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Bromodomains on the brain

By Joanne Kotz, Senior Editor

A Dana-Farber Cancer Institute-led team has found that neuroblastomas with *MYCN* amplification, which occurs in about 25% of pediatric brain tumors, are sensitive to small molecule inhibitors of the BET family of bromodomains.¹ The findings provide a genetic marker for this emerging epigenetic target, and **GlaxoSmithKline plc** already is using *MYCN* amplification as one criterion to select patients for a Phase I trial of its BET bromodomain inhibitor in cancer.

Bromodomain-containing proteins are a class of epigenetic regulators. These domains bind to histones in which lysine residues are modified by an acetyl group to regulate chromatin remodeling and gene transcription.

Two independent papers in *Nature* in 2010 first established the potential druggability of bromodomains by identifying JQ1 and I-BET as selective inhibitors of the BET bromodomain family, which includes bromodomain containing 2 (BRD2), BRD3 and BRD4.^{2,3}

One of those papers also provided the first suggestion that BET bromodomain inhibitors might have efficacy in cancer. JQ1 dramatically reduced tumors in a patient-derived xenograft mouse model for nuclear protein in testis (C15orf55; NUT) midline carcinoma, a rare cancer in which a chromosomal translocation fuses the N-terminal bromodomains of *BRD4* to *NUT*.²

Subsequently, BET bromodomain inhibitors showed efficacy in animal models for leukemias and multiple myeloma (MM), at least in part by downregulating the expression of *c-Myc* (*MYC*).⁴⁻⁶

I-BET was identified by GSK. JQ1 was reported by a team from Dana-Farber and the **Structural Genomics Consortium**. James Bradner, investigator in the Department of Medical Oncology at Dana-Farber and a lead author on the study, founded **Tensha Therapeutics Inc.**, which is developing drug-like analogs of JQ1 for cancer.

Outside of the rare *BRD4* fusion, the missing puzzle piece was genetic markers to guide patient selection. “To date, few genetic predictors of response exist for epigenomic drugs,” including histone deacetylases (HDACs) and DNA methyltransferases, said Bradner.

“The results described in the paper provide convincing preclinical evidence that *MYCN* amplification is a marker of sensitivity to BET inhibitors in a broad panel of cancer cell lines.”

—Peter Tummino,
GlaxoSmithKline plc

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As a result, the likelihood of identifying genetic markers that predicted response to epigenetic inhibitors, including JQ1 and I-BET, was not clear.

To look for potential markers, Bradner teamed up with Kimberly Stegmaier, assistant professor in pediatric oncology at Dana-Farber. The group screened more than 650 genetically characterized cancer cell lines and looked for ones in which JQ1 reduced viability with a submicromolar IC₅₀ value.

The cancer cell line panel was developed by researchers at the **Massachusetts General Hospital** and the **Wellcome Trust Sanger Institute**.⁷

In the screen, all four neuroblastoma cell lines with *MYCN* (*v-myc myelocytomatosis viral related oncogene neuroblastoma derived*; *NMYC*) amplification were sensitive to JQ1.

BET bromodomain inhibition also provided a therapeutic effect *in vivo*. In three distinct mouse models of *MYCN*-amplified neuroblastomas, JQ1 increased survival compared with vehicle.

Data were published in *Cancer Discovery*.

“While we expected to observe heterogeneity of response in broad cancer cell line screening, we did not expect to link discrete genetic lesions, here *MYCN* amplification, to response to an epigenomic transcriptional regulatory molecule,” Bradner told *SciBX*.

Clinical jump

GSK already is putting the predictive capacity of *MYCN* amplification to the test.

“The results described in the paper provide convincing preclinical evidence that *MYCN* amplification is a marker of sensitivity to BET inhibitors in a broad panel of cancer cell lines,” said Peter Tummino,

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head of biology in GSK's cancer epigenetics DPU. "The finding is strengthened by the mechanistic data demonstrating BET inhibitors induced decreased expression of *MYCN* and *MYCN* target genes. These results are consistent with GSK in-house results with GSK I-BET762 regarding both cell line sensitivity and expression changes."

GSK I-BET762 (GSK525762) is an analog of the I-BET molecule that GSK originally reported.

"There is a population of neuroblastomas with *MYCN* overexpression without gene amplification, and it will be worthwhile to determine if these tumors are highly sensitive to BET inhibition. *MYCN* amplification also occurs at a low frequency in lung cancer, both small cell and non-small cell, medulloblastoma and rhabdomyosarcoma," and these cancer subtypes may also respond to BET bromodomain inhibitors, Tummino added.

In March 2012, the pharma started a Phase I study of GSK I-BET762. The study is enrolling patients with NUT midline carcinoma, MM, small cell lung cancer (SCLC), colorectal cancer, neuroblastoma and *MYCN*-amplified solid tumors.

The Dana-Farber team also is moving toward the clinic and exploring additional markers and cancer indications that may respond to BET bromodomain inhibitors.

Stegmaier said the researchers plan to develop pharmacodynamic assays that could be used for clinical testing of BET bromodomain inhibition in relapsed/refractory pediatric neuroblastoma. The researchers also are exploring the effects of JQ1 in *MYCN*-amplified medulloblastoma.

Although the study published in *Cancer Discovery* identified *MYCN* amplification in neuroblastoma as one potential genetic biomarker for response to BET bromodomain inhibitors, genetic markers were not identified for a number of cancers that are known to respond dramatically to BET bromodomain inhibition in mouse models, said Bradner.

As a result, it may be necessary to search for epigenetic—rather than genetic—biomarkers that predict JQ1 response. "Our sense is that new types of epigenomic biomarker measurements are needed to understand BET bromodomain inhibition," Bradner told *SciBX*.

Tensha's TEN-010 BET bromodomain inhibitor is in preclinical development. "TEN-010 appears to have the desired profile for a therapeutic agent in the management of neuroblastoma as well as a broad range of other indications," said President and CEO Doug Onsi, although he declined to disclose details.

Dana-Farber has filed a patent application covering JQ1 and related analogs, and the IP is licensed to Tensha for clinical development.

Other BET bromodomain inhibitors in development include **Oncoethix S.A.**'s OTX015, which is in Phase I testing in patients with hematological malignancies. The molecule was in-licensed from **Mitsubishi Tanabe Pharma Corp.**

Constellation Pharmaceuticals Inc. has a preclinical BET bromodomain inhibitor program.

