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Liquid biopsy

By *Tim Fulmer, Senior Writer*

A **Cancer Research UK** team has developed a diagnostic platform that uses tumor-derived circulating DNA to noninvasively monitor a patient's response to therapy.¹ The researchers are now moving the technology into a hospital setting, where they will test its ability to diagnose ovarian cancer earlier than standard pelvic scans.

In cancer patients, 1%–10% of circulating or cell-free DNA (cfDNA) derives from tumor cells,² including fragments of mutated oncogenes such as RAS, p53 and phosphoinositide 3-kinase (PI3K).^{3–6}

Those findings have suggested it might be possible to develop a diagnostic assay that detects tumor-specific genes and gene mutations in the serum. A so-called liquid biopsy could help monitor treatment response and relapse in cases in which multiple tissue biopsies are impossible or not recommended.

The challenge has been designing assays that are sufficiently sensitive to detect low levels of rare cfDNA cancer mutants among the much higher background levels of wild-type cfDNA in circulation.⁷ Consequently, most liquid biopsy approaches have focused on detecting circulating levels of a single high-frequency mutation in a single oncogene, for example, the V600E mutation in BRAF.⁸ That mutation is found in 31% of primary melanoma and 57% of metastatic melanoma tumors.

The Cancer Research UK team, led by James Brenton and Nitzan Rosenfeld, hypothesized that it might be possible to harness the sensitivity of second-generation DNA sequencing to develop a liquid biopsy platform that detected both abundant and rare cancer mutations in the cfDNA of patients with cancer.

Brenton is a researcher in the Functional Genomics of Ovarian Cancer Laboratory at Cancer Research UK's **Cambridge Research Institute**. Rosenfeld is a researcher in the Molecular and Computational Diagnostics Laboratory at the Cambridge Research Institute.

The team first developed a method called tagged-amplicon deep sequencing (TAM-Seq), which allowed for the two-step amplification and deep sequencing of genomic regions spanning thousands of DNA base pairs. The group then designed a set of 48 primers to amplify genomic sequences covering the exons of several oncogenes, including p53, PTEN (MMAC1; TEP1), epidermal growth factor receptor (EGFR), BRAF, K-Ras and PI3K.

To validate the method, the team used TAM-Seq and the primers to amplify and sequence DNA extracted from 47 ovarian tumor samples and compared the results with data from first-generation Sanger sequencing. TAM-Seq identified 43 mutations, whereas Sanger sequencing identified 40 mutations.



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TAm-Seq was next used to identify mutations in the cDNA of patients with high-grade serous ovarian cancer (HGSOC), which is strongly associated with *p53* mutations.⁹ In two cohorts totaling 44 patients with HGSOC, TAm-Seq identified *p53* mutations at frequencies varying from 4%–54%, and in one patient identified an additional mutation in *EGFR*. The frequencies were confirmed by digital PCR.

TAm-Seq was then applied to three potential clinical scenarios.

First, TAm-Seq monitored the frequencies of circulating *p53* mutants in two patients with relapsed HGSOC during treatment and follow-up. In those patients, the *p53*-mutant frequencies reflected the clinical course of disease, showing decreases during treatment and increases paralleling disease progression.

Next, TAm-Seq monitored 10 mutations in a single patient with metastatic breast cancer over the course of 497 days before and after treatment. All 10 mutations showed a common decline in frequency at the start of therapy and increases in frequency after termination of therapy.

Finally, TAm-Seq analyzed samples from a patient with two primary cancers—bowel and ovarian. In tissue collected at surgical resection, both ovarian cancer- and colorectal cancer-associated mutations were detected. When a pelvic mass of uncertain origin was identified five years later, only the ovarian cancer-associated mutations were detected in the plasma, showing that TAm-Seq was robust enough to identify which cancer type was responsible for the relapse.

The results were published in *Science Translational Medicine*.

More validation in more patients

The accuracy and sensitivity of TAm-Seq now need to be validated against established platforms and assessed in a wider population of patients with cancer.

“Second-generation deep sequencing methods like the one developed for the liquid biopsy need to be routinely validated against one or more independent platforms to rigorously determine their rates of false positives and false negatives,” said Charles Cantor, CSO of **Sequenom Inc.**

“In this case, an ideal independent platform might be mass spectrometry, which can be multiplexed much the same way second-generation sequencing methods are,” said Cantor. “While the authors do a fine job using digital PCR to validate their method in the paper, that may not be the best choice of validation platform moving forward since it does not multiplex well and may have difficulty validating many mutations efficiently.”

Sequenom’s SEQuEreDx platform detects and analyzes cell-free fetal nucleic acids in the mother’s serum to prenatally diagnose chromosomal abnormalities associated with genetic disorders such as Down syndrome.¹⁰

“Second-generation deep sequencing methods like the one developed for the liquid biopsy need to be routinely validated against one or more independent platforms to rigorously determine their rates of false positives and false negatives.”

—Charles Cantor, Sequenom Inc.

Cantor also thinks improving the sensitivity of TAm-Seq will be necessary to ensure broad clinical applicability. “In the paper, they detect mutations down to about a 2% frequency. However, many clinically relevant diagnostic mutations occur orders of magnitude below that. For example, in some leukemias, a clinically actionable mutation can occur at a rate of 1 in 1,000,” he said.

Even in ovarian cancer, Stanley Kaye, professor of medical oncology at Cancer Research UK, had questions about applicability. He noted that the paper mainly addressed the high-grade serous subtype and its associated *p53* mutation. “I would like to know if the method can detect clinically relevant mutations occurring in other ovarian cancers at lower frequencies than the *p53* mutation,” he said.

The researchers should now apply the liquid biopsy “to low-grade serous ovarian cancer, which is associated with *BRAF*/*NRAS* mutations, as well as endometrioid and clear cell ovarian cancers, which are associated with mutations in the *AKT*/*PI3K* pathway,” said Kaye.

Kaye was not an author on the paper. In 2011, Kaye and colleagues published data in *Gynecologic Oncology* showing that high levels of detectable circulating tumor cells were associated with risk for disease progression and death in patients with relapsed ovarian cancer.¹¹

However, Kaye noted that “on average there are too few detectable circulating tumor cells in ovarian cancer using the current technology to make it a promising prognostic approach. We are now studying circulating tumor cells in breast and prostate cancer, where their numbers are greater than in ovarian cancer.”

Analysis of circulating tumor cells and circulating cell-free DNA “provide different indications of what is occurring in cancer patients,” said David Hoon. “Circulating tumor cells measure the actual metastatic spreading by the tumor, whereas cell-free DNA cannot always be interpreted that way.”

Nonetheless, combining analyses of circulating tumor cells and circulating cell-free DNA could have synergistic value in predicting disease outcome, said Hoon, who is chief of scientific intelligence and director of molecular oncology at the **John Wayne Cancer Institute**. He is developing cell-free DNA-based diagnostics for melanoma and breast, prostate and other cancers.^{8,12,13}

In 2006, Hoon and colleagues published data in *Cancer Research* that melanoma patients with detectable levels of both circulating tumor cells and methylated cell-free DNA had a poorer response to therapy than patients who had detectable levels of only one of the markers.¹⁴

Getting real

“We are now moving our liquid biopsy into a real-world hospital setting,” Brenton told *SciBX*. “We initially plan to use it early in the diagnostic

pathway, to diagnose low-bulk ovarian tumors prior to a pelvic scan. We will also use the liquid biopsy to monitor treatment response, and we plan to study mutations in other genes besides *p53*.”

Compared with tissue biopsy, the liquid biopsy has at least three advantages, said Brenton. “It’s noninvasive, it’s able to monitor multiple tumor-associated mutations through time without requiring serial tissue biopsies, and it’s relatively cheap.” He estimated a single liquid biopsy would cost around £20–£30 (\$31–\$47) compared with the £800–£1,000 (\$1,248–\$1,560) typically charged for a single tissue biopsy.

Kaye does not expect the team’s platform to replace conventional diagnostic biopsies. “However, the liquid biopsy could be very useful after the initial diagnosis, allowing the clinician to follow treatment response and disease progression without doing additional tissue biopsies,” he said.

Rosenfeld said the team will need to find a balance between breadth and depth of cancer genome coverage and speed of throughput.

