis	Calcineurin	<i>In vitro</i> and mouse studies suggest inhibiting calcineurin could help treat biliary pancreatitis. Biliary pancreatitis is caused by biliary acid reflux that increases Ca ²⁺ in pancreatic cells. In primary mouse pancreatic acinar cells, bile acid-induced Ca ²⁺ upregulation caused calcineurin activation and cell injury. The process was prevented by Ca ²⁺ chelation or calcineurin inhibition. In a mouse model of bile acid-induced pancreatitis, inhibition of calcineurin decreased disease severity compared with no inhibition. Next steps could include testing calcineurin inhibition in additional animal models. Isotechnika Pharma Inc., 3SBio Inc. and Paladin Labs Inc. have the calcineurin inhibitor Voclera voclosporin in clinical and preclinical testing for indications including lupus, psoriasis and renal transplant rejection. SciBX 5(47); doi:10.1038/scibx.2012.1235 Published online Dec. 6, 2012	Patent and licensing status unavailable	Muili, K.A. <i>et al. J. Biol. Chem.</i> ; published online Nov. 12, 2012; doi:10.1074/jbc.M112.428896 Contact: Sohail Z. Husain, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa. e-mail: sohail.husain@chp.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Hematology				
Neutropenia	Dipeptidyl peptidase-4 (DPP-4)	<p>Mouse studies suggest blocking DPP-4 could help prevent neutropenia during chemotherapy or radiation therapy. In mice receiving chemotherapy or radiotherapy, animals lacking <i>Dpp-4</i> had greater hematopoietic progenitor cell (HPC) recovery than wild-type mice. In wild-type mice receiving radiation or chemotherapy, pretreatment with the DPP-4 inhibitor Januvia sitagliptin led to increased HPC and hematopoietic stem cell (HSC) recovery in bone marrow compared with vehicle pretreatment. Ongoing work includes identifying the best timing and dosing of Januvia or other DPP-4 inhibitors to enhance recovery of neutrophils and platelets after radiation, chemotherapy or stem cell transplantation.</p> <p>Merck & Co. Inc. and Ono Pharmaceutical Co. Ltd. market Januvia to treat type 2 diabetes.</p> <p>At least five other DPP-4 inhibitors are approved to treat type 2 diabetes.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1236 Published online Dec. 6, 2012</p>	Patent pending; unlicensed	<p>Broxmeyer, H.E. <i>et al. Nat. Med.</i>; published online Nov. 18, 2012; doi:10.1038/nm.2991</p> <p>Contact: Hal E. Broxmeyer, Indiana University School of Medicine, Indianapolis, Ind. e-mail: hbroxmey@iupui.edu</p>
Infectious disease				
SARS-associated coronavirus	Not applicable	<p>Mouse studies suggest a mutant form of SARS-associated coronavirus could be used to vaccinate against the infection. In mice, infection with a mouse-adapted SARS-associated coronavirus carrying an inactivating mutation in an exonuclease generated viral titers in the lung without causing disease symptoms. In mice, vaccination with the mutant virus led to complete protection against infection with a virulent strain, whereas all saline-vaccinated mice died within three days of infection. Next steps could include testing the vaccine strategy in nonhuman primates.</p> <p>At least four companies have SARS-associated coronavirus vaccines and therapeutics in preclinical testing.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1237 Published online Dec. 6, 2012</p>	Patent and licensing status unavailable	<p>Graham, R.L. <i>et al. Nat. Med.</i>; published online Nov. 11, 2012; doi:10.1038/nm.2972</p> <p>Contact: Ralph S. Baric, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: rbaric@email.unc.edu</p>
Inflammation				
Asthma	Tumor necrosis factor- α -induced protein 6 (TNFAIP6; TSG6)	<p>Mouse studies suggest TSG6 inhibition could help treat asthma. In a mouse model of acute allergic pulmonary inflammation, knocking out <i>Tsg6</i> led to less pulmonary inflammation and lower airway hyperresponsiveness than what was seen in wild-type controls. <i>Tsg6</i> knockout mice had lower levels of inflammation-associated hyaluronan and eosinophils in bronchoalveolar fluid than wild-type controls. Next steps could include examining the role of TSG6 in inflammation-associated pathways.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1238 Published online Dec. 6, 2012</p>	Patent and licensing status unavailable	<p>Swaidani, S. <i>et al. J. Biol. Chem.</i>; published online Nov. 1, 2012; doi:10.1074/jbc.M112.389874</p> <p>Contact: Mark A. Aronica, Cleveland Clinic, Cleveland, Ohio e-mail: aronicm@ccf.org</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Neurology				