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GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Massachusetts General Hospital, Boston, Mass.
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Oncoethix S.A., Lausanne, Switzerland
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SMAD men

By *Tim Fulmer, Senior Writer*

University of Colorado Denver School of Medicine researchers have shown that topical application of the signaling protein Smad7 can treat and prevent oral mucositis in mice.¹ The team will now test the compound in mice with cancer-associated mucositis—a condition with limited therapeutic options.

Oral mucositis can occur in a variety of clinical settings. In particular, it is a serious side effect in about 80% of patients with head and neck cancer receiving high-dose radiotherapy.² It causes severe pain and can force patients to use a feeding tube and ventilation apparatus, and it may lead to serious infections in mucosal sores and ulcerations.

Standard of care is a combination of scrupulous oral hygiene and antibiotics. The only targeted oral mucositis drug is Kepivance palifermin, a recombinant keratinocyte growth factor (KGF) marketed by Swedish Orphan Biovitrum AB to treat oral mucositis in patients with blood cancer receiving radiation before bone marrow transplants.

However, the drug has shown only modest clinical benefit in two investigator-run head and neck cancer trials, in which it failed to significantly decrease the incidence of oral mucositis compared with placebo.^{3,4}

Because excessive inflammation and destruction of epithelial cells are the hallmarks of oral mucositis, the Colorado team hypothesized that local delivery of an anti-inflammatory with the additional ability to promote growth of oral epithelial cells might help treat the condition in patients with cancer.

Indeed, the group's prior work in mice showed that the endogenous intracellular signaling protein SMAD7 (mothers against decapentaplegic homolog 7; MADH7) both antagonized proinflammatory signaling pathways and blocked apoptosis of keratinocytes in the oral epithelia.⁵⁻⁷ The open question was whether a recombinant form of SMAD7 could be delivered directly to the oral mucosa and generate a therapeutic effect.

To confirm that high Smad7 levels reduced the damaging effects of radiation on the oral mucosa, the researchers first irradiated transgenic mice overexpressing Smad7 and compared them with irradiated wild-type mice.

The Smad7 animals were more resistant to radiation-induced oral mucositis and had significantly lower levels of multiple inflammation markers in the oral cavity, including leukocyte infiltration ($p < 0.001$), epithelial cell apoptosis ($p < 0.001$), NF- κ B expression ($p < 0.001$) and transforming growth factor- β (TGFB; TGF β) signaling ($p < 0.05$).

The researchers next looked for similar effects when they delivered Smad7 directly to the oral epithelia of irradiated wild-type mice. To do that, they generated a recombinant form of Smad7 and linked it to the Tat protein, which allowed Smad7 to cross the cell membrane and enter the nucleus of epithelial cells.

In mice, daily application of the Smad7-Tat protein fusion to the oral cavity 24 hours before irradiation significantly decreased ulcer formation compared with saline control application ($p < 0.01$). The fusion's effects were comparable to those of Kepivance. Immunostaining confirmed that Smad7-Tat significantly reduced apoptotic cells and NF- κ B signaling in the oral mucosa ($p < 0.01$).

Finally, in irradiated mice with existing oral mucositis, Smad7-Tat led to smaller ulcers and lower mucosal pathology than saline control, confirming that the compound had both a therapeutic and a preventative effect.

The study was published in *Nature Medicine*. It was led by Qinghong Zhang, assistant professor of dermatology at the University of Colorado School of Medicine, and Xiao-Jing Wang, professor and director of the Head, Neck and Skin Cancer Research Program at the university.

The researchers now will test Smad7 delivery in irradiated cancer models, Wang told *SciBX*. In addition, the group is “designing and testing different Smad7 constructs and production systems to optimize its large-scale production and purification so that it can be safely used in humans and also meet potential market demands,” she said.

The findings are covered by patent applications and available for partnering or licensing from the University of Colorado Denver School of Medicine, said Wang.

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COMPANIES AND INSTITUTIONS MENTIONED

Swedish Orphan Biovitrum AB (SSE:SOBI), Stockholm, Sweden
University of Colorado Denver School of Medicine, Aurora, Colo.

mAb attack on WT1

By Kai-Jye Lou, Staff Writer

Wilms tumor 1 is overexpressed in many different cancers, but most antibody and small molecule developers have deemed it undruggable because it is an intracellular transcription factor. Now, researchers at **Eureka Therapeutics Inc.** and the **Memorial Sloan-Kettering Cancer Center** have targeted Wilms tumor 1–positive cancer cells with a mAb against peptide fragments derived from the protein that are presented on the cells' surface.¹

The biotech hopes to have the mAb in a Phase I trial in leukemia within two years and is seeking a clinical development partner.

Wilms tumor 1 (WT1) is a transcription factor found in the cell nucleus that is overexpressed in a range of leukemias and solid tumors. Ongoing efforts to address WT1-positive cancers have focused on vaccines and T cell therapies as opposed to antibodies and small molecules.

Antibodies are unable to target intracellular proteins, whereas small molecules typically cannot modulate the protein-protein interactions in which transcription factors are involved.

In 2006, research teams led by David Scheinberg, chair of the Molecular Pharmacology & Chemistry Program at the **Sloan-Kettering Institute** at MSKCC, published a pair of studies identifying a series of nine-amino-acid, WT1-derived peptides that could be used to trigger a T cell immune response against some WT1-positive cancer cells.^{2,3} The peptides are processed and presented on the cell surface in a complex with a specific human leukocyte antigen (HLA) molecule called HLA-A 0201.

Like companies and other academics, Scheinberg's initial strategy was to develop a cancer vaccine because many such peptide-HLA complexes are recognized by T cell receptors (TCRs). In a pilot study led by MSKCC, the group's polyvalent WT1 peptide vaccine candidate stimulated a WT1-specific T cell response in patients with acute myelogenous leukemia (AML) who had finished chemotherapy and were in complete remission.⁴

At least three companies have clinical-stage immunotherapies for WT1-positive cancers. **Inovio Pharmaceuticals Inc.**'s WT1-targeting DNA vaccine is in Phase II testing in AML and chronic myelogenous leukemia (CML). **GlaxoSmithKline plc**'s GSK2130579A, an antigen-specific cancer immunotherapeutic using recombinant WT1, is in Phase I testing in AML. **Formula Pharmaceuticals Inc.** has exclusively licensed the WT1 peptide vaccine developed by Scheinberg's group and designated it FPI-01. Scheinberg said the vaccine is being evaluated in multiple MSKCC-sponsored Phase II trials in AML, acute lymphoblastic leukemia (ALL) and mesothelioma.

All of the immunotherapies are being tested in patients who are in remission or have minimal disease burden rather than those with more active disease.

Because the WT1 peptide-HLA complexes are found on the cell surface, Scheinberg wanted to revisit the idea of using therapeutic mAbs to target WT1-positive cells.