The findings and the platform described in the paper are not covered by patents.

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COMPANIES AND INSTITUTIONS MENTIONED

Cambridge Research Institute, Cambridge, U.K.
Cancer Research UK, London, U.K.
John Wayne Cancer Institute, Santa Monica, Calif.
Sequenom Inc. (NASDAQ:SQNM), San Diego, Calif.

Pharma compounds at the crossroads

By Michael J. Haas, Senior Writer

The NIH's National Center for Advancing Translational Sciences (NCATS) has disclosed details about the first library of therapeutics in its Discovering New Therapeutic Uses for Existing Molecules program (see Table 1, "Repurposing pharma compounds"). The compounds provided by the program's eight pharma participants have completed at least Phase I testing but did not reach registration for that indication and

are available to researchers for experimentation. Although it is not yet clear how researchers will use the library, hints about potential therapeutic avenues can be gleaned from similar compounds in development and from highlights of translational research in the literature. A complete list of library compounds, compound data provided by the participating companies and details about the NIH/NCATS program are available on the agency's [website](#).

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COMPANIES AND INSTITUTIONS MENTIONED

National Center for Advancing Translational Sciences,
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National Institutes of Health, Bethesda, Md.

Table 1. Repurposing pharma compounds.

Source: BCIQ: BioCentury Online Intelligence; National Center for Advancing Translational Sciences (NCATS) [website](#)

Company	Compound	Mechanism	Original indication(s) ^A	In commercial development ^B	Literature-based indication(s) ^C
Sanofi (Euronext:SAN; NYSE:SNY)	Canosimibe (AVE5530)	Sterol O-acyltransferase (SOAT; ACAT) inhibitor	Phase III to treat hypercholesterolemia	1 to treat atherosclerosis	Alzheimer's disease (AD)
Pfizer Inc. (NYSE:PFE)	Senicapoc (PF-05416266; ICA-17043)	Potassium channel KCa3.1 (KCNN4) inhibitor	Phase IIa to treat asthma, sickle cell disease (SCD)	Not available	Inflammatory bowel disease (IBD), renal fibrosis
Abbott Laboratories (NYSE:ABT)	ABT-639	Calcium channel voltage- dependent T type- α 1H subunit (CACNA1H; Cav3.2) inhibitor	Phase II to treat diabetic neuropathic pain (DNP)	1 to treat neuropathic pain	Hypertension, obesity
Pfizer	Otenabant (CP- 945598)	Cannabinoid CB ₁ receptor (CNR1) antagonist	Phase III to treat obesity in type 2 diabetes	4 to treat diabetes, obesity, dyslipidemia, liver disease	Pain
Eli Lilly and Co. (NYSE:LLY)	LY2828630	Cannabinoid CB ₂ receptor (CNR2) agonist	Phase II to treat pain in osteoarthritis (OA)	6 to treat pain, IBD, autoimmune disease, inflammatory disease	Brain inflammation, cocaine addiction, bone marrow transplant (BMT)
AstraZeneca plc (LSE:AZN; NYSE:AZN)	AZD1981	Prostaglandin D ₂ receptor subtype DP2 antagonist	Phase II to treat asthma, chronic obstructive pulmonary disease (COPD)	8 to treat asthma, COPD, allergy, inflammation	Alopecia (prostaglandin D ₂ receptor (CRTH2; GPR44; CD294) subtype unspecified)
AstraZeneca Pfizer	AZD2423 PF-04136309	CC chemokine receptor 2 (CCR2; CD192) antagonist	Phase IIa to treat pain and COPD Phase II to treat HCV infection, pain in OA	4 to treat diabetes, diabetic neuropathy, HIV/AIDS, inflammatory disease	Metastatic breast cancer, AD
Pfizer	CE-326597	Cholecystokinin A receptor (CCKAR; CCK1R) agonist	Phase II to treat obesity in type 2 diabetes	1 to treat IBD	Hyperglycemia
Bristol-Myers Squibb Co. (NYSE:BMJ)	Pexacerfont (BMS-562086)	Corticotropin- releasing factor 1 (CRF1) antagonist	Phase II to treat major depressive disorder (MDD), generalized anxiety disorder (GAD), irritable bowel syndrome (IBS)	2 to treat depression, post-traumatic stress disorder (PTSD), glioblastoma multiforme (GBM), breast cancer, colon cancer	AD
AstraZeneca	Zibotentan (ZD4054)	Endothelin A receptor antagonist	Phase III to treat castration-resistant prostate cancer (CRPC); Phase II to treat non-small cell lung cancer (NSCLC), ovarian cancer; Phase I to treat solid tumors	5 to treat prostate cancer, pulmonary arterial hypertension (PAH), renal disease, shock/trauma	SCD, tumor imaging

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Table 1. Repurposing pharma compounds (continued)

Company	Compound	Mechanism	Original indication(s) ^A	In commercial development ^B	Literature-based indication(s) ^C
Pfizer	Prinaberele (PF-00913086; ERB-041)	Estrogen receptor- β agonist	Phase II to treat endometriosis, rheumatoid arthritis (RA); Phase I to treat Crohn's disease	9 to treat menopause, pain, Parkinson's disease (PD), multiple sclerosis (MS), cancer, endocrine disease	Not available
Eli Lilly	LY500307		Phase II to treat lower urinary tract symptoms (LUTS) in benign prostatic hyperplasia (BPH)		
Sanofi	Riferminogene pectaplamid (temusi; NV1FGF; XRP0038)	Nonviral DNA plasmid encoding fibroblast growth factor 1 (FGF1)	Phase III to treat critical limb ischemia	6 to treat spinal cord injury (SCI), coronary artery disease (CAD), peripheral vascular disease (PVD), dermal ulcers, wounds, Huntington's disease (HD)	Diabetes, peripheral neuropathy
AstraZeneca	AZD7325	GABA _A receptor agonist	Phase IIa to treat GAD	16 to treat insomnia, seizures, epilepsy, cognitive impairment in both schizophrenia and AD	Not available
AstraZeneca	Lesogaberan (AZD3355)	GABA _B receptor agonist	Phase IIb to treat gastroesophageal reflux disease (GERD)	5 to treat incontinence, spasticity, autism, fragile X syndrome	Not available
Pfizer	PF-05190457	Ghrelin receptor (GHSR) antagonist	Phase I to treat type 2 diabetes	2 to treat obesity, diabetes	Alcohol dependence
AstraZeneca	AZD1656	Glucokinase (GCK; GK) activator	Phase IIb to treat type 2 diabetes	8 to treat diabetes	Not available
Bristol-Myers Squibb	BMS-820132		Phase I to treat type 2 diabetes		
Pfizer	PF-03463275	Glycine transporter type 1 (GlyT1; SLC6A9) inhibitor	Phase II to treat schizophrenia	4 to treat schizophrenia, cognitive dysfunction	Not available
Sanofi	Ataciguat (HMR1766)	Soluble guanylyl cyclase (sGC) activator	Phase II to treat peripheral artery disease (PAD), neuropathic pain, angina pectoris	2 to treat heart failure, hypertension	Attention deficit hyperactivity disorder (ADHD)
Abbott	ABT-288	Histamine H3 receptor (HRH3) antagonist	Phase II to treat cognitive impairment in both schizophrenia and AD	8 to treat cognitive dysfunction, AD, schizophrenia, narcolepsy, cataplexy, rhinitis, obesity	Not available
Pfizer	PF-03654746		Phase II to treat ADHD, narcolepsy, rhinitis; Phase I to treat cognitive impairment in both schizophrenia and AD		
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	GSK1004723	Dual HRH1 and HRH3 antagonist	Phase II to treat allergic rhinitis	19 to treat allergy, rhinitis, conjunctivitis, urticaria, insomnia, emesis	Malaria
GSK	GSK835726				
Pfizer	CE-210666	Serotonin (5-HT _{1B}) receptor antagonist	Phase III to treat MDD	7 to treat migraine, ADHD	Not available
Pfizer	Elzasonan (CP-448187)		Phase II to treat MDD		
Pfizer	Deramciclane (EGIS-3886; PH-670187)	Dual serotonin (5-HT _{2A}) receptor and serotonin (5-HT _{2C}) receptor antagonist	Phase III to treat GAD	6 to treat schizophrenia, psychosis, bipolar disorder, mania, depression, arterial thrombosis	Not available
			1 to treat OA	Post-SCI muscle spasticity	
Pfizer	PF-04995274	Serotonin (5-HT ₄) receptor agonist	Phase I to treat cognitive impairment in AD	12 to treat GERD, constipation, gastroparesis, IBS, gastrointestinal dysfunction, gastrointestinal motility disorder, cognitive dysfunction, AD	Not available
AstraZeneca	MEDI2338	IL-18 inhibitor	Phase I to treat COPD	1 to treat metabolic syndrome	MS, neuropathic pain
Pfizer	PF-04191834	5-Lipoxygenase (ALOX5; 5-LO) inhibitor	Phase II to treat asthma, pain in OA	1 to treat asthma	Inflammation, chronic myelogenous leukemia (CML)

