

## THIS WEEK

## ANALYSIS

## COVER STORY

**1 Rational approach to Xtandi resistance**

MSKCC researchers have identified a mutation in the androgen receptor that drives resistance to second-generation antiandrogen drugs such as Medivation's Xtandi. The team is testing a lead molecule that overcomes this resistance in mouse models for prostate cancer and is considering running a clinical trial.

## TRANSLATIONAL NOTES

**4 DREAM team**

The DREAM Project has teamed up with Sage Bionetworks and announced four open challenges in computational biology that tackle issues relevant to drug discovery and development. The publication of results from their first collaboration on improving breast cancer prognosis provides a case study for the approach.

**6 Structural guidance for malaria and TB**

The Structural Genomics Consortium, with grant support from the Bill & Melinda Gates Foundation, is spearheading a project to develop pharma-quality medicinal chemistry capabilities in malaria and tuberculosis. The plan is to develop therapeutic assets for product development by Medicines for Malaria Venture and the Global Alliance for TB Drug Development.

## TARGETS &amp; MECHANISMS

**8 AD vaccine redux**

Researchers at Harvard have teamed up with Mercia to design a next-generation Alzheimer's disease vaccine. The  $\beta$ -amyloid-targeted formulation features an adjuvant that promotes a beneficial anti-inflammatory response that the team hopes will enhance  $\beta$ -amyloid clearance without triggering neuroinflammation.

## THE DISTILLERY

**10 This week in therapeutics**

Reducing tumor growth with IQGAP1 inhibitors; treating human African trypanosomiasis with IARS inhibitors; preventing graft rejection with inhibitors of C3 and C5a; and more...

**14 This week in techniques**

Gene regulatory network mapping in late-onset AD; self-mineralizing viruses for improved efficacy and storage stability; colorectal cancer classification system that correlates cellular phenotype to clinical outcome; and more...

## INDEXES

**17 Company and institution index****17 Target and compound index**

# Rational approach to Xtandi resistance

By Kai-Jye Lou, Senior Writer

A group led by researchers at the **Memorial Sloan-Kettering Cancer Center** has identified a mutation in the androgen receptor that could drive resistance to second-generation antiandrogen drugs such as **Medivation Inc.**'s Xtandi enzalutamide. The team's subsequent rational drug design studies yielded a series of molecules that could overcome the resistance mechanism.<sup>1</sup>

The researchers now are testing their lead molecule in mouse xenograft models for prostate cancer. If the results are promising, MSKCC could consider running a clinical trial.

Antiandrogen drugs are one of the standard treatment options for prostate cancer, but many patients progress to castration-resistant disease in 12–18 months.<sup>2</sup> Acquired mutations in the androgen receptor (AR) are one of the key events that can cause resistance to antiandrogen drugs.<sup>3–5</sup>

Xtandi is a second-generation oral androgen receptor antagonist that received FDA approval in August 2012 to treat metastatic castration-resistant prostate cancer (CRPC) in patients who previously received docetaxel. Last month, the EMA's Committee for Medicinal Products for Human Use recommended approval of an MAA for Xtandi.

In the U.S., clinicians already are seeing patients whose tumors initially respond to Xtandi but then develop resistance.

"We wanted to know how this could happen," said Charles Sawyers, chair of the Human Oncology and Pathogenesis Program at MSKCC and an investigator at the **Howard Hughes Medical Institute**. "We suspected that mutations in the androgen receptor might be one mechanism and designed a screen to look specifically for them."

The researchers developed a mutagenesis screen to identify cells with mutations in AR that confer resistance to a particular drug. When applied to Xtandi, the screen implicated the F876L point mutation in AR as the dominant mutation that confers resistance to the drug.

In a series of validation studies using Xtandi-sensitive prostate cancer cell lines and mouse xenograft models, the researchers found that the F876L mutant AR could spontaneously emerge following prolonged

**"This work paves the way for the development of a new series of antiandrogens and further supports the case that the androgen receptor could remain a critical and valid target even in patients who have late-stage disease."**

—Jeffrey Hager,  
Aragon Pharmaceuticals Inc.

**EDITORIAL****Editor-in-Chief:** Karen Bernstein, Ph.D.**Managing Editor:** Gaspar Taroncher-Oldenburg, Ph.D.**Executive Editor:** Steve Edelson**Senior Editors:** Tracey Baas, Ph.D.; Amy Donner, Ph.D.; Simone Fishburn, Ph.D.**Writers:** Chris Cain, Ph.D.; Michael Flanagan; Tim Fulmer, Ph.D.;

Michael J. Haas; Stephen Hansen; Kai-Jye Lou; Lauren Martz;

Lev Osherovich, Ph.D.; Steve Usdin

**Research Director:** Walter Yang**Research Manager:** Kevin Lehnbeuter**Production Editors:** Brandy Cafarella; Carol Evangelista; Ivelisse Robles**Copy Editor:** Nicole DeGennaro**Editorial Assistant:** Mark Zipkin**Design:** Claudia Bentley; Miles DaviesFor inquiries, contact [editorial@scibx.com](mailto:editorial@scibx.com)**PUBLISHING****Publisher:** Peter Collins, Ph.D.**Associate Publishers:** Gaspar Taroncher-Oldenburg, Ph.D.; Eric Pierce**Marketing:** Sara Girard; Rosy Rogers**Technology:** Anthony Barrera; Julia Kulikova**Sales:** Ron Rabinowitz; Dean Sanderson; Tim Tulloch**OFFICES****BioCentury Publications, Inc.**San Francisco  
PO Box 1246  
San Carlos, CA 94070-1246  
T: +1 650 595 5333Chadds Ford  
223 Wilmington-West Chester Pike  
Chadds Ford, PA 19317  
T: +1 610 558 1873Chicago  
20 N. Wacker Drive, Suite 1465  
Chicago, IL 60606-2902  
T: +1 312 755 0798Oxford  
287 Banbury Road  
Oxford OX4 7JA  
United Kingdom  
T: +44 (0)18 6551 2184Washington, DC  
2008 Q Street, NW, Suite 100  
Washington, DC 20009  
T: +1 202 462 9582**Nature Publishing Group**New York  
75 Varick Street, 9th Floor  
New York, NY 10013-1917  
T: +1 212 726 9200London  
The Macmillan Building  
4 Crinan Street  
London N1 9XW  
United Kingdom  
T: +44 (0)20 7833 4000Tokyo  
Chiyoda Building 6F  
2-37 Ichigayatamachi  
Shinjuku-ku, Tokyo 162-0843  
Japan  
T: +81 3 3267 8751

SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchcoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

Copyright © 2013 Nature Publishing Group ALL RIGHTS RESERVED.