“Antibodies can be used when there is active cancer and are also far easier to apply than a patient-specific live T cell therapy.”

—David Scheinberg,
Memorial Sloan-Kettering
Cancer Center

“Vaccine approaches are most likely to be applicable in patients who have little detectable leukemia or cancer left,” he told *SciBX*. “Antibodies can be used when there is active cancer and are also far easier to apply than a patient-specific live T cell therapy.”

The MSKCC group thus teamed up with human antibody discovery and engineering company Eureka in 2010.

The research group used the biotech's phage display platform to screen for single-chain variable fragments that bound the WT1-derived peptide-HLA complexes identified in the 2006 studies. The lead fragments were then engineered into full-length human mAbs.

In panels of human cells isolated from healthy donors and patients, one of the leads, dubbed ESK1, bound to the majority of leukemic and solid tumor cell lines that were positive for both WT1 and the HLA-A0201 molecule but not to lines that were negative for one or

both markers. In a series of *in vitro* cytotoxicity studies, the mAb killed WT1-positive cancer cells via antibody-dependent, cell-mediated cytotoxicity.

In mouse xenograft models for human ALL and Philadelphia chromosome-positive ALL, ESK1 decreased tumor burden and increased survival compared with a control IgG. Some of the mice showed no evidence of disease after treatment.

Results were published in *Science Translational Medicine*.

“Our therapeutic antibody does not need to enter the cell because even though WT1 is intracellular, peptides derived from the transcription factor do move to the cell surface, where they can be targeted by our antibody,” said Cheng Liu, a coauthor on the paper and president, CEO and founder of Eureka. “ESK1 works by mobilizing the host immune system to kill WT1-positive cancer cells.”

The case for mAbs

Although companies and academics have advanced other immunotherapy candidates to treat WT1-positive cancers as far as Phase II trials, Liu and Scheinberg both think a therapeutic mAb will have utility because it offers the potential to treat patients with active disease.

Liu told *SciBX* that even though WT1 is overexpressed in many solid cancers, the plan is to start in hematological cancers because the endpoints are easier to monitor.

According to Scheinberg, the initial populations being considered for ESK1 are patients who have acute or chronic leukemias, myelodysplastic syndrome (MDS) or multiple myeloma (MM) who have not fared well on other treatments.

Haruo Sugiyama, a professor in the Department of Functional Diagnostic Science at the **Osaka University Graduate School of Medicine**, said that “for cure-oriented therapy in leukemia, cancer stem cells will have to be killed.” He noted that ESK1 could have potential for eradicating leukemia stem cells if the binding of ESK1 to the WT1-HLA complex on such cells is similar enough to that of WT1-specific cytotoxic T lymphocytes, which are induced by vaccine-based strategies.

Sugiyama added that one may also want to consider combining ESK1 with an existing WT1 vaccine as this could yield better outcomes than either treatment alone. “Simultaneous combination therapy of ESK1 and a WT1 vaccine, or the use of ESK1 together

with chemotherapy for remission induction and a WT1 vaccine for remission maintenance, may be advantageous,” he told *SciBX*.

Sugiyama and colleagues at the Osaka University Graduate School of Medicine are developing a WT1 peptide vaccine, which the group has in Phase II testing for various cancers.

Scheinberg said the group’s next steps are to evaluate ESK1 in additional animal safety studies and to scale up manufacturing of the antibody.

“We are hoping to have our antibody reach clinical-stage testing in one to two years,” added Liu. “We would like to engage with an industry partner that has extensive clinical and product development experience to help with the clinical development program.”

MSKCC and Eureka have an ongoing discovery and development collaboration that provides both parties with co-ownership rights to resulting drug candidates and related IP. The partners have cofiled for patents covering ESK1. The technology is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Formula Pharmaceuticals Inc., Berwyn, Pa.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Inovio Pharmaceuticals Inc. (NYSE-M:INO), Blue Bell, Pa.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Osaka University Graduate School of Medicine, Osaka, Japan
Sloan-Kettering Institute, New York, N.Y.

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Awakening tumor immunity

By Lev Osherovich, Senior Writer

Researchers at **The University of Texas MD Anderson Cancer Center** have determined why many cancer vaccines fail to elicit a robust T cell response—the cells hover near the vaccination site instead of migrating to the tumor.¹ The surprisingly simple solution is switching the vaccine formulation to a different carrier.

Vaccination with peptide antigens typically elicits both antibody- and cell-based immune responses that are mediated by B cells and T cells, respectively. A robust response by CD8⁺ cytotoxic T cells is especially important in fighting tumors.

Ideally, a tumor-derived antigen vaccine would cause antigen-presenting cells (APCs) such as dendritic cells (DCs) to pick up the antigen and carry it to lymph nodes, where they would then activate B cells that make tumor-targeting antibodies and CD8⁺ cytotoxic T cells that hunt tumor cells.

In practice, raising antibodies against tumor antigens is easy, but getting a robust T cell response has proven challenging.

The only marketed cancer vaccine in the U.S.—**Dendreon Corp.**'s Provenge sipuleucel-T for prostate cancer—takes a shortcut to eliciting

a strong T cell response. Provenge therapy involves extracting and activating patient-derived DCs *ex vivo*, then reintroducing the DCs into patients in large enough numbers to promote tumor-targeting T cell activity.

Direct *in vivo* vaccination could help avoid the cost and complexity of autologous cell therapies like Provenge but would only be effective if a stronger T cell response could somehow be elicited.

Thus, Willem Overwijk, associate professor of melanoma medical oncology at MD Anderson, set out to understand why typical tumor vaccines lead to poor T cell responses.

He said prior preclinical and clinical studies have shown that cancer vaccines typically cause an initial burst of T cell activity, but the response quickly peters out.

Failure to launch

Overwijk's team vaccinated a mouse model for melanoma with a short fragment of the melanoma antigen silver homolog (SILV; PMEL17; GP100) in a solution of incomplete Freund's adjuvant (IFA), a commonly used mineral oil-based carrier.

As expected, the formulation elicited a strong B cell response but only a weak T cell response.

To understand why the vaccine-induced T cells were not very effective, Overwijk's team used a luciferase-based imaging system to look

at the localization of T cells in tumor-bearing mice. Instead of migrating to the tumors, the antigen-specific T cells lingered around the vaccine injection site for weeks.

"We saw that T cells were getting hung up at the injection site," said Overwijk. "They expanded in number and hung out in the blood near the injection site. Very few of them went to the tumor sites."