(Continues on p. 6)

Table 1. Repurposing pharma compounds (continued)

Company	Compound	Mechanism	Original indication(s) ^A	In commercial development ^B	Literature-based indication(s) ^C
Pfizer	SD-7300 (SC-81490)	Inhibitor of matrix metalloproteinase 2 (MMP2), MMP9 and MMP13	Phase I to treat myocardial infarction (MI), OA	Not available	Cancer, congestive heart failure (CHF), thrombosis, OA, neuropathic pain, acute myelogenous leukemia (AML), tuberculosis (TB), vaginal prolapse
AstraZeneca	AZD1236	Dual MMP9 and MMP12 inhibitor	Phase IIa to treat COPD	1 to treat COPD, MS, liver fibrosis	Asthma, emphysema, bacterial infection
Bristol-Myers Squibb	BMS-830216	Melanin-concentrating hormone receptor 1 (MCHR1; GPR24) antagonist	Phase I/II to treat obesity	Not available	IBD
AstraZeneca	AZD5904	Myeloperoxidase (MPO) inhibitor	Phase I to treat COPD and MS	1 to treat PD	Atrial fibrillation (AF)
Abbott	ABT-089	Nicotinic acetylcholine receptor $\alpha_4\beta_2$ agonist	Phase II to treat ADHD, AD	2 to treat AD, ADHD	Not available
AstraZeneca	AZD0328	Nicotinic acetylcholine receptor α_7 (CHRNA7) agonist	Phase IIa to treat cognitive impairment in schizophrenia	3 to treat ADHD, AD, schizophrenia, cognitive dysfunction	Epilepsy, brain damage associated with cardiac arrest/stroke
Johnson & Johnson (NYSE:JNJ)	JNJ-39393406		Phase I to treat AD, cognitive impairment in schizophrenia		
GSK	GW274150	Inducible nitric oxide synthase 2 (NOS2; iNOS) inhibitor	Phase II to treat RA, migraine; Phase I to treat asthma	3 to treat neuropathic pain, postherpetic neuralgia (PHN), mucositis	Brain cancer, arthritis, inflammation, genetic association with psoriasis
Pfizer	SD-6010 (SC-84250)		Phase III to treat pain in OA, asthma		
AstraZeneca	AZD7268	Opioid receptor δ_1 (OPRD1; DOR) agonist	Phase II to treat MDD	1 to treat pain in OA	Not available
Sanofi	AVE8134	Peroxisome proliferation-activated receptor- α (PPAR α ; PPAR α) agonist	Phase II to treat type 2 diabetes	13 to treat diabetes, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, metabolic syndrome, cardiovascular disease	Not available
Sanofi	AVE0847	Dual PPAR α and PPAR γ (PPAR γ) agonist	Phase I to treat type 2 diabetes	6 to treat diabetes, dyslipidemia, AD,	Not available cardiovascular disease
Pfizer	PF-05019702 (PRA-27)	Progesterone receptor antagonist	Phase I to treat endometriosis	1 to treat depression, Cushing's disease	Not available
AstraZeneca	AZD9056	Purinergic receptor P2X ligand-gated ion channel 7 (P2RX7; P2X7) antagonist	Phase II to treat COPD, RA, Crohn's disease	5 to treat pain, RA, OA, MS	Cancer, MI, heart failure, arterial thrombosis, graft-versus-host disease (GvHD), SCI, PD, neuroinflammatory diseases
Eli Lilly	LY2245461	Selective estrogen receptor modulator (SERM)	Phase unknown, to treat hot flashes in postmenopausal women	10 to treat osteoporosis, menopause, androgen deficiency, hypogonadism, breast cancer, pain	Cervical cancer

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Table 1. Repurposing pharma compounds (continued)

Company	Compound	Mechanism	Original indication(s) ^A	In commercial development ^B	Literature-based indication(s) ^C
Sanofi	SAR115740	Transient receptor potential vanilloid 1 (TRPV1; VR1) antagonist	Phase I to treat acute and chronic pain	7 to treat pain, itch, rhinitis, incontinence	Not available
AstraZeneca	Recentin cediranib (AZD2171)	Inhibitor of VEGF receptor 1 (FLT1; VEGFR-1), VEGFR-2 (KDR/Flk-1) and VEGFR-3 (FLT4)	Phase II or III to treat multiple solid tumor types	4 to treat multiple solid tumors, lymphoma, sarcoma, age-related macular degeneration (AMD)	Not available

^ADenotes the disease indication(s) in which the company has already tested the compound in the clinic; in most cases, the company discontinued development of the compound because of lack of efficacy, failure to meet trial endpoint(s) or for undisclosed reasons. ^BDenotes the number of compounds with the same mechanism of action that at least one company has or had in preclinical and/or clinical development to treat the listed indication(s). ^CDenotes additional disease indications in which a compound with the same mechanism of action could have efficacy, based on preclinical results reported in selected scientific literature.



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Fragmentary progress in endometriosis

By Michael J. Haas, Senior Writer

A team from the **Baylor College of Medicine** has treated endometriosis in mice by blocking a pathway that produces a fragment of nuclear receptor coactivator 1 in endometrial tissue.¹ Now, small molecule inhibitors are needed to elucidate the fragment's precise role in endometriosis and determine whether other pathway components are potential disease targets as well.

Endometriosis affects about 10% of women of reproductive age and involves the ectopic growth of tissue from the uterine lining (endometrium) in the peritoneal cavity, resulting in pelvic pain, infertility and other symptoms. The underlying pathogenesis of the disease is not well understood. What is known is that endometriotic lesions produce high levels of estrogen that enable growth of the lesion.

As a result most therapies reduce levels of estradiol and other estrogens. Treatments include GnRH/LHRH receptor-targeting compounds, aromatase inhibitors or contraceptives that can only halt—not reverse—lesion growth and may not completely control pain. Additionally, these therapies can have side effects such as cognitive deficits, hirsutism (excessive hairiness), the inability to conceive and an increased risk of osteoporosis.

Previous studies have shown that levels of nuclear receptor coactivator 1 (NCOA1; SRC1) were lower in patients' endometriotic tissue than in their normal endometrial tissue. However, the studies did not investigate whether the protein actually played a role in the disease.^{2,3}

Thus, the Baylor College of Medicine team decided to take a closer look at whether SRC1 might be a therapeutic target to treat endometriosis.

The group began by confirming that endometriotic tissues from patients and mouse models of the indication had lower levels of intact (160 kDa) SRC1 than normal endometrial tissues. In doing so, the team found endometriotic tissue from patients and models had higher levels of a 70 kDa, C-terminal fragment of SRC1.

In human endometrial cell lines, overexpression of the SRC1 fragment induced greater invasiveness than overexpression of full-length SRC1 by promoting epithelial-mesenchymal transition (EMT). The fragment also enabled the cell lines to evade normal caspase-mediated apoptosis that is triggered by the proinflammatory cytokine tumor necrosis factor- α (TNF- α) and occurs in endometrial cells during menstruation.

Additional studies in endometrial and endometriotic tissue from the mouse models showed that Tnf- α upregulated matrix metalloproteinase 9 (Mmp9), which in turn cleaved full-length Src1 to produce the fragment (see Figure 1, "SRC1 fragments on the endometriotic pathway").