No part of the SciBX publication or website may be copied, reproduced, retransmitted, disseminated, sold, distributed, published, broadcast, circulated, commercially exploited or used to create derivative works without the written consent of the Publishers. Information provided by the SciBX publication and website is gathered from sources that the Publishers believe are reliable; however, the Publishers do not guarantee the accuracy, completeness, or timeliness of the information, nor do the Publishers make any warranties of any kind regarding the information. The contents of the SciBX publication and website are not intended as investment, business, tax or legal advice, and the Publishers are not responsible for any investment, business, tax or legal opinions cited therein.

exposure to Xtandi or ARN-509, a second-generation AR antagonist from **Aragon Pharmaceuticals Inc.** that is in Phase II testing for CRPC.

Xtandi and ARN-509 are both bisaryl-thiohydantoin AR antagonists. Sawyers co-discovered both molecules and is a cofounder of Aragon.

Follow-up structural modeling studies and *in vitro* assays showed that Xtandi and ARN-509 both antagonized wild-type AR but actually activated the F876L mutant receptor. Not surprisingly, both were ineffective at killing prostate cancer cells that expressed the mutant receptor.

Modeling studies suggested that modifications to the central B-ring structure in the Xtandi scaffold might restore antagonistic activity against F876L mutant AR.

The researchers used the insights gained from these assays and structural modeling studies to design and synthesize analogs from the Xtandi scaffold that have an additional cyclic hydrocarbon ring—dubbed the D-ring—attached to the molecule's central B-ring.

In prostate cancer cell lines, three of the resulting D-ring-substituted molecules from the series inhibited growth of prostate cancers that expressed the F876L mutant AR, whereas Xtandi did not.

Results were published in *eLife*. The MSKCC group collaborated with researchers at the **Toyota Technological Institute at Chicago** and **The University of Chicago** on the study.

“The key finding is the discovery of a mutation in AR that causes resistance to enzalutamide,” said Sawyers, the co-corresponding author. “Now that we know about it, we can start to look for it in patients. We also showed that certain chemical modifications can be made to enzalutamide that overcome the drug resistance.”

“This work paves the way for the development of a new series of antiandrogens and further supports the case that the androgen receptor

SciBX: Science–Business eXchange

*SciBX welcomes editorial queries,  
comments and press releases.*

To contact the editorial team at SciBX  
please e-mail [editorial@scibx.com](mailto:editorial@scibx.com)

could remain a critical and valid target even in patients who have late-stage disease,” said Jeffrey Hager, senior director of biology at Aragon. “The data from this study suggest that among the patients that progress after initially responding to enzalutamide or ARN-509, there exists a subset who have tumors that remain fully addicted to the androgen receptor.”

Hager said the findings also improve the field’s understanding of ligand-specific mutations in AR by providing insights on how such a mutation can affect the activity of a given class of antiandrogens and how to modify such molecules to circumvent the mutation. “The androgen receptor is known to acquire ligand-selective mutations that can flip a molecule from being an antagonist into an agonist,” he said.

Importantly, Hager added that such mutations do not typically impart agonist activity across all chemical classes of antiandrogens. Indeed, *in vitro* cellular assay data showed that structurally distinct first-generation AR antagonists such as Casodex bicalutamide and the generic hydroxyflutamide did not activate F876L mutant AR.

The assay also showed that mutant ARs activated by Casodex or hydroxyflutamide were not activated by Xtandi and ARN-509.

**AstraZeneca plc** markets Casodex to treat prostate cancer.

### Clinical occurrences

The next step is determining the relevance of the F876L mutation in a clinical setting.

“It will be important to determine whether the identified mutation is found in patients who are being treated with enzalutamide or ARN-509 and if so the frequency at which it occurs,” said Hager. “The latter will have a strong influence on how excited drug developers such as Aragon will be to develop compounds that can circumvent the resistance mutation.”

Hager added that any compounds that do block the mutant receptor could be accompanied by a companion diagnostic to identify patients who are most likely to respond and to guide treatment decisions. He also said it would be a good idea to do sequencing studies on tumor samples from patients receiving second-generation antiandrogens to determine if there are mutations in AR that can spontaneously arise in the clinic but not in preclinical models.

“For such mutations, one will then need to go back to preclinical

studies to elucidate how they affect the activity and function of the androgen receptor,” he told *SciBX*.

Aragon has an ongoing internal program focused on understanding potential resistance mechanisms against second-generation antiandrogens such as ARN-509 and Xtandi, which parallels the work of Sawyers’ group. Hager said the company is not disclosing additional details.

Meanwhile, Sawyers’ group at MSKCC is evaluating DR103, the lead D-ring-substituted AR antagonist identified from the study, in mouse xenograft models. “If the results from these studies look promising, we will consider scaling up for more preclinical testing and a possible clinical trial at MSKCC,” he told *SciBX*.

MSKCC has filed two provisional patent applications covering the AR mutation and the new chemical entities described in the *eLife* paper. MSKCC declined to disclose licensing details.

Medivation did not respond to requests for comment.

Lou, K.-J. *SciBX* 6(18); doi:10.1038/scibx.2013.429

Published online May 9, 2013

### REFERENCES

- Balbas, M.D. *et al. eLife*; published online April 9, 2013; doi:10.7554/eLife.00499  
**Contact:** Charles L. Sawyers, Memorial Sloan-Kettering Cancer Center, New York, N.Y.  
e-mail: [sawyersc@mskcc.org](mailto:sawyersc@mskcc.org)
- Contact:** Yang Shen, Toyota Technological Institute at Chicago, Chicago, Ill.  
e-mail: [yangshen@ttic.edu](mailto:yangshen@ttic.edu)
- Gulley, J. *et al. Clin. Adv. Hematol. Oncol.* **1**, 49–57 (2003)
- Brooke, G.N. & Bevan, C.L. *Curr. Genomics* **10**, 18–25 (2009)
- Feldman, B.J. & Feldman, D. *Nat. Rev. Cancer* **1**, 34–45 (2001)
- Shi, X.-B. *et al. Cancer Res.* **62**, 1496–1502 (2002)

### COMPANIES AND INSTITUTIONS MENTIONED

**Aragon Pharmaceuticals Inc.**, San Diego, Calif.

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

**European Medicines Agency**, London, U.K.

**Food and Drug Administration**, Silver Spring, Md.

**Howard Hughes Medical Institute**, Chevy Chase, Md.

**Medivation Inc.** (NASDAQ:MDVN), San Francisco, Calif.

**Memorial Sloan-Kettering Cancer Center**, New York, N.Y.

**Toyota Technological Institute at Chicago**, Chicago, Ill.

**The University of Chicago**, Chicago, Ill.

# DREAM team

By *Chris Cain, Senior Writer*

The **DREAM Project** has teamed up with **Sage Bionetworks** and announced four open challenges in computational biology that tackle issues relevant to drug discovery and development, including prediction of drug responses. The publication of results from their first collaboration on improving breast cancer prognosis provides a case study for the team's approach.<sup>1,2</sup>

DREAM—Dialogue on Reverse Engineering Assessment and Methods—was founded in 2006 by Gustavo Stolovitzky and Andrea Califano to organize open challenges aimed at improving computational biology. DREAM is sponsored by **Columbia University**, the **NIH**, **IBM Corp.** and **The New York Academy of Sciences**. Past challenges have tackled problems ranging from predicting drug sensitivity of cancer cell lines to modeling epitope-antibody interactions.