Overwijk found that IFA did not readily disperse in the bloodstream and instead formed a long-lived depot of antigen that trapped T cells. Instead of homing to tumor cells, the T cells were sequestered near the vaccination site, formed a dense granuloma-like mass, became inactive and eventually underwent apoptosis.

"We think it's the long persistence of the vaccine that leads to this effect. The mineral oil is not biodegradable," he noted.

To overcome this problem, Overwijk's team experimented with various vaccine formulations that are shorter lived than IFA. The team settled on a formulation of GP100 and a cocktail of adjuvants suspended in a saline buffer.

With the new saline-based formulation, "the vaccine site becomes cleared of antigen in 4–5 days rather than 90 days with IFA," said Overwijk.

Mice vaccinated with the saline-based formulation showed T cell migration away from the vaccination site and toward the tumor (see **Figure 1, "Improving tumor vaccine formulation"**). The result was greater tumor-specific T cell responses at the tumor site than those seen when using IFA-based controls.

Findings were reported in *Nature Medicine*.

Cancer and beyond

Benjamin Chen, executive chairman of **Immune Targeting Systems Ltd.**, said Overwijk's findings are potentially relevant to a variety of T cell-targeted vaccines for cancer and possibly other indications.

"It's been known that the IFA-like adjuvant used in humans can cause granulomas and necrosis at injection sites," but the significance of these structures was unclear, said Chen. "The phenomenon of getting T cell infiltration and sequestration at the vaccination site and absence of T cells at the tumors is a very important finding. We now know the problem, and there's now a hypothesis to address this."

Immune Targeting is developing self-adjuvanting, T cell-targeted peptide vaccines. A Phase IIa trial of the company's most advanced product—Flunisyn influenza A vaccine (FP-01.1)—met its primary endpoint of T cell induction. The company also has preclinical vaccine candidates for HBV and an undisclosed cancer indication.

Cornelis Melief, CSO of vaccine maker **ISA Pharmaceuticals B.V.**, suspects that the carrier may not be the only culprit that hinders T cell migration. He noted that the poor efficacy of the mineral oil-based vaccine in the paper could result from the excessively short peptides used in the study.

ISAs vaccines use long peptides in an IFA-like carrier. The company's ISA-HPV-01, a therapeutic vaccine for HPV, is expected to start Phase II testing this year for advanced cervical cancer and is in Phase I/II trials for anal intraepithelial neoplasia.

Melief said the short GP100 antigen peptide used by Overwijk's team binds to MHC I receptors found on a multitude of cells, including the T cells themselves. As a result, vaccination with this short peptide can overstimulate the T cells and discourage proper presentation of antigens by DCs and other APCs.

"The phenomenon of getting T cell infiltration and sequestration at the vaccination site and absence of T cells at the tumors is a very important finding. We now know the problem, and there's now a hypothesis to address this."

—Benjamin Chen, Immune Targeting Systems Ltd.

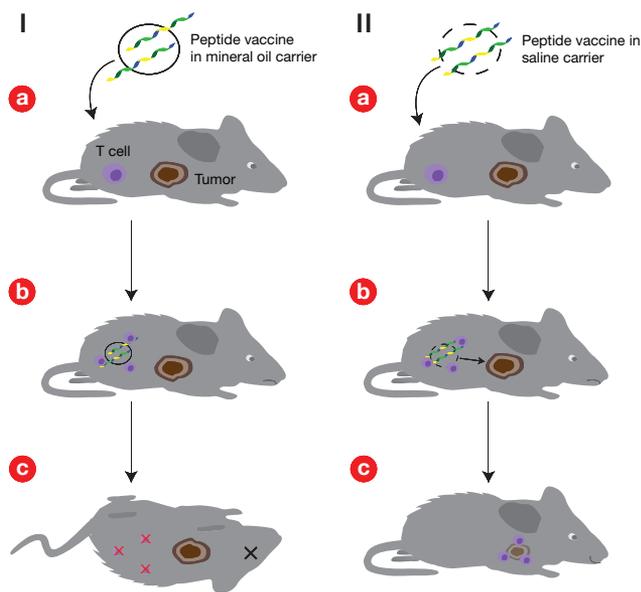


Figure 1. Improving tumor vaccine formulation. Hailemichael *et al.* have shown that a widely used adjuvant leads to T cell inactivity that impairs the efficacy of cancer vaccines and have devised a workaround.

A typical T cell–targeted cancer vaccine is formulated in a mineral oil–based carrier (I[a]). In a mouse tumor model, subcutaneous injection of this formulation draws T cells to the injection site (I[b]), where they accumulate instead of migrating toward the tumor. These locally trapped T cells eventually undergo apoptosis (I[c]), leading to tumor growth and death.

Hailemichael *et al.* formulated peptide antigens in a saline-based carrier (II[a]) and observed transient localization of T cells to the injection site followed by migration of the T cells toward the tumor (II[b]), leading to an improved antitumor immune response (II[c]).

Many researchers prefer using short-peptide antigens because they are easier to work with than longer peptides and do not require additional processing by APCs.

Melief believes a better approach is to use long-peptide antigens. Long peptides do not readily bind to MHC I and can only be taken up by DCs, which are less numerous than other cell types, including T cells. Instead of the excessive local response caused by short peptides, long peptides are carried from the injection site by DCs to lymph nodes, leading to a more measured and productive immune response.

“MHC I–binding peptides are lousy vaccines because they exogenously load onto all cells with class I MHC,” said Melief. “This leads to a tolerizing mode of vaccination. If you are going to deliver short

peptides, Overwijk clearly shows that the only way is to provide them along with strong adjuvants and saline.”

Last year, Melief and collaborators at the **Leiden University Medical Center** reported that long-peptide vaccines induce an effective antitumor T cell response and tumor regression in a mouse model for HPV even when formulated with an IFA-like carrier.²

Likewise, Melief noted that the supplementary data in Overwijk’s paper suggest that when the team used longer peptides, the melanoma vaccine appeared to work well even in IFA.

Overwijk said Melief is correct that “when given in IFA, long peptides are superior to short peptides, possibly because the intensity of antigen presentation of long peptides is lower.”

However, he said, “we still see eventual T cell dysfunction after vaccination with long peptides in IFA, probably since the persistence of antigen is still too long.”

Chen said the challenge now for vaccine makers is to maximize the exposure of antigens to APCs without causing long-term T cell sequestration. He said optimal local persistence of the antigen may vary from one vaccine to another.

“You want to attract antigen-presenting cells to come in and pick up the antigen and prime T cells, but you don’t want the depot to be around for too long,” said Chen. “You need to make sure the T cells get primed and home to where they are needed as quickly as possible.”