Lastly, the team showed that mice deficient in *Tnf- α* , *Mmp9* or *Src1* had endometriotic lesions that were up to five times smaller than lesions

in wild-type control models.

In its report in *Nature Medicine*,¹ the team noted that the role of the TNF- α -MMP9-SRC1 fragment pathway in endometriosis agreed with a host of previous studies. These included papers that described an association between high peritoneal levels of TNF- α and endometriosis progression in patients,⁴ showed a treatment effect for anti-TNF- α antibodies in rat⁵ and baboon⁶ models of the disease, and found higher levels of MMPs in invasive endometriotic cells than in normal endometrial cells from patients and chicken models.^{7,8}

Trial and trial again?

Of the three proteins in the pathway, the SRC1 fragment is the logical therapeutic target, team leader Bert O'Malley told *SciBX*.

"Drugs that inhibit TNF- α are already available, but their immunosuppressive activity has severe side effects, such as increased risk of pneumonia, tuberculosis and—worst of all—cancer, while inhibiting MMP9 can also have musculoskeletal and many other side effects," he said.

O'Malley is professor and chair of molecular and cellular biology at the Baylor College of Medicine.

Other endometriosis researchers agreed that the potential side effects of MMP9 inhibition ruled out the proteinase as an endometriosis target. Opinions were mixed on whether TNF- α or the SRC1 fragment will be the better therapeutic target.

Thomas D'Hooghe, coordinator of the Leuven University Fertility Center at **University Hospitals Leuven** and leader of the baboon model study, said the findings in the new paper actually bolster the case for TNF- α as a therapeutic target in endometriosis. "TNF- α inhibitors should be explored in a relevant clinical study, since all nonhuman primate studies suggest a treatment effect for them," he said.

D'Hooghe is also professor of medicine at **Catholic University Leuven** and adjunct professor of medicine at **Yale University**.

Thomas Collet, president and CEO of **Meditrina Pharmaceuticals Inc.**, cautioned that anti-TNF- α therapy already has failed in at least one clinical trial to treat the disease.

In 2008, researchers from University Hospitals Leuven, the **University of Oxford** and **Johnson & Johnson's** Centocor Inc. unit reported that Remicade infliximab, the pharma's chimeric mAb against TNF- α , failed to reduce pain and lesion growth in a Phase II trial to treat endometriosis.⁹

D'Hooghe countered that patients in the infliximab trial "were those awaiting surgery for fibrotic, deeply invasive endometriotic nodules. We know that drug therapy has only limited success in such patients and that surgery is the best option for them." Thus, it was not surprising that infliximab failed to have an effect in this population, he said.

Instead, he wanted to see anti-TNF- α antibodies tested "in women with peritoneal endometriosis, who may have some small growths on their ovaries and a significant inflammatory phenotype" but less severe

"TNF- α inhibitors should be explored in a relevant clinical study, since all nonhuman primate studies suggest a treatment effect for them."

**— Thomas D'Hooghe,
University Hospitals Leuven**

Four TNF- α inhibitors are marketed to treat rheumatoid arthritis (RA), Crohn's disease, inflammatory bowel disease (IBD), psoriasis, ankylosing spondylitis and/or other autoimmune diseases: Humira adalimumab, a human mAb against TNF- α from **Abbott Laboratories** (NYSE:ABT) and **Eisai Co. Ltd.** (Tokyo:4523; Osaka:4523); Enbrel etanercept, a recombinant p75 TNF receptor linked to the Fc portion of human IgG1 (TNFR:Fc) from **Amgen Inc.** (NASDAQ:AMGN), **Pfizer Inc.** (NYSE:PFE) and **Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502); Remicade infliximab, a chimeric mAb against TNF- α from **Johnson & Johnson** (NYSE:JNJ), **Merck & Co. Inc.** (NYSE:MRK) and **Mitsubishi Tanabe Pharma Corp.** (Tokyo:4508; Osaka:4508); and Cimzia certolizumab pegol, a pegylated humanized antibody fragment against TNF- α from **UCB Group** (Euronext:UBC) and **Astellas Pharma Inc.** (Tokyo:4503).

Additionally, Johnson & Johnson markets Remicade to treat Behçet's disease and spinal cord injury (SCI); and **Marnac Inc.**, **Ildong Pharmaceutical Co. Ltd.**, **InterMune Inc.** (NASDAQ:ITMN) and **Shionogi & Co. Ltd.** (Tokyo:4507; Osaka:4507) market Esbriet pirfenidone, a small molecule inhibitor of proinflammatory cytokines such as TNF- α and profibrotic cytokines, to treat pulmonary fibrosis.

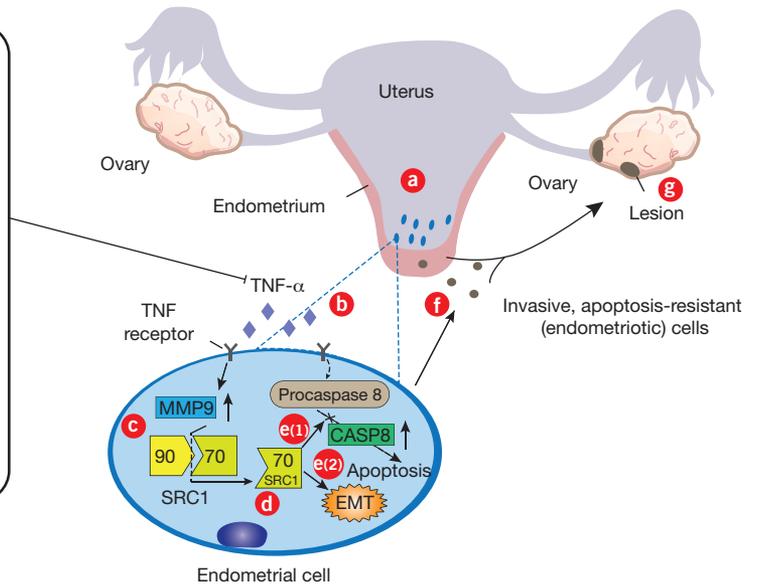


Figure 1. SRC1 fragments on the endometriotic pathway. According to a study in *Nature Medicine*, inhibition of a pathway that produces a fragment of nuclear receptor coactivator 1 (NCOA1; SRC1) in endometrial (uterine lining) cells could help treat endometriosis.

During menstruation, cells shed from the endometrium [a] can respond to local increases in tumor necrosis factor- α (TNF- α) [b] by upregulating matrix metalloproteinase 9 (MMP9) [c], which cleaves a 70 kDa, C-terminal fragment from full-length (160 kDa) SRC1 [d]. In turn, the fragment prevents TNF- α -induced activation of procaspase-8 to caspase-8 (CASP8; FLICE) [e(1)] and consequent apoptotic signaling, and it promotes the epithelial-mesenchymal transition (EMT) [e(2)] by an unknown mechanism, thereby inducing antiapoptotic and invasive phenotypes, respectively. These characteristics are the hallmarks of endometriotic cells [f] and enable them to form endometriotic lesions [g] on the ovaries and/or elsewhere in the peritoneum.

overall disease than the infliximab trial participants.

Eija Lundström, medical director at **Debiopharm Group**, agreed with O'Malley that TNF- α inhibitors were probably not ideal therapies for endometriosis.

Pamorelin LA triptorelin, a GnRH/LHRH receptor agonist from Debiopharm and **Galenica Ltd.**'s Vifor Pharma Ltd. unit, is approved to treat endometriosis, female infertility and advanced hormone-dependent prostate cancer.

"Anything that could target the lesions locally without suppressing estradiol production would be advantageous" over current estrogen-suppressing therapies, said James Symons, VP of clinical development at Meditrina.

Meditrina's MPI-676, an anastrozole-based aromatase inhibitor, is in Phase II testing to treat endometriosis.

J&J, **Merck & Co. Inc.** and **Mitsubishi Tanabe Pharma Corp.** market Remicade to treat rheumatoid arthritis (RA) and other autoimmune diseases. J&J also markets the antibody to treat Behçet's disease and spinal cord injury (SCI).