Stolovitzky is a manager of functional genomics and systems biology at IBM's computational biology center. Califano is a professor of systems biology and chief of the Division of Biomedical Informatics at Columbia.

DREAM has launched sets of three to five challenges each year for the past six years. Typically, the organization hosts an experimental data set and then asks computational biologists to generate a predictive model that can explain the data. For each challenge, researchers submit computational models to DREAM over a defined time period of a few months. The winning team(s) who develop the best-performing model

or models are then invited to an annual conference to discuss the results.

Last year, as part of the DREAM7 series of challenges, Stolovitzky said DREAM changed tack and partnered more closely with supportive organizations than it had in the past. DREAM launched three initiatives with partners—the DREAM Phil Bowen ALS Prediction Prize4Life Challenge to predict disease progression in amyotrophic lateral sclerosis (ALS), the **National Cancer Institute**–DREAM Drug Sensitivity Prediction Challenge to predict the response of cancer cell lines to a set of small molecules and the Sage Bionetworks–DREAM Breast Cancer Prognosis Challenge.

Unlike earlier challenges, the ALS challenge was run in collaboration with open-innovation company **InnoCentive Inc.**, whereas the breast cancer challenge was run on Sage's Synapse online platform. The challenges are now closed, and Stolovitzky said results from the National Cancer Institute and ALS challenges are being prepared for publication.

Stolovitzky said that as the breast cancer challenge progressed, “it was so clear that the vision and outlook for what we were doing was in sync. We had the know-how for operating these challenges, and they had a great software platform and engineering experience, so it was a good marriage.”

In particular, he said, Synapse allowed DREAM to achieve a long-standing goal of enabling independent researchers to share data in real time and reproduce each other's results. “The platform allows people to input their own algorithms and have everyone take a look at them. This allowed

us to accomplish shared goals such as ensuring the reproducibility of results and of how we score models,” he said.

Previously, some interaction among teams could take place through an online discussion forum while the challenges were active. The extent of this communication was limited, though, because no online interface existed for the teams to easily share the experimental methodology developed over the course of the challenge.

Stolovitzky told *SciBX* that the limited ability to share data was due to resource constraints. “It has to do with the history of how DREAM grew organically; it was sort of a garage effort at first. Once the idea got traction, we launched additional challenges but never got a complete set of funding agencies to fully support this outside of limited support for individual challenges. Because of this we didn't have an infrastructure to create a platform to enable collaboration.”

On February 19, DREAM announced it was joining with Sage to collaboratively run challenges using the Synapse platform going forward. Last month at the Sage Commons Congress in San Francisco, the first four challenges from the partners were announced as DREAM8 (*see Table 1*, “**Sage Bionetworks–DREAM Project spring 2013 challenges**”).

Although the challenges deal with diverse sources of data, Sage president, cofounder and director Stephen Friend said the framework upon which Synapse is built is adaptable.

“For the breast cancer challenge, we built the necessary tools into the system as the challenge got up and going in real time. For added functionality, such as dealing with proteomic data or imaging data, it requires little additional effort,” he said.

## Breast cancer pilot

The results from the breast cancer challenge provide a detailed example of how the future Sage-DREAM challenges will operate.<sup>1,2</sup> The goal of the challenge was to take available gene expression, copy number and clinical data and use computational modeling to develop an improved prediction methodology for breast cancer prognosis.

The data were sourced from METABRIC, a large, publically available data set of clinical and genomic information from 1,981 patients with breast cancer.<sup>3</sup>

About a decade ago, Friend participated in the development of a 70-gene prognosis profile for breast cancer that eventually gave rise to **Agendia B.V.**'s marketed MammaPrint prognostic test for breast cancer recurrence.<sup>4</sup>

“Ten years ago, we developed this method using breast cancer data, but the methodology hadn't really evolved from there. So we asked if the crowd could evolve a better variation of the approach,” he said.

The METABRIC data were adapted into Synapse, and 354 participants registered for the challenge to analyze the data and develop prognostic models. The source code for each model was made available on Synapse to encourage collaboration between participants. To promote competition and model improvement, results from the challenge were updated in a real-time online leaderboard that had not been available in earlier DREAM challenges.

After two phases of model development and validation on subsets of the METABRIC data, the final models were tested on an independent data set from 184 patients to determine a winner.

The winning model came from a research team at Columbia University led by Dimitris Anastassiou, a professor of electrical engineering. The model built upon his group's previous work defining attractor metagenes, which

“We believe that the attractor metagenes reflect the underlying biological mechanisms precisely, and we think of them as bioinformatic hallmarks of cancer.”

—*Dimitris Anastassiou, Columbia University*

**Table 1. Sage Bionetworks–DREAM Project spring 2013 challenges.** Sage Bionetworks and The DREAM Project have announced four open-innovation computational challenges that tackle issues relevant to drug discovery and development. The challenges will run between May and September. The partners expect to announce another round of challenges in the fall.

Source: [Sage Bionetworks](#)

Title	Description	Data source	Sponsor
HPN-DREAM Breast Cancer Network Interference Challenge	Use quantitative proteomic data to: (i) build network models that represent the active pathways and their response to different stimuli during drug treatment; (ii) predict the responses of phosphoproteins to various drugs; and (iii) propose new visualization strategies for the high-dimensional data sets	Oregon Health & Science University; The University of Texas MD Anderson Cancer Center; The Netherlands Cancer Institute	Heritage Provider Network Inc. (HPN); National Cancer Institute
NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge	Use genetic and toxicology data to build computational models that can predict: (i) the toxic response of individuals to each chemical based on genetics and genomics data; and (ii) the parameters of distribution for the toxic effects of each chemical based primarily on chemical information about the compounds being evaluated	National Institute of Environmental Health Sciences (NIEHS); National Center for Advancing Translational Sciences (NCATS); The University of North Carolina at Chapel Hill (UNC)	To be announced
National Brain Tumor Society–DREAM Cancer Prediction Challenge	Determine whether systems biology–based models of human glioblastoma multiforme (GBM) are sufficiently advanced to allow the correct prediction of single agents or combinations of drugs that may abrogate tumorigenesis or significantly delay tumor growth <i>in vivo</i>	Multiple sources to be announced	National Brain Tumor Society
Whole-Cell Parameter Estimation DREAM Challenge	Refine a whole-cell computational model describing the biology of <i>Mycobacterium genitalium</i> by predicting a subset of the kinetic parameters used to represent fundamental biological processes, with the goal of determining how accurately the kinetics of cellular processes can be reverse engineered	Stanford University	To be announced

are signatures of coexpressed genes in cancer identified through an iterative computational approach.<sup>5</sup>

This approach identified sets of coexpressed genes associated with particular cancer phenotypes, including mitotic chromosome instability, mesenchymal transition and lymphocyte-specific immune recruitment.