Overwijk said a saline-based carrier is probably too short-lived to produce optimal DC responses. His team is now testing a variety of water-soluble carriers and materials including gels, microsomes and nanoparticles. The goal is to deliver the antigen in a way that mimics acute viral infection, which is familiar territory for the immune system.

“We’re currently working with industry and academia to try a variety of particle-based, intermediate-release formulations,” said Overwijk. “We haven’t found the ideal formulation yet, but we think we want it to be around for around five days, which is about as long as a virus hangs around.”

Overwijk did not disclose the companies with whom he is working. He did not patent his findings.

Osherovich, L. *SciBX* 6(12); doi:10.1038/scibx.2013.280
Published online March 28, 2013

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1. Hailemichael, Y. *et al. Nat. Med.*; published online March 3, 2013; doi:10.1038/nm.3105
Contact: Willem W. Overwijk, The University of Texas MD Anderson Cancer Center, Houston, Texas
e-mail: woverwijk@mdanderson.org
2. van Duikeren, S. *et al. J. Immunol.* **189**, 3397–3403 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

Dendreon Corp. (NASDAQ:DNDN), Seattle, Wash.
Immune Targeting Systems Ltd., London, U.K.
ISA Pharmaceuticals B.V., Leiden, the Netherlands
Leiden University Medical Center, Leiden, the Netherlands
The University of Texas MD Anderson Cancer Center, Houston, Texas

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				
Acute lymphoblastic leukemia (ALL)	B cell lymphoma 2 (BCL-2; BCL2); tyrosine kinase 2 (TYK2); signal transducer and activator of transcription 1 (STAT1)	<p>Mouse and cell culture studies suggest inhibiting the TYK2-STAT1-BCL2 signaling pathway could help treat T cell ALL. In mice grafted with leukemic cells from patients with T cell ALL, small interfering RNA against TYK2 in the grafted cells decreased leukemic cell viability compared with control siRNA in five of eight cases. A series of cell culture studies identified STAT1 and BCL2 as downstream mediators of TYK2. In 19 T cell ALL cell lines, pharmacological blockade of TYK2 with pan-Janus kinase inhibitors reduced ALL cell viability. Next steps could include evaluating pharmacological TYK2 inhibitors in animal models of ALL.</p> <p>Sareum Holdings plc has a TYK2 inhibitor in preclinical development to treat autoimmune diseases.</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.281 Published online March 28, 2013</p>	Patent and licensing status unavailable	<p>Sanda, T. <i>et al. Cancer Discov.</i>; published online March 7, 2013; doi:10.1158/2159-8290.CD-12-0504 Contact: A. Thomas Look, Dana-Farber Cancer Institute, Boston, Mass. e-mail: thomas_look@dfci.harvard.edu</p>
Brain cancer	Bromodomain containing 4 (BRD4); <i>v-myc myelocytomatosis viral related oncogene neuroblastoma derived (MYCN; NMYC)</i>	<p>Cell profiling and mouse studies suggest inhibiting BET bromodomains could help treat neuroblastomas with <i>MYCN</i> amplification. In a screen of 673 genetically characterized cancer cell lines, <i>MYCN</i> amplification was the most strongly correlated marker for sensitivity to JQ1, a small molecule inhibitor of BRD4 and other BET bromodomains. In three different mouse models for <i>MYCN</i>-amplified neuroblastoma, JQ1 increased survival compared with vehicle. Next steps include looking at the effects of inhibiting BET bromodomains in <i>MYCN</i>-amplified medulloblastoma.</p> <p>Tensha Therapeutics Inc. has the BET bromodomain inhibitor TEN-010 in preclinical development for cancer.</p> <p>At least three other companies have BET bromodomain inhibitors in Phase I or preclinical development in cancer (<i>see Bromodomains on the brain, page 1</i>).</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.282 Published online March 28, 2013</p>	Patent application filed covering JQ1 and derivatives; licensed to Tensha Therapeutics	<p>Puissant, A. <i>et al. Cancer Discov.</i>; published online Feb. 21, 2013; doi:10.1158/2159-8290.CD-12-0418 Contact: Kimberly Stegmaier, Dana-Farber Cancer Institute, Boston, Mass. e-mail: kimberly_stegmaier@dfci.harvard.edu Contact: James E. Bradner, same affiliation as above e-mail: james_bradner@dfci.harvard.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Endothelial PAS domain protein 1 (EPAS1; HIF2A)	<i>In vitro</i> and cell culture studies identified a small molecule inhibitor of HIF2A that could help treat cancer. HIF2A is overexpressed in various cancers. A high throughput screen and medicinal chemistry optimization identified a compound that bound an internal cavity in HIF2A with a K_D value of 81 nM and disrupted the formation of heterodimeric hypoxia-inducible factor 2 (HIF2) transcription factor complexes. In human cells grown under hypoxic conditions, the lead molecule decreased the expression of HIF2 target genes compared with vehicle. Next steps could include testing the effects of the lead small molecule in preclinical models for HIF2-driven cancers, such as renal cell carcinoma (RCC). SciBX 6(12); doi:10.1038/scibx.2013.283 Published online March 28, 2013	Patent status undisclosed; licensed to Peloton Therapeutics Inc.	Scheuermann T.H. <i>et al. Nat. Chem. Biol.</i> ; published online Feb. 24, 2013; doi:10.1038/nchembio.1185 Contact: Rick K. Bruick, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: richard.bruick@utsouthwestern.edu Contact: Kevin H. Gardner, same affiliation as above e-mail: kevin.gardner@utsouthwestern.edu
Cancer	Unknown	<i>In vitro</i> and mouse studies identified fucosylation inhibitors that could help treat various diseases including cancers. A screen of about 200 synthetic fucose-related compounds identified molecules that inhibited fucosylation of antibodies. <i>In vitro</i> , the lead fucosylation inhibitor was used to generate fucose-deficient antibodies, which showed greater binding affinity and cytotoxicity than parent antibodies. In mice, oral treatment with 2-fluorofucose increased survival in a lymphoma model compared with no treatment and delayed tumor growth in a colorectal cancer model. Next steps could include testing the fucosylation inhibitors in other indications. SciBX 6(12); doi:10.1038/scibx.2013.284 Published online March 28, 2013	Patent and licensing status unavailable	Okeley, N.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 14, 2013; doi:10.1073/pnas.1222263110 Contact: Peter D. Senter, Seattle Genetics Inc., Bothell, Wash. e-mail: psenter@seagen.com
Colorectal cancer	Epiregulin (EREG)	<i>In vitro</i> and mouse studies suggest inhibiting EREG could help treat colitis-associated colorectal cancer. EREG expression was upregulated in tumor tissues from patients and mice with colitis-associated colorectal cancer but not in tissues from those with spontaneous colorectal cancer. In a mouse model for colitis-associated cancer, <i>Ereg</i> knockout decreased tumor growth compared with no knockout. Next steps could include developing pharmacological inhibitors of EREG. SciBX 6(12); doi:10.1038/scibx.2013.285 Published online March 28, 2013	Patent and licensing status unavailable	Neufert, C. <i>et al. J. Clin. Invest.</i> ; published online March 15, 2013; doi:10.1172/JCI63748 Contact: Clemens Neufert, University of Erlangen-Nuremberg, Erlangen, Germany e-mail: clemens.neufert@uk-erlangen.de