Autism	Eukaryotic translation initiation factor 4E (eIF4E); eIF4E binding protein 2 (eIF4EBP2)	<p>Mouse studies suggest inhibition of eIF4E signaling could help treat autism spectrum disorder (ASD). In mice, knocking out <i>eif4ebp2</i> led to electrophysiological abnormalities and autistic behaviors. In those autistic mice, a small molecule inhibitor of eIF4E signaling reversed the electrophysiological abnormalities and decreased autistic behaviors compared with vehicle. Next steps include developing mouse models with brain region-specific or conditional knockout of <i>eif4ebp2</i>.</p> <p>Isis Pharmaceuticals Inc.'s eIF-4E ASO, a second-generation antisense compound targeting eIF4E, is in Phase II testing to treat prostate cancer and non-small cell lung cancer (NSCLC).</p> <p>Clavis Pharma ASA and Translational Therapeutics Inc. have TRX-201, a Lipid Vector Technology (LVT) derivative of ribavirin that inhibits eIF4E, in preclinical development to treat thyroid cancer.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1239 Published online Dec. 6, 2012</p>	<i>Eif4ebp2</i> knockout mouse model unpatented; available for licensing	Gkogkas, C.G. <i>et al. Nature</i> ; published online Nov. 21, 2012; doi:10.1038/nature11628 Contact: Nahum Sonenberg, McGill University, Montreal, Quebec, Canada e-mail: nahum.sonenberg@mcgill.ca
Neurology	Tissue inhibitor of metalloproteinases 3 (TIMP3)	<p>Mouse studies suggest TIMP3 could help treat traumatic brain injury (TBI). In a mouse model of TBI, i.v. delivery of recombinant TIMP3 increased vascular stability and blood brain barrier integrity compared with delivery of vehicle. Ongoing work includes determining the therapeutic dose range, therapeutic window, toxicities and exact mechanisms of action.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1240 Published online Dec. 6, 2012</p>	Unpatented; licensing status not applicable	Menge, T. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 21, 2012; doi:10.1126/scitranslmed.3004660 Contact: Shibani Pati, Blood Systems Research Institute, San Francisco, Calif. e-mail: spati@bloodsystems.org
Parkinson's disease (PD)	Opiate receptor-like 1 (OPRL1)	<p>Rat and primate studies suggest OPRL1 agonists could help treat dyskinesias induced by the PD drug L-dopa. In a rat model of L-dopa-induced dyskinesia (LID), exogenous nociceptin or an agonist targeting the nociceptin receptor OPRL1 decreased LID and increased motor functions compared with saline control. In a nonhuman primate model for PD with LID, the OPRL1 agonist decreased dyskinesia compared with saline without decreasing the therapeutic effect of L-dopa. Next steps include lead identification and optimization of OPRL1 agonists.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1241 Published online Dec. 6, 2012</p>	Patents filed internationally and in Italy; use of OPRL1 agonists for LID is available for licensing	Marti, M. <i>et al. J. Neurosci.</i> ; published online Nov. 14, 2012; doi:10.1523/JNEUROSCI.6408-11.2012 Contact: Michele Morari, University of Ferrara, Ferrara, Italy e-mail: m.morari@unife.it

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This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Profiling tumor-derived microvesicles in the blood of patients with glioblastoma multiforme (GBM)	<p>A microfluidic system for profiling tumor-derived microvesicles in the blood of patients with GBM could help guide treatment decisions. On a microfluidic chip, microvesicles were first labeled with a protein-targeted antibody conjugated to a magnetic nanoparticle and then detected by micro-NMR. The assay was able to distinguish between blood samples from patients with GBM and those from healthy volunteers with 90% accuracy based on the expression of four protein markers on microvesicles. In patients with GBM treated with Temodar temozolomide, changes in microvesicle numbers and biomarker expression could be used to distinguish responders from nonresponders. Next steps include expanding the approach to other tumor types and developing a platform for comprehensive analysis of microvesicle biomarkers, including proteins, mRNAs and microRNAs. Merck & Co. Inc. markets Temodar to treat GBM.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1242 Published online Dec. 6, 2012</p>	Patent application filed on the micro-NMR system; unavailable for licensing	<p>Shao, H. <i>et al. Nat. Med.</i>; published online Nov. 11, 2012; doi:10.1038/nm.2994 Contact: Ralph Weissleder, Massachusetts General Hospital, Boston, Mass. e-mail: rweissleder@mgh.harvard.edu Contact: Hakho Lee, same affiliation as above e-mail: hlee@mgh.harvard.edu</p>
Disease models			
Mouse model for Parkinson's disease (PD)	<p>Nontransgenic mice receiving α-synuclein (SNCA) could be useful for studying pathogenesis of PD and evaluating therapeutic candidates. Aggregation of SNCA leads to degeneration of dopaminergic cells in the substantia nigra. In mice, striatal injection of aggregated recombinant SNCA promoted the conversion of endogenous soluble SNCA into an aggregated form throughout the brain and led to histological and clinical signs of PD. Next steps include identifying cellular factors involved in the spreading of SNCA aggregates and raising antibodies against those targets.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1243 Published online Dec. 6, 2012</p>	Unpatented; licensing status not applicable	<p>Luk, K.C. <i>et al. Science</i>; published online Nov. 16, 2012; doi:10.1126/science.1227157 Contact: Virginia M.-Y. Lee, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: vmylee@upenn.edu</p>