“We believe that the attractor metagenes reflect the underlying biological mechanisms precisely, and we think of them as bioinformatic hallmarks of cancer,” said Anastassiou.

Models were scored based on their prediction of the concordance index (CI). For every two randomly selected patients, the CI is the probability that a model will correctly predict which of the two patients will die before the other. So for random chance, the CI would be 0.5. On the test set, the attractor metagene signature had a CI of 0.756, whereas the previously identified 70-gene signature had a CI of 0.60.

Results were published in *Science Translational Medicine*, which embedded peer reviewers into the challenge process to evaluate the results and help determine criteria for selecting a winner.

### Crowd to clinic

Agendia CMO Neil Barth told *SciBX* that the data-analysis crowdsourcing approach could provide a future effective model for diagnostics development.

“This provides a unique platform for the development and refinement of models. As we are beginning to enrich databases with all kinds of new information at all levels, including gene and protein expression, this kind of modeling to get to clinical answers is probably the most efficient way to go about it,” he said.

He cautioned that several steps need to be taken to further clinically validate the results. First and foremost, Barth said, it would be important to set and validate a threshold at which the test could provide clinically meaningful results. “If you have a test like MammaPrint, you have to set a threshold of minimal performance for the low-risk population. So, for example, in our case, low risk means having a 10-year survival rate of 90% or better. There is no threshold set for the performance of these models; it’s simply which one is performing statistically better, not necessarily held against the defined threshold of outcome,” said Barth. “These models were designed to try to get to the best *p* value, but you aren’t given that luxury in the clinical arena.”

He also noted that two other differences between MammaPrint and this approach are that the marketed test is focused on the risk of an individual patient, not a cohort of patients, and that the test does not look at metagenetic signatures.

The new models blend both clinical data and gene expression data, which Barth said realistically resembles how most doctors make decisions using marketed gene expression tests. However, he noted that diagnostic development is different and more difficult because an expression-based test must show a statistically significant benefit by itself as a stand-alone assay.

Anastassiou added that commercially available tests including Oncotype DX and MammaPrint use genes related to the attractor metagenes, and he plans to test whether replacing any of the genes in these tests could improve the accuracy of the products.

Oncotype DX is a breast cancer prognostic marketed by **Genomic Health Inc.**, which declined to comment.

(Continues on p. 6)

# Structural guidance for malaria and TB

By Kai-Jye Lou, Senior Writer

The **Structural Genomics Consortium** is spearheading the three-year Structure-guided Drug Discovery Consortium, which aims to bring pharma-quality medicinal chemistry capabilities to targets against malaria and tuberculosis. With a 3-year, \$5 million grant from the **Bill & Melinda Gates Foundation** and another \$10 million in supporting funds already available to its members, the drug discovery consortium will focus on projects that put early stage therapeutic assets in the hands of its key product development partners—**Medicines for Malaria Venture** and the **Global Alliance for TB Drug Development**.

Data generated under the new consortium also will be made publicly accessible to the broader scientific community.

“After AIDS, TB and malaria are the next two infectious diseases that have the highest global rates of mortality and morbidity,” said Christopher Walpole, program director of the Structure-guided Drug Discovery Consortium (SDDC) at Structural Genomics Consortium (SGC) Toronto.

He noted that the SDDC steps in at a time when there is a new wave of targets in TB and malaria that have emerged from whole-cell screening and sequencing studies but there are only limited resources in pharma and academia to pursue drug discovery against them.

“SDDC will use its structural genomics pipelines to solve the 3D structures of as many of these high-value targets as possible and support collaborative, structure-based drug design programs while sharing information openly to minimize duplication of effort,” Walpole told *SciBX*.

.....  
(Continued from “DREAM Team,” p. 5)

Barth also said that once approved, a test such as MammaPrint cannot be significantly changed without requiring further clinical validation. “If we had the ability to have an open-source community look at the signature, there is no question in my mind we could be further ahead at bringing to the clinic a more optimized tool. I have no doubt this type of approach has the opportunity to collaboratively improve these signatures.”

Anastassiou said Columbia has filed patent applications covering biomarkers used in its model. He did say open sharing in community challenges such as this is vital for developing better diagnostics.

Stolovitzky agreed. “I work for IBM, and I clearly understand the value of IP, but at the same time I believe that in some ways being too concerned with privacy and IP protection can delay progress,” he said. “That doesn’t mean that people should not consider filing a patent on their methods, but once you are a part of a challenge, our thinking is that you should share with others. If you are the best performer, let us know what you did, allow us to see that there is reproducibility and work with us to advance the field.”

He added, “I won’t claim this is completely sorted out, but I think there is a place for IP and a place for collaborative learning, and we are trying to sort out the right way to do this.”

Cain, C. *SciBX* 6(18); doi:10.1038/scibx.2013.430  
Published online May 9, 2013

Current members of the consortium include SGC, the **Seattle Structural Genomics Center for Infectious Disease**, the **Midwest Center for Structural Genomics**, the **Center for Structural Genomics of Infectious Diseases**, the **TB Structural Genomics Consortium** and several academic drug discovery and pharmaceutical research groups.

The Gates Foundation is SDDC’s main sponsor, and the foundation’s \$5 million grant is designated specifically for the consortium’s structure-guided medicinal chemistry efforts for generating lead molecules.

Walpole said the additional \$10 million in supporting funds stems from the funding that consortium members already have for their structural genomics work on TB and malaria targets. He said the structural genomics work carried out by the SDDC’s members will provide a crucial foundation for performing structure-guided drug discovery.

Most of the structural genomics centers and consortia under the SDDC have funding from the NIH.

## From targets to leads

SDDC is working with its product development partners, sponsors and consultants who work in these disease spaces to sift through a portfolio of about 20–30 TB targets and 15 malaria targets.

“Our objective is to deliver pharma-quality early lead compounds and the associated scientific packages to our product development partners so they can optimize these leads to a clinical candidate within 12–18 months,” Walpole told *SciBX*.

He added that the consortium will work with its product development partners to define project-specific criteria that would need to be satisfied before an asset is considered ready to be handed off.

Walpole said SDDC’s objective is to deliver three such therapeutic asset packages to its partners over the next three years.