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Leukemia; solid tumors	Human leukocyte antigen (HLA); Wilms tumor 1 (WT1)	<p>Mouse and cell culture studies suggest a human mAb targeting the WT1-HLA complex could help treat leukemia and solid tumors. In panels of cells from healthy donors and patients, the human mAb, called ESK1, bound to the majority of leukemic and solid tumor cell lines that were positive for WT1 and the WT1-HLA complex. In a mouse xenograft model for acute lymphoblastic leukemia (ALL), ESK1 decreased tumor burden and increased survival compared with a control IgG. Next steps include evaluating ESK1 in additional animal safety studies and scaling up manufacturing of the antibody.</p> <p>Eureka Therapeutics Inc. has ESK1 in preclinical development to treat leukemia.</p> <p>GlaxoSmithKline plc's GSK2130579, an antigen-specific cancer immunotherapeutic utilizing recombinant WT1, is in Phase II testing to treat acute myelogenous leukemia (AML) and Phase I testing to treat breast cancer.</p> <p>Inovio Pharmaceuticals Inc. has a WT1 DNA vaccine in Phase II testing to treat leukemia (<i>see mAb attack on WT1, page 5</i>).</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.286 Published online March 28, 2013</p>	<p>Patent applications filed; available for licensing from Memorial Sloan-Kettering Cancer Center and Eureka Therapeutics</p> <p>Contact: Sharon Seiler, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: seilers@mskcc.org</p> <p>Contact: Elisa Pan, Eureka Therapeutics Inc., Emeryville, Calif. e-mail: elisa_pan@eurekainc.com</p>	<p>Dao, T. <i>et al. Sci. Transl. Med.</i>; published online March 13, 2013; doi:10.1126/scitranslmed.3005661</p> <p>Contact: David A. Scheinberg, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: d-scheinberg@ski.mskcc.org</p> <p>Contact: Cheng Liu, Eureka Therapeutics Inc., Emeryville, Calif. e-mail: cheng_liu@eurekainc.com</p>