If the SRC1 fragment is deemed a better target than TNF- α , "it will be important to identify the intercellular partners of the SRC1 fragment" in addition to procaspase-8, said Michael Teifel, VP of preclinical development at **Aeterna Zentaris Inc.**'s Aeterna Zentaris GmbH unit. The reason, he said, is selective inhibition of the SRC1 fragment could block its antiapoptotic effects on endometrial cells but would not necessarily prevent it from promoting EMT.

Furthermore, the *Src1* knockout models used by the team cannot distinguish between the fragment's role in disease onset and disease

progression, said Joachim Fensterle, director of translational medicine at Aeterna Zentaris GmbH. "Validation of the pathway as a target for established disease would require additional *in vivo* experiments, such as a model in which *Src1* could be conditionally knocked out or knocked down at different stages of disease," he said.

D'Hooghe added that he wants to see SRC1 fragment inhibitors tested in mouse and baboon models of endometriosis.

AEZS-115, a GnRH/LHRH receptor antagonist peptidomimetic from Aeterna Zentaris, is in preclinical development to treat endometriosis.

More broadly, Collet said any potential therapy to treat endometriosis has to account for the heterogeneity of the clinical presentation of the disease.

"For instance, while high estrogen levels are linked to disease progression, postmenopausal women can present with endometriosis" despite having lower estrogen levels than premenopausal women, which suggests several etiologies may contribute to disease onset or progression, he said.

"Also, pain symptoms don't necessarily correlate with the size or the site of the lesion" but instead result from variability between individual patients and their pain experiences, Symons said.

"The key question is whether the findings reported in *Nature Medicine* could apply to all patients," Collet said.

O'Malley said his team has already conducted screens and identified inhibitors of the SRC1 fragment. The researchers plan to test the molecules in mice and potentially in monkey models.

His team also is considering testing the inhibitors in combination with existing therapies to look for potential additive or synergistic effects.

“It is possible that inhibitors of the pathway identified by the *Nature Medicine* team could have an additive or synergistic effect in combination with other therapies” to treat endometriosis, noted Lundström.

Longer term, the team wants to run prospective studies in patients to determine how broad a role the SRC1 fragment plays in endometriosis and to begin looking for specific links between that disease and cancer.

O’Malley said endometriotic cells undergo EMT and exhibit invasiveness similar to that seen in early stage cancers, and statistical studies have shown that endometriosis predisposes women to ovarian, uterine, colon, breast and other cancers.

The relationship between endometriosis and cancer is still poorly understood, he said.

If future studies uncover mechanistic links between the two diseases, “I think physicians will have to treat women who have endometriosis with more than just long-term therapies that address symptoms of pain,” he said.

Baylor College of Medicine has applied for a patent covering the SRC1 fragment inhibitors, and the findings are available for partnering or licensing, he said.

Haas, M.J. *SciBX* 5(26); doi:10.1038/scibx.2012.670
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COMPANIES AND INSTITUTIONS MENTIONED

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Debiopharm Group, Lausanne, Switzerland
Galenica Ltd. (SIX:GALN), Bern, Switzerland
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Meditrina Pharmaceuticals Inc., Ann Arbor, Mich.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Mitsubishi Tanabe Pharma Corp. (Tokyo:4508; Osaka:4508), Osaka, Japan
University Hospitals Leuven, Leuven, Belgium
University of Oxford, Oxford, U.K.
Yale University, New Haven, Conn.

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Endostatin for fibrosis

By Lauren Martz, Staff Writer

University of Pittsburgh School of Medicine researchers have shown that a compound derived from endostatin prevented and reversed organ fibrosis in mice.¹ The findings may suggest a new use for endostatin, which is approved in China as an antiangiogenic agent to treat cancer.

Endostatin is a fragment of the C-terminus of collagen XVIII. In 1996, **EntreMed Inc.** began developing endostatin, and preclinical results showed the fragment inhibited endothelial cell proliferation and tumor growth.²

EntreMed took the compound into the clinic in 1999 but in 2004 discontinued the endostatin program during a Phase II trial due to their refocusing on small molecule cancer therapeutics. In 2004, EntreMed transferred rights to the peptide back to the original owner—**Boston Children's Hospital**—and to **Alchemgen Therapeutics Inc.**

Endostatin is approved in China, where **Simcere Pharmaceutical Group** markets a recombinant form of the peptide called Endostar to treat non-small cell lung cancer (NSCLC).

EntreMed declined to comment, and Simcere and Boston Children's Hospital did not respond to interview requests.

Now, a University of Pittsburgh team led by Carol Feghali-Bostwick has tested whether increasing levels of endostatin has a protective role in organ fibrosis. Feghali-Bostwick is associate professor of medicine and pathology.

The researchers built on previous papers from other groups that showed elevated levels of endostatin in the serum and bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis (IPF) or systemic sclerosis (SSc)-associated pulmonary fibrosis.^{3,4} However, in those studies it was unclear whether the high levels promoted fibrosis or served as a protective response against disease progression.

To determine whether endostatin was helping or aggravating fibrosis, Feghali-Bostwick's group used an *ex vivo* model of human skin fibrosis.

The researchers found that an intradermal injection of recombinant human endostatin prevented transforming growth factor- β (TGF β ; TGF β)-mediated increases in dermal thickness without affecting the thickness of normal skin.

Next, the team generated peptide fragments of endostatin to identify the region responsible for the antifibrotic effects and found that a section from endostatin's C-terminus had efficacy similar to that for the full-length peptide in the *ex vivo*

model. They modified the fragment to improve its serum stability and resistance to proteolytic degradation, calling the final peptide E4.

Feghali-Bostwick told *SciBX* that E4 has multiple advantages over the parent endostatin molecule, including stability and ease of manufacturing.

"What makes our peptide different is that it is shorter and less expensive to manufacture, and it has a modification at its carboxy terminal end that protects it from degradation and makes it more stable," she said.

In the *ex vivo* human skin model, injection of E4 during profibrotic TGF β administration prevented skin thickening. When E4 was given two days after TGF β , the peptide fragment decreased skin thickening compared with vehicle control.

In mouse models of dermal fibrosis induced by either TGF β or the chemotherapeutic bleomycin, E4 prevented fibrosis or decreased fibrosis compared with vehicle control. Similarly, in mouse models of bleomycin-induced pulmonary fibrosis, intratracheal or intraperitoneal administration of E4 prevented or reversed fibrosis.

Data were published in *Science Translational Medicine*.

"[E4] seems to exert antifibrotic activity even when given after fibrosis has started, whereas most other compounds and molecules are tested for their ability to prevent fibrosis," Feghali-Bostwick told *SciBX*. "The next steps are to conduct pharmacokinetic and toxicology studies."

Fibrosis company **Actelion Ltd.** said additional studies need to flesh out the precise mechanism by which E4 works. In addition, the company cautioned that animal models of fibrosis typically are acute, whereas human fibrosis is chronic and progressive.

Actelion's Macitentan, a tissue-targeting endothelin receptor antagonist, is in Phase II testing to treat pulmonary fibrosis. The compound is in Phase III testing to treat essential hypertension, pulmonary arterial hypertension (PAH) and pulmonary hypertension (PH).

But Feghali-Bostwick noted that her group has "tested the peptide in human skin to show that it would be effective in human tissues, whereas other molecules were tested in animal models only, usually in mice, and then failed in the clinic when used in humans."

The university has filed a patent application covering E4 and is interested in partnering with a company to explore sponsored research, optioning and licensing opportunities.

Martz, L. *SciBX* 5(26); doi:10.1038/scibx.2012.671
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Actelion Ltd. (SIX:ATLN), Allschwil, Switzerland
Alchemgen Therapeutics Inc., Houston, Texas
Boston Children's Hospital, Boston, Mass.
EntreMed Inc. (NASDAQ:ENMD), Rockville, Md.
Simcere Pharmaceutical Group (NYSE:SCR), Nanjing, China
University of Pittsburgh School of Medicine, Pittsburgh, Pa.

"[E4] seems to exert antifibrotic activity even when given after fibrosis has started, whereas most other compounds and molecules are tested for their ability to prevent fibrosis."