(Continues on p. 7)

## REFERENCES

- Margolin, A.A. *et al. Sci. Transl. Med.*; published online April 17, 2013; doi:10.1126/scitranslmed.3006112  
**Contact:** Stephen H. Friend, Sage Bionetworks, Seattle, Wash.  
e-mail: [friend@sagebase.org](mailto:friend@sagebase.org)  
**Contact:** Adam A. Margolin, same affiliation as above  
e-mail: [margolin@sagebase.org](mailto:margolin@sagebase.org)
- Cheng, W.-Y. *et al. Sci. Transl. Med.*; published online April 17, 2013; doi:10.1126/scitranslmed.3005974  
**Contact:** Dimitris Anastassiou, Columbia University, New York, N.Y.  
e-mail: [da8@columbia.edu](mailto:da8@columbia.edu)
- Curtis, C. *et al. Nature* 486, 346–352 (2012)
- Van de Vijver, M.J. *et al. N. Engl. J. Med.* 347, 1999–2009 (2002)
- Cheng, W.-Y. *et al. PLoS Comput. Biol.* 9, e1002920; published online Feb. 21, 2013; doi:10.1371/journal.pcbi.1002920

## COMPANIES AND INSTITUTIONS MENTIONED

**Agendia B.V.**, Amsterdam, the Netherlands  
**Columbia University**, New York, N.Y.  
**The DREAM Project**, Seattle, Wash.  
**Genomic Health Inc.** (NASDAQ:GHDX), Redwood City, Calif.  
**IBM Corp.** (NYSE:IBM), Armonk, N.Y.  
**InnoCentive Inc.**, Waltham, Mass.  
**National Cancer Institute**, Bethesda, Md.  
**National Institutes of Health**, Bethesda, Md.  
**The New York Academy of Sciences**, New York, N.Y.  
**Sage Bionetworks**, Seattle, Wash.

SDDC will deliver the compounds it discovers to the relevant product development partner at the end of the hit-to-lead stage of development. The partner will then be responsible for lead optimization and setting up preclinical and clinical development programs.

With respect to IP, Walpole said SDDC intends to keep its work as open as possible.

“All new protein structures generated under the consortium will be deposited to the Protein Data Bank once they are available, and we intend to publish the small molecule hits we generate and make them publicly available,” he told *SciBX*. “We don’t expect to be restricted by IP before handing off an asset package to our product development partners, but our partners may later opt to file IP on optimized molecules to ensure that they have the freedom to develop the compound.”

The Protein Data Bank archive is the single publicly accessible online repository of 3D structures for large biological molecules. The archive is maintained by members of the Research Collaboratory for Structural Bioinformatics consortium.

#### Partner perspectives

The Global Alliance for TB Drug Development and Medicines for Malaria Venture (MMV) see SDDC as a vehicle for augmenting their respective drug discovery pipelines.

“MMV has achieved a lot of success in the use of phenotypic screens to identify new antimalarial agents, but there is still an urgent need to identify new agents that can block transmission of the parasite, kill the dormant liver form of *Plasmodium vivax* and eventually eradicate malaria,” said David Waterson, director of drug discovery at MMV. “The SDDC will aim to increase the number of validated biological targets and, by its use of structure-based design, provide MMV with an alternative strategy to strengthen its portfolio of discovery projects. Such an approach will be particularly valuable when high throughput phenotypic screens are not available.”

“Projects undertaken by the SDDC will generate the crystal structures

**“Projects undertaken by the SDDC will generate the crystal structures that will allow us to see how various molecules bind to their targets in *Mycobacterium*.”**

**— Christopher Cooper,  
Global Alliance for TB Drug  
Development**

that will allow us to see how various molecules bind to their targets in *Mycobacterium*, which is going to be of paramount importance for doing structure-based drug design,” added Christopher Cooper, senior director of chemistry at the TB Alliance. “If you look for crystal structures of *Mycobacterium*-specific proteins, you will see that they are few compared with the number of crystal structures of proteins from other clinically relevant bacteria such as *Escherichia coli* and *Staphylococcus aureus*.”

Like MMV, Cooper said SDDC establishes a mechanism for feeding high-quality chemical series into the TB Alliance’s early stage drug development pipeline.

Cooper said that although the TB Alliance and SDDC still need to confirm the short list of a half-dozen or so essential, high-priority biochemical targets for drug discovery in TB, ATP synthase, RNA polymerase and DNA gyrase B of *M. tuberculosis* would likely be at the top of such a list.

Waterson said new biological targets identified from recent phenotypic screening efforts will form the basis of initial malaria-focused projects undertaken by SDDC. He said MMV has suggested a number of potential targets to the SDDC but declined to provide details.

Lou, K.-J. *SciBX* 6(18); doi:10.1038/scibx.2013.431  
Published online May 9, 2013

#### COMPANIES AND INSTITUTIONS MENTIONED

**Bill & Melinda Gates Foundation**, Seattle, Wash.  
**Center for Structural Genomics of Infectious Diseases**, Evanston, Ill.  
**Global Alliance for TB Drug Development**, New York, N.Y.  
**Medicines for Malaria Venture**, Geneva, Switzerland  
**Midwest Center for Structural Genomics**, Argonne, Ill.  
**National Institutes of Health**, Bethesda, Md.  
**Seattle Structural Genomics Center for Infectious Disease**, Seattle, Wash.  
**Structural Genomics Consortium**, Toronto, Ontario, Canada  
**TB Structural Genomics Consortium**, Los Angeles, Calif.



### SciBX: Science-Business eXchange

“Understanding the business context and commercial relevance of new science is the key to lowering investment risk and stimulating industry innovation”

Become a Charter Subscriber today!

Visit [scibx.com](http://scibx.com) for details on the special SciBX Charter Subscriber Offer

# AD vaccine redux

By Lev Osherovich, Senior Writer

Researchers at **Harvard Medical School** have teamed up with vaccine maker **Mercia Pharma Inc.** to design a next-generation Alzheimer's disease vaccine with an adjuvant that promotes a beneficial anti-inflammatory response that the team hopes will enhance  $\beta$ -amyloid clearance without triggering neuroinflammation.<sup>1</sup>

AD is caused by accumulation of  $\beta$ -amyloid ( $A\beta$ ), an extracellular protein fragment that forms deposits around neurons. Those deposits, or plaques, trigger neuronal degeneration and attract inflammatory microglia, which further accelerate neuron death. Preventing the formation of  $A\beta$  plaques or clearing away  $A\beta$  before it reaches toxic levels is the central focus of AD therapeutic development.

In principle,  $A\beta$  can be targeted with injected antibodies, but this passive immunotherapy approach has thus far met with failure. Two  $A\beta$ -binding mAbs—bapineuzumab (AAB-001) from **Johnson & Johnson** and **Pfizer Inc.** and solanezumab (LY2062430) from **Eli Lilly and Co.**—failed in Phase III testing to prevent AD progression in patients with mild to moderate disease.

The most recent casualty is Gammagard Liquid 10%, a polyclonal mixture of antibodies from **Baxter International Inc.** that failed in a Phase III trial in a population of patients with mild to moderate AD.