Dermatology

Dermal ulcers	Wiskott-Aldrich syndrome-like (WASL; N-WASP)	<p><i>In vitro</i> and mouse studies suggest inhibiting the interaction between mycolactone and N-WASP could help treat Buruli ulcers. In cultured epithelial cells, wiskostatin inhibited the activation of N-WASP family proteins and the impairment of epithelial cell adhesion and direction sensing caused by mycolactone, the <i>Mycobacterium ulcerans</i> secretion that causes Buruli ulcers.</p> <p>In mice injected with mycolactone in the ear, wiskostatin prevented epithelial damage. Next steps could include testing wiskostatin in mouse models for <i>M. ulcerans</i> infection and developing additional N-WASP inhibitors.</p> <p>Wiskostatin is a chemical reagent.</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.287 Published online March 28, 2013</p>	<p>Patent and licensing status unavailable</p>	<p>Guenin-Macé, L. <i>et al. J. Clin. Invest.</i>; published online March 15, 2013; doi:10.1172/JCI66576</p> <p>Contact: Caroline Demangel, Pasteur Institute, Paris, France e-mail: demangel@pasteur.fr</p>
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This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Sirtuin 1 (SIRT1)	<p><i>In vitro</i> and mouse studies suggest inhibiting SIRT1 specifically in neurons could help treat type 2 diabetes. Prior studies have suggested that peripheral SIRT1 activation could help treat the disease, but results have been inconsistent. In mice, neuron-specific knockout of <i>Sirt1</i> increased insulin sensitivity and glucose tolerance compared with no knockout. Next steps could include identifying strategies to prevent peripherally acting SIRT1 activators from accessing the CNS. Elixir Pharmaceuticals Inc.'s EX-527, an oral SIRT1 inhibitor, is in Phase II testing to treat Huntington's disease (HD). GlaxoSmithKline plc's GSK2245840 SIRT1 activator is in Phase II testing to treat psoriasis. The compound completed Phase I/II trials for type 2 diabetes, but the pharma said it is no longer pursuing that indication with the compound. Ildong Pharmaceutical Co. Ltd.'s SIRT1 activator, ID2244, is in preclinical development to treat metabolic syndrome.</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.288 Published online March 28, 2013</p>	Findings unpatented; available for partnerships	<p>Lu, M. <i>et al. J. Biol. Chem.</i>; published online March 1, 2013; doi:10.1074/jbc.M112.443606 Contact: Jerrold M. Olefsky, University of California, San Diego, La Jolla, Calif. e-mail: jolefsky@ucsd.edu</p>
Diabetes	Sirtuin 1 (SIRT1)	<p><i>In vitro</i> studies identified a SIRT1 mutation that could be associated with type 1 diabetes. Genotyping and sequencing identified a leucine to proline substitution at residue 107 of SIRT1 in four family members with type 1 diabetes and one with ulcerative colitis (UC). In β cells, expression of the mutant <i>SIRT1</i> disrupted normal SIRT1 activity and increased production of cytokines, chemokines and nitric oxide compared with expression of wild-type <i>SIRT1</i>. In myoblasts isolated from healthy controls, transduction with the SIRT1 mutant caused insulin resistance. Next steps include developing SIRT1 activators to treat type 1 diabetes. Elixir Pharmaceuticals Inc.'s EX-527, an oral SIRT1 inhibitor, is in Phase II testing to treat Huntington's disease (HD). GlaxoSmithKline plc's GSK2245840 SIRT1 activator is in Phase II testing to treat psoriasis. The compound completed Phase I/II trials for type 2 diabetes, but the pharma said it is no longer pursuing that indication with the compound. Ildong Pharmaceutical Co. Ltd.'s SIRT1 activator, ID2244, is in preclinical development to treat metabolic syndrome.</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.289 Published online March 28, 2013</p>	Patent and licensing status unavailable	<p>Biason-Lauber, A. <i>et al. Cell Metab.</i>; published online March 5, 2013; doi:10.1016/j.cmet.2013.02.001 Contact: Marc Y. Donath, University Hospital Basel, Basel, Switzerland e-mail: marc.donath@usb.ch</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Hyperuricemia/ gout	ATP-binding cassette sub- family G WHITE member 2 (ABCG2; MXR; BCRP1)	<i>In vitro</i> studies identified small molecule structural correctors of ABCG2 that could help treat gout. The Q141K mutation in ABCG2 decreases urate transport and has been associated with an increased risk of developing gout. SAR studies identified a small molecule that corrected the folding of the Q141K mutant ABCG2 and increased expression of the protein in cultured cells compared with vehicle. Next steps include screening for and developing additional Q141K corrector molecules to treat gout. SciBX 6(12); doi:10.1038/scibx.2013.290 Published online March 28, 2013	Patent application filed; available for licensing	Woodward, O.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 14, 2013; doi:10.1073/pnas.1214530110 Contact: William B. Guggino, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: wguggino@jhmi.edu Contact: Owen M. Woodward, same affiliation as above e-mail: owenw@jhmi.edu or owenw1@gmail.com
Hematology				
Stem cell transplant	Prostaglandin E ₂ receptor EP4 subtype (prostanoid EP4 receptor; PTGER4)	<i>In vivo</i> studies suggest PTGER4 inhibition could help stimulate hematopoietic progenitor cell (HPC) mobilization into peripheral blood for transplantation. In mice, injection of Mobic meloxicam to decrease prostaglandin E ₂ (PGE ₂) production or knockout of <i>Ptger4</i> both induced mobilization of HPCs to peripheral blood without reducing white blood cell counts. In these mice, meloxicam followed by G-CSF (CSF3) increased mobilization of HPCs for transplant compared with G-CSF alone. In nonhuman primates and in humans, meloxicam also stimulated HPC mobilization to peripheral blood. Next steps could include evaluating the effect of current pharmacological inhibitors of PTGER4 on HPC mobilization in animal models. Boehringer Ingelheim GmbH markets Mobic to treat pain and various autoimmune and inflammatory diseases. At least five companies have PTGER4 antagonists in Phase II testing or earlier to treat various diseases. SciBX 6(12); doi:10.1038/scibx.2013.291 Published online March 28, 2013	Patent and licensing status unavailable	Hoggatt, J. <i>et al. Nature</i> ; published online March 13, 2013; doi:10.1038/nature11929 Contact: Louis M. Pelus, Indiana University School of Medicine, Indianapolis, Ind. e-mail: lpelus@iupui.edu
Infectious disease				
Bacterial infections	Not applicable	Two studies suggest reactive oxygen species (ROS) production may not be the major contributor to bactericidal activity. Previous studies have suggested a unifying theory of antibiotic action in which induction of ROS leads to cell death. <i>In vitro</i> , ampicillin or norfloxacin killed <i>Escherichia coli</i> grown in anaerobic conditions at rates comparable to those for bacteria grown in aerobic conditions. In titration experiments using different quantities of norfloxacin in combination with an ROS-detecting dye, a correlation was not observed between ROS and antibacterial activity. Next steps include identifying new mechanisms that explain the bactericidal effects of antibiotics. EnBiotix Inc. is discovering compounds that increase production of ROS to treat bacterial infections. SciBX 6(12); doi:10.1038/scibx.2013.292 Published online March 28, 2013	Patent and licensing status not applicable	Keren, I. <i>et al. Science</i> ; published online March 8, 2013; doi:10.1126/science.1232688 Contact: Kim Lewis, Northeastern University, Boston, Mass. e-mail: k.lewis@neu.edu Liu, Y. & Imlay, J.A. <i>Science</i> ; published online March 8, 2013; doi:10.1126/science.1232751 Contact: James A. Imlay, University of Illinois at Urbana-Champaign, Urbana, Ill. e-mail: jimlay@illinois.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Musculoskeletal disease				
Osteoarthritis (OA)	Proteoglycan 4 (PRG4; HAPO)	<p>A study in mice suggests enhancing levels of PRG4 in joints could help treat OA. In aging mice, <i>Prg4</i> overexpression in cartilage tissue decreased age-related OA compared with normal <i>Prg4</i> expression. In mice subjected to knee ligament transection, local delivery of an adenoviral vector containing <i>Prg4</i> decreased OA-associated joint pathology compared with delivery of a sham vector. Next steps include testing the <i>Prg4</i> gene therapy in a horse model of OA.</p> <p>GeneQuine Biotherapeutics GmbH's GQ-203 is a gene therapy using the same vector as in the study but containing a different, undisclosed gene. It is in preclinical development to treat OA.</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.293 Published online March 28, 2013</p>	Findings covered by provisional patents; licensed to GeneQuine Biotherapeutics	<p>Ruan, M.Z.C. <i>et al. Sci. Transl. Med.</i>; published online March 13, 2013; doi:10.1126/scitranslmed.3005409</p> <p>Contact: Brendan H.L. Lee, Baylor College of Medicine, Houston, Texas e-mail: blee@bcm.tmc.edu</p>
Other				
Oral mucositis	Mothers against decapentaplegic homolog 7 (MADH7; SMAD7)	<p>A study in mice suggests delivering recombinant SMAD7 directly to the oral mucosa could help treat oral mucositis, which is often associated with cancer radiotherapy. In mice, <i>Smad7</i> overexpression in the mucosa increased resistance to radiation-induced mucositis compared with normal <i>Smad7</i> expression. In irradiated wild-type mice, delivery of a <i>Smad7</i>-Tat protein fusion to the oral mucosa decreased tissue pathology compared with delivery of saline control. Next steps include testing the <i>Smad7</i>-Tat protein fusion in mice with cancer-associated oral mucositis.</p> <p>Kepivance palifermin, a recombinant keratinocyte growth factor (KGF), is marketed by Swedish Orphan Biovitrum AB to treat oral mucositis in blood cancer patients receiving radiation before bone marrow transplants (<i>see SMAD men, page 4</i>).</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.294 Published online March 28, 2013</p>	Patented; available for licensing	<p>Han, G. <i>et al. Nat. Med.</i>; published online March 10, 2013; doi:10.1038/nm.3118</p> <p>Contact: Xiao-Jing Wang, University of Colorado Denver School of Medicine, Aurora, Colo. e-mail: xj.wang@ucdenver.edu</p> <p>Contact: Qinghong Zhang, same affiliation as above e-mail: qinghong.zhang@ucdenver.edu</p>
Transplantation				
Graft-versus-host disease (GvHD)	Delta-like 1 (DLL1); DLL4	<p>Mouse studies suggest mAbs against DLL1 and DLL4 could be useful for preventing GvHD. In a mouse model for GvHD, transient treatment with mAbs against <i>Dll1</i> and <i>Dll4</i> decreased disease severity and increased survival compared with control mAbs. Next steps include characterizing the long-term effects of the anti-DLL1/DLL4 mAbs.</p> <p>The Genentech Inc. unit of Roche collaborated on the study but has not disclosed whether it has an anti-DLL1/DLL4 mAb in preclinical development. At least four companies have compounds targeting DLL4 in Phase I testing or earlier to treat various cancers.</p> <p>SciBX 6(12); doi:10.1038/scibx.2013.295 Published online March 28, 2013</p>	Patents filed by Genentech; licensing status undisclosed	<p>Tran, I.T. <i>et al. J. Clin. Invest.</i>; published online March 1, 2013; doi:10.1172/JCI65477</p> <p>Contact: Ivan Maillard, University of Michigan, Ann Arbor, Mich. e-mail: imaillar@umich.edu</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			
Mutant methionyl-tRNA synthetase for protein labeling	Expression of a mutant methionyl-tRNA synthetase derived from <i>Escherichia coli</i> could be useful for producing modified variants of therapeutic proteins. The mutant <i>E. coli</i> methionyl-tRNA synthetase was expressed in a human cell line and designed to incorporate azidonorleucine at the N-terminus of proteins. In the same human cell line, supplementation with azidonorleucine led to the synthesis of azidonorleucine-labeled proteins that were detectable with mass spectrometry. Next steps could include generating therapeutic proteins that are fluorescently labeled or have improved pharmacological properties. SciBX 6(12); doi:10.1038/scibx.2013.296 Published online March 28, 2013	Patent and licensing status unavailable	Ngo, J.T. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 11, 2013; doi:10.1073/pnas.1216375110 Contact: David A. Tirrell, California Institute of Technology, Pasadena, Calif. e-mail: tirrell@caltech.edu
Disease models			
Models for pathogenic mutations in vasolin containing protein (VCP)	Fruit flies and human cells with pathogenic mutations in VCP could be useful as models to study diseases associated with such mutations, such as frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). In patient fibroblasts or human CNS cell lines, mutant VCP decreased mitochondrial membrane potential and increased mitochondrial respiration compared with wild-type VCP. Fruit flies with pathogenic mutations in the VCP ortholog showed defects in neuromuscular junction morphology, muscle degeneration and other myopathy. Next steps could include using the models to evaluate therapeutic candidates. SciBX 6(12); doi:10.1038/scibx.2013.297 Published online March 28, 2013	Patent and licensing status unavailable for both studies	Bartolome, F. <i>et al. Neuron</i> ; published online March 14, 2013; doi:10.1016/j.neuron.2013.02.028 Contact: Helene Plun-Favreau, UCL Institute of Neurology, London, U.K. e-mail: h.plun-favreau@ucl.ac.uk Contact: Andrey Y. Abramov, same affiliation as above e-mail: a.abramov@ucl.ac.uk Kim, N.C. <i>et al. Neuron</i> ; published online March 14, 2013; doi:10.1016/j.neuron.2013.02.029 Contact: J. Paul Taylor, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: jpaul.taylor@stjude.org
Drug platforms			
Automated, high throughput, microfluidic SAR platform	An automated, microfluidic SAR platform could be used to rapidly optimize kinase inhibitors. Gleevec imatinib, a small molecule inhibitor of BCR-ABL tyrosine kinase, was subjected to repeated cycles of computer-assisted derivatization, synthesis, purification and screening using a microfluidic system. The best of the resulting compounds had about 100-fold more potent IC ₅₀ values for BCR-ABL than imatinib. The molecules also were more effective against imatinib-resistant mutant versions of the enzyme and were cell permeable. Next steps include adapting the platform for cell culture and screening against nonsoluble targets. Gleevec is marketed by Novartis AG to treat multiple cancers. SciBX 6(12); doi:10.1038/scibx.2013.298 Published online March 28, 2013	Platform patented; available for partnering	Desai, B. <i>et al. J. Med. Chem.</i> ; published online Feb. 26, 2013; doi:10.1021/jm400099d Contact: Christopher N. Selway, Cyclofluidic Ltd., Welwyn Garden City, U.K. e-mail: chris.selway@cyclofluidic.co.uk