—Carol Feghali-Bostwick,
University of Pittsburgh

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 myelogenous leukemia (AML)	BCL2-like I1 apoptosis facilitator (BCL2L11; BIM)	A study in mice suggests a stapled BIM peptide could help treat AML. The stapled BIM peptide is a helical peptide from the Bcl2 homology domain (BH3) of BIM that is stabilized by a chemical cross-link. In a xenograft mouse model of human AML, the stapled BIM peptide alone or in combination with navitoclax significantly decreased tumor growth compared with vehicle. Next steps include developing stapled BIM peptide analogs with improved potency and testing them in hematologic and other cancers. Abbott Laboratories and Roche's Genentech Inc. have navitoclax (ABT-263), a pan-inhibitor of B cell lymphoma 2 (BCL-2; BCL2) family proteins, in Phase I/II testing in small cell lung cancer and Phase I testing in additional cancers. At least six additional companies have antagonists of BCL2 family members in development stages from preclinical to Phase II testing for cancer. SciBX 5(26); doi:10.1038/scibx.2012.672 Published online June 28, 2012	Patented; licensed to Aileron Therapeutics Inc.	LaBelle, J.L. <i>et al. J. Clin. Invest.</i> ; published online May 24, 2012; doi:10.1172/JCI46231 Contact: Loren D. Walensky, Dana-Farber Cancer Institute, Boston, Mass. e-mail: loren_walensky@dfci.harvard.edu
Cancer	Not applicable	<i>In vitro</i> and cell culture studies suggest electron-donor compounds could be useful adjuncts to improve cisplatin therapy for cancer. <i>In vitro</i> , the electron-donor compound <i>N,N,N',N'</i> -tetramethyl- <i>p</i> -phenylenediamine (TMPD) increased DNA damage caused by cisplatin compared with vehicle. In HeLa cells and ovarian tumor cells, TMPD in combination with cisplatin decreased cell viability compared with cisplatin treatment alone. Next steps include <i>in vivo</i> testing of TMPD in combination with cisplatin. SciBX 5(26); doi:10.1038/scibx.2012.673 Published online June 28, 2012	Patent pending; available for licensing	Luo, T. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 8, 2012; doi:10.1073/pnas.1203451109 Contact: Qing-Bin Lu, University of Waterloo, Waterloo, Ontario, Canada e-mail: qblu@uwaterloo.ca
Colorectal cancer	Lipoteichoic acid (LTA)	Mouse studies suggest LTA-deficient <i>Lactobacillus acidophilus</i> could help prevent formation of gastrointestinal polyps, which are precursors to colorectal cancer. In mice with gastrointestinal polyps, oral treatment with LTA-deficient <i>L. acidophilus</i> decreased the frequency of polyps in the colon and ileum compared with treatment using an LTA-expressing strain or vehicle. Next steps include identifying and purifying <i>L. acidophilus</i> surface proteins that could be responsible for the antipolyp effect. SciBX 5(26); doi:10.1038/scibx.2012.674 Published online June 28, 2012	Patent application filed; available for licensing from the University of Florida	Khazaie, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 11, 2012; doi:10.1073/pnas.1207230109 Contact: Mansour Mohamadzadeh, University of Florida, Gainesville, Fla. e-mail: m.zadeh@ufl.edu Contact: Todd R. Klaenhammer, North Carolina State University, Raleigh, N.C. e-mail: klaenhammer@ncsu.edu

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Colorectal cancer	Tumor necrosis factor receptor-associated factor 2 (TRAF2)	<p>Mouse and patient sample studies suggest inhibiting TRAF2 could help treat colon cancer. In samples from 40 patients, TRAF2 levels in tumor tissues were higher than those in matched normal tissue. In a mouse xenograft model of human colon cancer, small hairpin RNA against <i>Traf2</i> decreased tumor growth compared with control shRNA. Next steps include determining whether TRAF2 could be useful as a marker or therapeutic target in various cancers.</p> <p>SciBX 5(26); doi:10.1038/scibx.2012.675 Published online June 28, 2012</p>	Unpatented; available for licensing	<p>Peng, C. <i>et al. J. Biol. Chem.</i>; published online June 8, 2012; doi:10.1074/jbc.M112.359521 Contact: Zigang Dong, University of Minnesota, Austin, Minn. e-mail: zgdong@hi.umn.edu</p>
Lung cancer; breast cancer	Signal transducer and activator of transcription 3 (STAT3)	<p><i>In vitro</i>, cell culture and mouse studies identified orally available STAT3 inhibitors that could help treat lung and breast cancer. In cell culture, a lead compound bound to STAT3 with high affinity and inhibited its activation and decreased tumor growth compared with vehicle. In mouse xenograft models of lung and breast cancers, oral delivery of the compound decreased STAT3 activity and tumor growth compared with vehicle. Next steps include toxicology studies in animals.</p> <p>Otsuka Pharmaceutical Co. Ltd.'s small molecule STAT3 inhibitor, OPB-31121, is in Phase I testing for solid tumors. GLG Pharma LLC has three STAT3 inhibitors in preclinical development for cancer.</p> <p>SciBX 5(26); doi:10.1038/scibx.2012.676 Published online June 28, 2012</p>	Patent pending; available for licensing	<p>Zhang, X. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 23, 2012; doi:10.1073/pnas.1121606109 Contact: James Turkson, University of Hawaii Cancer Center, Honolulu, Hawaii e-mail: jturkson@cc.hawaii.edu</p>
Infectious disease				
Malaria	Not applicable	<p><i>In vitro</i> and mouse studies suggest pyrroloiminoquinones could help treat malaria. An <i>in vitro</i> screen identified two pyrroloiminoquinone analogs—tsitsikammamine C and makaluvamine G—from the marine sponge <i>Zyzya</i> sp. that inhibited growth of chloroquine-sensitive and chloroquine-resistant strains of <i>Plasmodium falciparum</i> at low nanomolar IC₅₀ values. In mice infected with <i>P. berghei</i>, makaluvamine G inhibited parasite growth by up to 48% and chloroquine inhibited growth by 35%. Future studies could include isolating or synthesizing sufficient tsitsikammamine C for <i>in vivo</i> efficacy and safety testing. The generic chloroquine is marketed to prevent and treat malaria.</p> <p>SciBX 5(26); doi:10.1038/scibx.2012.677 Published online June 28, 2012</p>	Patent and licensing status unavailable	<p>Davis, R.A. <i>et al. J. Med. Chem.</i>; published online June 11, 2012; doi:10.1021/jm3002795 Contact: Ronald J. Quinn, Griffith University, South Brisbane, Queensland, Australia e-mail: r.quinn@griffith.edu.au</p>
Pseudomonas	Extended-spectrum β-lactamase (ESBL); <i>Pseudomonas aeruginosa</i> OXA-28	<p>Bacterial cell culture studies suggest blocking the migration of a gene cassette in <i>P. aeruginosa</i> could help prevent antibiotic resistance. A ceftazidime-resistant clinical isolate of <i>P. aeruginosa</i> had higher levels of an OXA-28-containing gene cassette that encodes ESBL than its ceftazidime-sensitive parent strain. In the parent strain, transient treatment with the antibiotic metronidazole led to mobilization of the gene cassette and resistance to ceftazidime. Next steps include screening for compounds that block the mobilization of the gene cassette in response to metronidazole.</p> <p>GlaxoSmithKline plc markets Fortaz ceftazidime for bacterial infections. Sanofi markets Flagyl metronidazole to treat bacterial and parasitic infections.</p> <p>SciBX 5(26); doi:10.1038/scibx.2012.678 Published online June 28, 2012</p>	Unpatented; licensing status not applicable	<p>Hocquet, D. <i>et al. PLoS Pathog.</i>; published online June 14, 2012; doi:10.1371/journal.ppat.1002778 Contact: Samuel I. Miller, University of Washington, Seattle, Wash. e-mail: millersi@u.washington.edu Contact: Didier Mazel, Pasteur Institute, Paris, France e-mail: mazel@pasteur.fr</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Allergy; asthma; inflammatory disease	Prostaglandin D ₂ receptor (CRTH2; GPR44; CD294)	Rodent and sheep studies identified a diazine indole acetic acid-based CRTH2 antagonist that could help treat allergic inflammatory diseases such as asthma. In mouse models of contact hypersensitivity and dust mite allergy, the CRTH2 antagonist decreased ear swelling and airway inflammation compared with vehicle. In a sheep model of asthma, the CRTH2 antagonist lowered airway bronchoconstriction and airway hyperresponsiveness compared with vehicle. Next steps could include testing the lead CRTH2 inhibitor in additional animal models of allergic inflammatory diseases. At least eight companies have CRTH2 antagonists in Phase II testing or earlier to treat allergy, asthma and inflammation.	Patent application filed covering indole-based CRTH2 antagonists; licensing status unavailable	Kaila, N. <i>et al. J. Med. Chem.</i> ; published online May 31, 2012; doi:10.1021/jm300007n Contact: Neelu Kaila, Pfizer Worldwide Medicinal Chemistry, Cambridge, Mass. e-mail: neelu.kaila@pfizer.com
		SciBX 5(26); doi:10.1038/scibx.2012.679 Published online June 28, 2012		
Musculoskeletal disease				
Muscular dystrophy	Tripartite motif-containing 72 (TRIM72; MG53)	<i>In vitro</i> and mouse studies suggest MG53 could help treat Duchenne muscular dystrophy (DMD) and other indications involving damage to cellular membranes. In mouse skeletal muscle fibers damaged by UV laser, MG53 pretreatment increased membrane resealing and repair compared with pretreatment using a control protein. In mouse models of DMD, MG53 pretreatment decreased circulating markers of muscle damage compared with pretreatment using vehicle. Ongoing work includes testing MG53 in rodent and pig models of myocardial infarction (MI), which also involves damage to cellular membranes.	Patented; licensed to TRIM-edicine Inc.; available for partnering	Weisleder, N. <i>et al. Sci. Transl. Med.</i> ; published online June 20, 2012; doi:10.1126/scitranslmed.3003921 Contact: Noah Weisleder, Robert Wood Johnson Medical School, Piscataway, N.J. e-mail: noah.weisleder@umdnj.edu Contact: Jianjie Ma, same affiliation as above e-mail: maj2@umdnj.edu
		SciBX 5(26); doi:10.1038/scibx.2012.680 Published online June 28, 2012		
Neurology				
Epilepsy; seizures	MicroRNA-134 (miR-134)	Mouse studies suggest inhibiting miR-134 could help treat and prevent seizures. In mice, hippocampal neurons damaged by prolonged seizures had higher miR-134 levels than undamaged neurons. In mice, an antagomir against miR-134 decreased seizure activity and seizure-associated neuronal damage compared with a nontargeting antagomir. Next steps include developing an miR-134 inhibitor and evaluating it in additional animal seizure models.	Patent application filed covering inhibitors of miR-134 to treat or prevent seizure-related disorders and neurologic injuries; available for licensing from the Royal College of Surgeons in Ireland Contact: Gearóid Tuohy, Royal College of Surgeons in Ireland, Dublin, Ireland e-mail: gearoidtuohy@rcsi.ie	Jimenez-Mateos, E.M. <i>et al. Nat. Med.</i> ; published online June 10, 2012; doi:10.1038/nm.2834 Contact: David C. Henshall, Royal College of Surgeons in Ireland, Dublin, Ireland e-mail: dhenshall@rcsi.ie
		SciBX 5(26); doi:10.1038/scibx.2012.681 Published online June 28, 2012		
Neuroinflammation	Endothelial cell nitric oxide synthase 3 (NOS3; eNOS); VEGF-A	Mouse studies suggest antagonizing eNOS or VEGF-A could help prevent neuroinflammation. In a mouse model of neuroinflammation, Vegf-a knockout in astrocytes resulted in increased blood brain barrier integrity and decreased eNos activity and lymphocyte infiltration of the brain compared with wild-type Vegf-a expression. Mice treated with a generic eNOS inhibitor had lower neuroinflammation than mice given vehicle. Next steps include developing brain-penetrant VEGF-A and eNOS antagonists.	Patent pending for use of eNOS antagonists in neuroinflammation; available for licensing	Argaw, A.T. <i>et al. J. Clin. Invest.</i> ; published online June 1, 2012; doi:10.1172/JCI60842 Contact: Gareth R. John, Mount Sinai School of Medicine, New York, N.Y. e-mail: gareth.john@mssm.edu
		SciBX 5(26); doi:10.1038/scibx.2012.682 Published online June 28, 2012		