An alternative approach consists of building up a patient's natural immune response against  $A\beta$  before the onset of disease. The simplest way to do so is with active immunotherapy or vaccination, in which  $A\beta$  is introduced to the peripheral immune system in a nontoxic form that stimulates a robust antibody-based response.

This was the idea behind the AN-1792 AD vaccine candidate from **Elan Corp. plc** and Wyeth (now Pfizer). However, that product failed to prevent AD progression in Phase II testing in 2002, partly because of a poor antibody response in the majority of patients. Moreover, about 6% of patients developed meningoencephalitis, a neuroinflammatory condition thought to be caused by T cell activity in the brain.

Since then, academic researchers and companies have pursued a range of strategies to increase antibody production and decrease inflammatory

T cell activity in second-generation AD vaccine candidates (see Table 1, "Alzheimer's disease vaccine pipeline").

Now, a team lead by Cynthia Lemere, associate professor of neurology at **Brigham and Women's Hospital** and Harvard Medical School, has designed a new AD vaccine that appears to achieve both goals.

"This is the third-generation vaccine since the AN-1792 trial concluded," said Lemere. "Since that trial halted, there has been a strong interest in developing an AD vaccine that would avoid a T cell response."

Lemere said second-generation vaccines are designed to avoid interacting with T cells entirely, but such an approach limits the robustness of the B cell-mediated antibody response, which requires assistance from T cells.

Rather than completely avoiding T cells, Lemere's vaccine skews T cell activity away from the proinflammatory T helper type 1 (Th1) cell response and promotes an anti-inflammatory Th2 cell-type response. The Th2 cell response enhances the activity of B cells and provides anti-inflammatory cytokines that promote  $A\beta$  clearance.

"This vaccine initiates a Th2 anti-inflammatory response, so it's a two-pronged approach with a strong humoral response as well as a protective cellular response," said Lemere.

## Antibodies vs. plaques

Lemere's vaccine, termed MER5101, consists of the first 15 amino acids of  $A\beta$  attached by a flexible covalent linker to diphtheria toxoid, a carrier protein. The team collaborated with Mercia to formulate the vaccine in the company's MAS-1 adjuvant, an oil-and-water nanoparticle emulsion.

Peter Blackburn, cofounder and president of Mercia, said MAS-1 had previously been used in Aphton Corp.'s Insegia (G17DT), a cancer vaccine against gastrin-17 that failed in Phase III testing for pancreatic cancer. Aphton's cancer vaccine program was acquired by Receptor BioLogix Inc., now a part of **Symphogen A/S**.

Mercia acquired rights to MAS-1 as part of Aphton's Chapter 11 bankruptcy sale in 2006.

In a mouse model for AD, animals receiving MER5101 had higher levels of  $A\beta$ -specific antibodies than untreated controls. The elicited antibodies were predominantly of the IgG2b isotype, which is associated with Th2 cell responses.

**Table 1. Alzheimer's disease vaccine pipeline.** At least seven vaccines against  $\beta$ -amyloid ( $A\beta$ ) are in preclinical through Phase II testing to prevent AD.

Source: *BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Status
<b>Johnson &amp; Johnson</b> (NYSE:JNJ)/ <b>Pfizer Inc.</b> (NYSE:PFE)	PF-5236806 (ACC-001)	$A\beta$ -related immunotherapeutic conjugate	Phase II
<b>Affiris AG/GlaxoSmithKline plc</b> (LSE:GSK; NYSE:GSK)	AD02	Vaccine against a peptide mimic of $A\beta$	Phase II
<b>Cytos Biotechnology AG</b> (SIX:CYTN)/ <b>Novartis AG</b> (NYSE:NVS; SIX:NOVN)	CAD106	Vaccine against $A\beta$	Phase II
<b>AC Immune S.A.</b>	ACI-24	Vaccine that stimulates the production of $\beta$ -sheet conformation-specific antibodies	Phase I/II
Affiris/GlaxoSmithKline	AD03	Vaccine against a peptide mimic of $A\beta$	Phase I
<b>Intellect Neurosciences Inc.</b> (OTCBB:ILNS)	RV-01	Four-amino-acid amino-terminal fragment of $A\beta$ conjugated to tetanus toxoid	Preclinical
<b>Mercia Pharma Inc.</b>	MER5101	Fifteen-amino-acid amino-terminal fragment of $A\beta$ conjugated to diphtheria toxoid in an anti-inflammatory oil-based adjuvant	Preclinical

In samples from human brains with AD, IgG2b antibodies from MER5101-immunized mice readily stained amyloid plaques, whereas proinflammatory IgG2a antibodies did not.

Immunized mice also had a robust anti-inflammatory T cell response to the vaccine. Cultured splenocytes from immunized mice responded to re-stimulation with the original A $\beta$ -diphtheria toxoid conjugate by proliferating and secreting a range of anti-inflammatory cytokines.

The result of the combination of antibody production and anti-inflammatory T cell activity was prevention of AD progression in immunized mice. Animals immunized with MER5101 had lower A $\beta$  levels in the brain and performed better in cognitive tests than unvaccinated controls. Additionally, brain slices from vaccinated mice showed fewer proinflammatory microglia than slices from untreated controls.

Results were published in *The Journal of Neuroscience*.

#### AD infinitum

Although prior vaccine candidates have not shown the anti-inflammatory Th2 cell profile seen with MER5101, it remains to be seen whether the new vaccine's

anti-inflammatory effects will improve efficacy in the clinic.

"Whether this would translate into a sustained Th2 response in humans is an open question," said Lemere. "What you see in the mouse is more or less irrelevant to what you see in humans. You can certainly ask questions about what's happening to A $\beta$ , but there's no animal model for the human immune system."

Daniel Chain, chairman and CEO of **Intellect Neurosciences Inc.**, said Lemere's findings are a step toward eliciting a potent but safe immune response in AD.

"I think the challenge for an AD vaccine is to get a strong humoral response as well as a Th2 response," said Chain. "The 1-15 fragment and diphtheria toxoid fragment are used in the second-generation vaccines, but the adjuvant they use here is novel and gives a strong Th2 response."

Intellect's RV-01 vaccine against A $\beta$  is in preclinical development for AD.

The next challenge, said Chain, is "to get a strong antibody response and have it be sustained over time." He recommended a long-term study of antibody responses to MER5101.

Another question is whether the anti-inflammatory effects of MER5101 in the periphery will translate to an effect on antibody activity in the brain. It is not yet clear whether A $\beta$  antibodies penetrate into the brain to directly clear up plaques or act primarily in the brain's vasculature to neutralize loose A $\beta$  and thus prevent plaque growth.

Thus, further mouse studies are needed to see whether the antibodies and Th2 cells induced by MER5101 act in the brain or in the periphery.

"You get anti-inflammatory activation in the periphery, but you also get a bystander or passive effect from the secretion of anti-inflammatory cytokines that do get into the brain," said Blackburn.