Drug platforms			
Engineered HPV particles that encapsulate viral genes for intravaginal vaccination against infection	<p>Mouse studies suggest intravaginal immunization using engineered HPV particles could help protect against mucosal pathogens. In mice, intravaginal vaccination with different engineered HPV particles that encapsulate a proof-of-concept antigen led to strong, durable antigen-specific CD8⁺ T cell responses in the cervicovaginal mucus, whereas intramuscular or intranasal vaccine delivery methods led to dampened antigen-specific CD8⁺ T cell responses. Mice that received the intravaginal vaccine were protected against challenge with a virus expressing the proof-of-concept antigen two months after immunization boost. Next steps include testing the engineered HPV particles as prophylactic vaccines for herpes simplex virus (HSV) and HPV infection.</p> <p>SciBX 5(47); doi:10.1038/scibx.2012.1244 Published online Dec. 6, 2012</p>	Patent application filed; vectors and use in preventing cancer and sexually transmitted infections available for licensing	<p>Çuburu, N. <i>et al. J. Clin. Invest.</i>; published online Nov. 12, 2012; doi:10.1172/JCI63287 Contact: John T. Schiller, National Cancer Institute, Bethesda, Md. e-mail: schillej@dc37a.nci.nih.gov</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Optogenetic gene therapy to treat focal neocortical epilepsy	Rat studies suggest optogenetic gene therapy could help treat focal neocortical epilepsy. In a rat model of focal neocortical epilepsy, a lentivirus vector was used to express a photoactivated inhibitory chloride pump in the motor cortex. Photoactivation of the modified cortical neurons decreased epileptiform electroencephalographic activity compared with unactivated control neurons. Next steps could include developing nonlentivirus vectors to deliver genes that encode inhibitory ion channels or pumps to neurons. SciBX 5(47); doi:10.1038/scibx.2012.1245 Published online Dec. 6, 2012	Patent and licensing status unavailable	Wykes, R.C. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 12, 2012; doi:10.1126/scitranslmed.3004190 Contact: Dimitri M. Kullmann, UCL Institute of Neurology, London, U.K. e-mail: d.kullmann@ucl.ac.uk Contact: Stephanie Schorge, same affiliation as above e-mail: s.schorge@ucl.ac.uk Contact: Matthew C. Walker, same affiliation as above e-mail: m.walker@ucl.ac.uk
Peptide-linked microparticles for inducing immune tolerance	Mouse studies suggest peptide-linked microparticles that induce immune tolerance could be useful for treating immune-mediated diseases such as multiple sclerosis (MS). In a mouse model of experimental autoimmune encephalomyelitis (EAE), i.v. infusion of polystyrene or poly(lactide-co-glycolide) (PLG) microparticles linked to encephalitis-associated peptides induced tolerance and decreased symptom severity compared with microparticles linked to a control peptide. Next steps include evaluating other peptide-linked PLG microparticles in models of other immune-mediated diseases (<i>see Micromanaging tolerance, page 7</i>). SciBX 5(47); doi:10.1038/scibx.2012.1246 Published online Dec. 6, 2012	Patent pending; available for licensing from the Myelin Repair Foundation	Getts, D.R. <i>et al. Nat. Biotechnol.</i> ; published online Nov. 18, 2012; doi:10.1038/nbt.2434 Contact: Stephen D. Miller, Northwestern University, Evanston, Ill. e-mail: s-d-miller@northwestern.edu
Imaging			
Imaging immune disease using multicolor light sheet fluorescent microscopy (LSFM)	High-resolution LSFM could help characterize the immune response in preclinical disease models. A fixation and deep tissue multicolor staining protocol enabled the visualization of single T cells and cellular nuclei in reconstructed 3D images of intact mouse tissue. In a mouse model of graft-versus-host disease (GvHD), computational analysis quantified the dynamics of the immune response during disease progression. Next steps include using the approach to study tumor-immune cell interactions. SciBX 5(47); doi:10.1038/scibx.2012.1247 Published online Dec. 6, 2012	Unpatented; available for collaboration	Brede, C. <i>et al. J. Clin. Invest.</i> ; published online Nov. 12, 2012; doi:10.1172/JCI65100 Contact: Christian Brede, Wuerzburg University Clinics, Wuerzburg, Germany e-mail: brede_c@medizin.uni-wuerzburg.de Contact: Andreas Beilhack, same affiliation as above e-mail: beilhack_a@klinik.uni-wuerzburg.de

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