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pain	μ -Opioid receptor (OPRM1; MOR)	Rat studies identified an orally active glycosylated endomorphin-1 that could help treat pain. In a rat model of chronic constriction injury, the compound caused dose-dependent decreases in pain sensitivity compared with vehicle. In the same model, the compound's analgesic effect was comparable to that of morphine without the latter's constipation side effects. Next steps could include testing the compound in large animal models of pain. SciBX 5(26); doi:10.1038/scibx.2012.683 Published online June 28, 2012	Patent and licensing status unavailable	Varamini, P. <i>et al. J. Med. Chem.</i> ; published online June 8, 2012; doi:10.1021/jm300418d Contact: Istvan Toth, The University of Queensland, Brisbane, Queensland, Australia e-mail: i.toth@uq.edu.au
Parkinson's disease (PD); Huntington's disease (HD)	Sirtuin 2 (SIRT2)	A SAR study identified SIRT2 inhibitors that could be useful for treating PD and HD. Screening of a 2-anilinobenzamide compound library identified two leads that inhibited SIRT2 <i>in vitro</i> and in cell culture more potently and selectively than a previously reported reference compound. Next steps include evaluating the lead compounds in animal models. Indus Biotech Pte. Ltd. has the SIRT2 inhibitors INDUS815B and INDUS815C in preclinical development for PD and HD, respectively. Elixir Pharmaceuticals Inc. and Siena Biotech S.p.A. have EX-527, an inhibitor of the related enzyme SIRT1, in Phase I testing for HD. SciBX 5(26); doi:10.1038/scibx.2012.684 Published online June 28, 2012	Unpatented; licensing status not applicable	Suzuki, T. <i>et al. J. Med. Chem.</i> ; published online May 29, 2012; doi:10.1021/jm3002108 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
Spinal and bulbar muscular atrophy (SBMA)	MicroRNA-196a (miR-196a)	Studies in cell culture and in mice suggest viral delivery of miR-196a could help treat SBMA. In cell culture, an adeno-associated virus (AAV) vector bearing transgenic miR-196a, compared with an empty control vector, decreased expression of the polyglutamine-expanded mutant version of androgen receptor, which causes SBMA. In a mouse model of SBMA, peripheral injection of an miR-196a-expressing AAV vector improved gait and increased body weight and survival compared with injection of a nonspecific miRNA-expressing AAV vector. Next steps include optimizing a dosing and delivery route for the virus in a mouse model. SciBX 5(26); doi:10.1038/scibx.2012.685 Published online June 28, 2012	Patent pending; available for licensing	Miyakazi, Y. <i>et al. Nat. Med.</i> ; published online June 3, 2012; doi:10.1038/nm.2791 Contact: Gen Sobue, Nagoya University Graduate School of Medicine, Nagoya, Japan e-mail: sobueg@med.nagoya-u.ac.jp