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Single-component, polymer optoelectronic interface to restore retinal light sensitivity	A single-component, polymer optoelectronic interface that restores retinal light sensitivity could be useful in the development of implantable devices to treat blindness. The interface consists of a single-component organic film of poly(3-hexylthiophene) that triggers neuronal firing in response to light. In degenerate rat retina explants lacking photoreceptor cells and cultured on top of the organic film, illumination of the film led to firing in neuronal cells in the retina explant. Next steps could include using the organic film in the development of a device designed to restore vision. SciBX 6(12); doi:10.1038/scibx.2013.299 Published online March 28, 2013	Patent and licensing status unavailable	Ghezzi, D. <i>et al. Nat. Photonics</i> ; published online March 17, 2013; doi:10.1038/nphoton.2013.34 Contact: Fabio Benfenati, Italian Institute of Technology, Genoa, Italy e-mail: fabio.benfenati@iit.it
Transglutaminase (TGM)-mediated synthesis of antibody-drug conjugates (ADCs)	<i>In vitro</i> and rodent studies suggest conjugating chemotherapeutics to engineered glutamine residues could improve the <i>in vivo</i> pharmacokinetics of ADCs. mAbs against three common tumor targets were engineered with recognition sites for <i>Streptovorticillium mobaraense</i> tgm and conjugated to a tubulin inhibitor. In mouse and rat tumor models, the best of these glutamine-conjugated ADCs had similar potency but better stability and pharmacokinetics compared with conventional cysteine-conjugated ADCs. Next steps could include optimizing the engineered conjugation target sites for therapeutic mAbs. SciBX 6(12); doi:10.1038/scibx.2013.300 Published online March 28, 2013	Patent pending; licensing status undisclosed	Strop, P. <i>et al. Chem. Biol.</i> ; published online Feb. 21, 2013; doi:10.1016/j.chembiol.2013.01.010 Contact: Arvind Rajpa, Rinat-Pfizer, South San Francisco, Calif. e-mail: arvind.rajpal@pfizer.com Contact: Pavel Strop, same affiliation as above e-mail: pavel.strop@pfizer.com



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