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			
Computational strategy for predicting drug activity on side-effect targets	A computational strategy for predicting a compound's activity against targets associated with side effects could aid the design of drugs with reduced adverse effects. The strategy uses a computational methodology called the similarity ensemble approach, which predicts where a molecule will bind its target based on how similar that molecule's chemical features are to features of known ligands of the target. The strategy was used to predict the ability of 656 drugs to bind to 73 targets associated with drug adverse reactions. In the study, 48% of the predicted drug-target associations were confirmed using a chemical database or follow-up experimental assays. Next steps include using the computational strategy to help identify new therapeutic indications for existing drugs and to predict adverse effects.	Algorithmic methods underlying approach unpatented; software using the method protected by trademark and copyright; software available for licensing from SeaChange Pharmaceuticals Inc.	Lounkine, E. <i>et al. Nature</i> ; published online June 10, 2012; doi:10.1038/nature11159 Contact: Brian K. Shoichet, University of California, San Francisco, Calif. e-mail: bshoichet@gmail.com Contact: Laszlo Urban, Novartis Institutes for BioMedical Research, Boston, Mass. e-mail: laszlo.urban@novartis.com
	SciBX 5(26); doi:10.1038/scibx.2012.686 Published online June 28, 2012		
Noninvasive whole-genome sequencing of a fetus	Noninvasive whole-genome sequencing of two mother-father-child cohorts suggests the method could be useful as a prenatal genetics diagnostic. Genome sequencing and genomewide haplotyping of parental DNA obtained from blood and deep sequencing of fetal DNA from maternal plasma were combined to noninvasively determine the genome sequence of one human fetus at about 19 weeks of gestation and another at about 8 weeks of gestation. In one fetus, inheritance was predicted at 2.8×10^6 parental sites with 98.1% accuracy, and 39 of 44 point mutations were detected. In the other fetus, inheritance was predicted at maternal-only sites with 95.7% accuracy. Next steps include improving the scalability and accuracy of the method.	Patent and licensing status undisclosed	Kitzman, J.O. <i>et al. Sci. Transl. Med.</i> ; published online June 6, 2012; doi:10.1126/scitranslmed.3004323 Contact: Jay Shendure, University of Washington, Seattle, Wash. e-mail: shendure@uw.edu Contact: Jacob O. Kitman, same affiliation as above e-mail: kitz@uw.edu
	SciBX 5(26); doi:10.1038/scibx.2012.687 Published online June 28, 2012		
Chemistry			
Synthesis of small molecule phosphoserine mimetic prodrugs that could inhibit protein-protein interactions	A method to synthesize small molecule prodrugs could be useful for generating compounds that block disease-associated protein-protein interactions. A multistep synthesis process generated a phosphoserine mimetic prodrug. In a human leukemia cell line, the prodrug inhibited growth with an IC_{50} of 5 μ M. An <i>in vitro</i> assay showed that the compound worked by inhibiting the activity of 14-3-3 proteins on forkhead box O (FOXO) transcription factors. Next steps include developing more potent and selective compounds.	Patent application filed covering undisclosed indications; available for licensing from the Purdue Research Foundation Contact: Thomas Hutton, Purdue Research Foundation, West Lafayette, Ind. phone: 765-588-3486 e-mail: tkhutton@prf.org	Arrendale, A. <i>et al. Chem. Biol.</i> ; published online June 22, 2012; doi:10.1016/j.chembiol.2012.05.011 Contact: Richard F. Borch, Purdue University, West Lafayette, Ind. e-mail: borch@purdue.edu
	SciBX 5(26); doi:10.1038/scibx.2012.688 Published online June 28, 2012		
Disease models			
Double infection for genetic dissection of motor neuron circuits in nonhuman primates	Simultaneous delivery of two gene vectors to the brain could help map motor neuron circuits and be useful for developing nonhuman primate models of neurological diseases. The technique involved injection of a lentiviral vector encoding a tetanus neurotoxin light chain and injection of an adeno-associated viral (AAV) vector encoding a variant of a reverse tetracycline transactivator. In nonhuman primates receiving injections of the two vectors into different parts of a motor neuron circuit, expression of vector-encoded genes inhibited the pathway and led to reversible impairment of arm reaching and grasping movements. Next steps include using the method to study additional neural circuits in animal models.	Patent application filed covering lentiviral vector; available for licensing from the Japan Science and Technology Agency	Kinoshita, M. <i>et al. Nature</i> ; published online June 17, 2012; doi:10.1038/nature11206 Contact: Tasashi Isa, National Institute for Physiological Sciences, Okazaki, Japan e-mail: tisa@nips.ac.jp
	SciBX 5(26); doi:10.1038/scibx.2012.689 Published online June 28, 2012		

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
Polymer nanoparticles for delivering polymerized therapeutic small interfering RNA to tumors	Polymer nanoparticles loaded with polymerized siRNA molecules could help treat solid tumors. Thiolated glycol chitosan polymers and polymerized siRNA formed nanoparticles that had better uptake by a mouse melanoma cell line and greater <i>in vitro</i> stability than nanoparticles formed by chitosan polymers and monomeric siRNA. In mice with xenograft prostate tumors, nanoparticles loaded with polymerized anti-VEGF siRNA decreased tumor microvessel density and tumor growth compared with free polymerized VEGF siRNA or chitosan nanoparticles loaded with a polymerized scrambled control siRNA. Future studies could include testing additional polymerized siRNAs in animal models of cancer. SciBX 5(26); doi:10.1038/scibx.2012.690 Published online June 28, 2012	Patent and licensing status unavailable	Lee, S. <i>et al. Angew. Chem. Int. Ed.</i> ; published online June 13, 2012; doi:10.1002/anie.201201390 Contact: Ick Chan Kwon, Korea Institute of Science and Technology, Seoul, South Korea e-mail: ikwon@kist.re.kr Contact: Kwangmeyung Kim, same affiliation as above e-mail: kim@kist.re.kr
Polymeric glucocorticoid-containing micelles with tailored release kinetics for rheumatoid arthritis (RA)	Polymeric micelles containing glucocorticoids could be useful for treating RA. The micelles were prepared from block copolymers consisting of hydrophilic polyethylene glycol (PEG) and a polymer with temperature-dependent hydrophobic properties. In a mouse model of collagen antibody-induced arthritis, a single injection of dexamethasone-loaded polymeric micelles decreased disease severity compared with injection of unloaded micelles. The dexamethasone-loaded polymeric micelles also had a longer duration of effect than free dexamethasone. Next steps include conducting pharmacokinetic and pharmacodynamic studies to determine the mechanism of action and comparing the polymeric micelles with other drug delivery systems. Cristal Delivery B.V., a spin-off from Utrecht University, has three preclinical programs evaluating the polymeric nanoparticles for drug delivery. SciBX 5(26); doi:10.1038/scibx.2012.691 Published online June 28, 2012	Patent application filed; exclusively licensed to Cristal Delivery; available for licensing and/or co-development from Cristal Delivery	Crielaard, B.J. <i>et al. Angew. Chem. Int. Ed.</i> ; published online June 12, 2012; doi:10.1002/anie.201202713 Contact: Gert Storm, Utrecht University, Utrecht, the Netherlands e-mail: g.storm@uu.nl Contact: Twan Lammers, RWTH Aachen University, Aachen, Germany e-mail: tlammers@ukaachen.de
Drug platforms			
Cell-free circulating tumor DNA as a cancer diagnostic	A method to isolate, amplify and sequence tumor-derived circulating DNA fragments could help track cancer progression without requiring a biopsy. A high throughput deep-sequencing platform was adapted to amplify and sequence DNA fragments in blood samples from patients with ovarian cancer. In two cohorts of patients, the platform identified mutations in the <i>p53</i> gene associated with advanced ovarian cancer. The method also tracked treatment response and disease progression in 2 patients with ovarian cancer and detected 10 different mutations in a breast cancer patient. Next steps include validating and optimizing the platform for use in a hospital setting (<i>see Liquid biopsy, page 1</i>). SciBX 5(26); doi:10.1038/scibx.2012.692 Published online June 28, 2012	Unpatented; freely available to public	Forshew, T. <i>et al. Sci. Transl. Med.</i> ; published online May 30, 2012; doi:10.1126/scitranslmed.3003726 Contact: Nitzan Rosenfeld, Cambridge Research Institute, Cancer Research UK, Cambridge, U.K. e-mail: nitzan.rosenfeld@cancer.org.uk Contact: James D. Brenton, same affiliation as above e-mail: james.brenton@cancer.org.uk
Protocol for generating optic cups and storable neural retina from human embryonic stem cells (ESCs)	A protocol for generating optic cups and neural retina from human ESCs could increase the supply of tissue available for retinal transplant procedures. In cultured human ESCs, the protocol triggered the self-formation of 3D optic cup structures and retinal pigment epithelium. The optic cup structures contained neural retina tissues and were amenable to cryopreservation and thawing. Next steps include developing a protocol to transplant the ESC-derived retina into animal models and using the generated tissues as disease models. SciBX 5(26); doi:10.1038/scibx.2012.693 Published online June 28, 2012	Patent and licensing status undisclosed	Nakano, T. <i>et al. Cell Stem Cell</i> ; published online June 14, 2012; doi:10.1016/j.stem.2012.05.009 Contact: Yoshiki Sasai, RIKEN Center for Developmental Biology, Kobe, Japan e-mail: yoshikisasai@cdb.riken.jp

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