Blackburn said Mercia is conducting toxicology studies of MER5101 in preparation for an IND submission. He did not disclose a timeline.

MER5101 and the MAS-1 adjuvant are covered by patents owned by Mercia. The company, founded in 2004, has raised about \$6 million from private investors and from grants. It hopes to partner the MER5101 project to advance it.

Osherovich, L. *SciBX* 6(18); doi:10.1038/scibx.2013.432  
Published online May 9, 2013

#### REFERENCES

- Liu, B. *et al. J. Neurosci.*; published online April 17, 2013; doi:10.1523/JNEUROSCI.5924-12.2013  
**Contact:** Cynthia A. Lemere, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.  
e-mail: [clemere@rics.bwh.harvard.edu](mailto:clemere@rics.bwh.harvard.edu)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Baxter International Inc.** (NYSE:BAX), Deerfield, Ill.  
**Brigham and Women's Hospital**, Boston, Mass.  
**Elan Corp. plc** (NYSE:ELN), Dublin, Ireland  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**Harvard Medical School**, Boston, Mass.  
**Intellect Neurosciences Inc.** (OTCBB:ILNS), New York, N.Y.  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**Mercia Pharma Inc.**, New York, N.Y.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Symphogen A/S**, Copenhagen, Denmark

## SciBX: Science-Business eXchange

Kick-start your knowledge management—and leave your competitors behind...

Can you afford not to subscribe?

Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

## 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
<b>Cancer</b>				
Brain cancer	H3 histone family 3A (H3.3A; H3F3A); v-myc myelocytomatosis viral related oncogene neuroblastoma derived (MYCN; NMYC); checkpoint kinase 1 (Chk1); aurora kinase A (AURKA; Aurora-A)	<p>Cell culture studies suggest inhibiting Chk1 or AURKA may help treat pediatric and young adult patients with <i>H3F3A</i>-driven glioblastoma. In a glioblastoma cell line with G34-mutant <i>H3F3A</i>, <i>MYCN</i> was identified as the most highly overexpressed gene, and Chk1 and AURKA were identified as regulators of cell proliferation. In the same cell line, an AURKA inhibitor dose-dependently decreased <i>MYCN</i> levels and cell viability compared with no treatment. Next steps include testing AURKA and Chk1 inhibitors in a larger number of glioblastoma cell lines and building <i>in vivo</i> models to test the effects of the inhibitors in orthotopic brain tumors.</p> <p>At least eight companies have AURKA inhibitors in preclinical to Phase III testing in various cancers. At least six companies have Chk1 inhibitors in preclinical to Phase II trials in various cancer indications.</p> <p><b>SciBX 6(18); doi:10.1038/scibx.2013.433</b> Published online May 9, 2013</p>	Unpatented; licensing status not applicable	Bjerke, L. <i>et al. Cancer Discov.</i> ; published online March 28, 2013; doi:10.1158/2159-8290.CD-12-0426 <b>Contact:</b> Chris Jones, The Institute of Cancer Research, Surrey, U.K. e-mail: <a href="mailto:chris.jones@icr.ac.uk">chris.jones@icr.ac.uk</a>
Brain cancer	Not applicable	<p><i>In vitro</i> and mouse studies suggest inhibiting hypoxic exosomes could help treat brain cancer. Hypoxia-associated proteins that contributed to tumor pathology were present in exosomes isolated from patients with glioblastoma multiforme (GBM) but not in those from healthy controls. In mouse xenograft models for human GBM, hypoxic exosomes were associated with faster tumor expansion, increased tumor vasculature and greater tumor volume compared with normoxic exosomes. Next steps could include identifying specific mediators of hypoxic signaling within exosomes and evaluating their potential as drug targets.</p> <p><b>SciBX 6(18); doi:10.1038/scibx.2013.434</b> Published online May 9, 2013</p>	Findings patented; licensing status unavailable	Kucharzewska, P. <i>et al. Proc. Natl. Acad. Sci. USA.</i> ; published online April 15, 2013; doi:10.1073/pnas.1220998110 <b>Contact:</b> Mattias Belting, Lund University, Lund, Sweden e-mail: <a href="mailto:mattias.belting@med.lu.se">mattias.belting@med.lu.se</a>
Cancer	IQ motif containing GTPase activating protein 1 (IQGAP1); MAP kinase 1 (MAPK1; ERK-2); MAPK3 (ERK-1)	<p>Cell culture and mouse studies identified a peptide-based inhibitor of IQGAP1 that could help treat cancer. A 32-amino-acid residue domain of IQGAP1 that interacts with ERK-1 and ERK-2 was isolated and subsequently modified with a Tat peptide sequence to improve cell permeability. In a mouse model for pancreatic cancer, intraperitoneal injection of the peptide increased survival compared with injection of a scrambled peptide. In cultured, drug-resistant BRAF mutant melanoma cell lines, the peptide decreased growth compared with a scrambled peptide. Next steps include further developing peptide and small molecule inhibitors of IQGAP1.</p> <p><b>SciBX 6(18); doi:10.1038/scibx.2013.435</b> Published online May 9, 2013</p>	Patent application filed; available for licensing	Jameson, K.L. <i>et al. Nat. Med.</i> ; published online April 21, 2013; doi:10.1038/nm.3165 <b>Contact:</b> Paul A. Khavari, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:khavari@stanford.edu">khavari@stanford.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Head and neck cancer	Epidermal growth factor receptor (EGFR); hedgehog pathway	<p>Cell culture and mouse studies suggest combined inhibition of EGFR and the hedgehog pathway could help prevent drug resistance in head and neck cancers. In human head and neck squamous cell carcinoma (HNSCC) cells with acquired resistance to the EGFR inhibitor Tarceva erlotinib, treatment with the drug caused an epithelial-to-mesenchymal transition that increased invasiveness and resistance compared with no treatment. In a mouse xenograft model for HNSCC, the EGFR inhibitor Erbitux cetuximab plus a hedgehog pathway inhibitor delayed or prevented tumor regrowth, whereas Erbitux alone did not. Next steps could include testing combined treatment regimens in additional cancer models.</p> <p>Eli Lilly and Co., Bristol-Myers Squibb Co. and Merck KGaA market Erbitux to treat head and neck cancer. Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd. and Roche market Tarceva to treat liver cancer, pancreatic cancer and non-small cell lung cancer (NSCLC).</p> <p><b>SciBX 6(18); doi:10.1038/scibx.2013.436</b>  <b>Published online May 9, 2013</b></p>	Patent and licensing status unavailable	<p>Keysar, S.B. <i>et al. Cancer Res.</i>; published online April 10, 2013;  doi:10.1158/0008-5472.CAN-12-4047  <b>Contact:</b> Antonio Jimeno, University of Colorado Cancer Center, Aurora, Colo.  e-mail:  <a href="mailto:antonio.jimeno@ucdenver.edu">antonio.jimeno@ucdenver.edu</a></p>
Prostate cancer	Androgen receptor	<p>Cell culture and mouse studies identified androgen receptor antagonists that could help treat prostate cancers that acquire resistance to Xtandi enzalutamide. Structural modeling and <i>in vitro</i> mutagenesis assays identified F876L as a mutation in the androgen receptor that prevents antagonism by Xtandi and instead causes the drug to behave as a partial agonist. A series of compounds with D-ring substitutions to the enzalutamide scaffold were synthesized and shown to inhibit the F876L mutant androgen receptor. In mouse xenograft models for prostate cancer and in cell lines, the lead D-ring-substituted compound inhibited growth of F876L mutant prostate cancers, whereas enzalutamide did not. Next steps include evaluating the lead compound in additional mouse xenograft models for prostate cancer and determining the clinical relevance of the mutation.</p> <p>Medivation Inc. and Astellas Pharma Inc. market Xtandi, a triple-acting oral antiandrogen receptor, to treat castration-resistant prostate cancer.</p> <p>Aragon Pharmaceuticals Inc.'s ARN-509, a second-generation androgen receptor antagonist, is in Phase II testing to treat prostate cancer.</p> <p>Corresponding author Charles Sawyers is a cofounder of Aragon Pharmaceuticals and a co-inventor of both Xtandi and ARN-509 (<i>see Rational approach to Xtandi resistance, page 1</i>).</p> <p><b>SciBX 6(18); doi:10.1038/scibx.2013.437</b>  <b>Published online May 9, 2013</b></p>	Two provisional patent applications filed; licensing status undisclosed	<p>Balbas, M.D. <i>et al. eLife</i>; published online April 9, 2013;  doi:10.7554/eLife.00499  <b>Contact:</b> Charles L. Sawyers, Memorial Sloan-Kettering Cancer Center, New York, N.Y.  e-mail:  <a href="mailto:sawyersc@mskcc.org">sawyersc@mskcc.org</a>  <b>Contact:</b> Yang Shen, Toyota Technological Institute at Chicago, Chicago, Ill.  e-mail:  <a href="mailto:yangshen@ttic.edu">yangshen@ttic.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cardiovascular disease</b>				
Cardiomyopathy	MicroRNA-146a (miR-146a)	<i>In vitro</i> and mouse studies suggest inhibiting miR-146a could help treat peripartum cardiomyopathy (PPCM). In patients with PPCM and in mouse models for the indication, plasma or cardiac levels of miR-146a were higher than those in healthy postpartum controls. In the PPCM mouse models, a locked nucleic acid (LNA) anti-miR-146a increased cardiac function and capillary density and decreased cardiac fibrosis compared with a control oligonucleotide. Future studies could include testing the LNA anti-miR-146a in additional models for PPCM.	Patent and licensing status unavailable	Halkein, J. <i>et al. J. Clin. Invest.</i> ; published online April 24, 2013; doi:10.1172/JCI64365 <b>Contact:</b> Ingrid Struman, University of Liege, Liege, Belgium e-mail: <a href="mailto:i.struman@ulg.ac.be">i.struman@ulg.ac.be</a>
<b>Endocrine/metabolic disease</b>				
Diabetes	Betatrophin	Mouse studies suggest betatrophin could be useful for treating type 2 diabetes. In three mouse models for type 2 diabetes, betatrophin injection increased blood glucose levels and islet $\beta$ cell mass compared with vehicle. Next steps include identification of the betatrophin receptor and preclinical development of a recombinant injectable form of the protein. Evotec AG and Johnson & Johnson's Janssen Pharmaceuticals Inc. unit have a program based on the technology in the lead optimization stage for type 2 diabetes.	Patent pending; licensed to Evotec	Yi, P. <i>et al. Cell</i> ; published online April 25, 2013; doi:10.1016/j.cell.2013.04.008 <b>Contact:</b> Douglas A. Melton, Harvard University, Cambridge, Mass. e-mail: <a href="mailto:dmelton@harvard.edu">dmelton@harvard.edu</a>
Dyslipidemia; metabolic syndrome; obesity	Transcription factor EB (TFEB)	Mouse studies suggest increasing TFEB activity could help prevent dyslipidemia and associated conditions such as metabolic syndrome and obesity. Mice with liver-specific <i>Tfeb</i> knockout had increased peripheral adipose tissue and lipid accumulation in the liver compared with wild-type mice. In mice, adenoviral vector-induced overexpression of human TFEB prevented diet-induced obesity and decreased markers of metabolic syndrome compared with no overexpression. Next steps include testing in additional animal models for metabolic disease.	Patent application filed; available for licensing from Fondazione Telethon	Settembre, C. <i>et al. Nat. Cell Biol.</i> ; published online April 21, 2013; doi:10.1038/ncb2718 <b>Contact:</b> Andrea Ballabio, Telethon Institute of Genetics and Medicine, Naples, Italy e-mail: <a href="mailto:ballabio@tigem.it">ballabio@tigem.it</a> <b>Contact:</b> Carmine Settembre, same affiliation as above e-mail: <a href="mailto:settembre@tigem.it">settembre@tigem.it</a>
<b>Infectious disease</b>				
Trypanosome	Isoleucyl tRNA synthetase (IARS)	A study in mice suggests inhibiting IARS could help treat human African trypanosomiasis. In mice infected with <i>Trypanosoma brucei</i> , IARS knockdown in the parasite or treatment with an IARS inhibitor led to rapid clearance of infection. Next steps include partnering with medicinal chemists to identify lead compounds.	Unpatented; licensing status not applicable	Cestari, I. & Stuart, K. <i>J. Biol. Chem.</i> ; published online April 2, 2013; doi:10.1074/jbc.M112.447441 <b>Contact:</b> Kenneth Stuart, Seattle Biomedical Research Institute, Seattle, Wash. e-mail: <a href="mailto:ken.stuart@seattlebiomed.org">ken.stuart@seattlebiomed.org</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Neurology	Unknown	<i>In vitro</i> studies identified neurotrophic, secoyohimbane-derived compounds that could help treat neurological diseases. A library of compounds based on the natural compound rhynchophylline was synthesized. In rat hippocampal neurons and in mouse motor neurons derived from embryonic stem cells, the lead compounds increased neurite outgrowth compared with vehicle. Next steps include optimizing the lead compounds to enable testing in animal models.  <b>SciBX 6(18); doi:10.1038/scibx.2013.442</b> <b>Published online May 9, 2013</b>	Unpatented; licensing status not applicable	Antonchick, A.P. <i>et al. Chem. Biol.</i> ; published online April 18, 2013; doi:10.1016/j.chembiol.2013.03.011 <b>Contact:</b> Herbert Waldmann, Max Planck Institute of Molecular Physiology, Dortmund, Germany e-mail: <a href="mailto:herbert.waldmann@mpi-dortmund.mpg.de">herbert.waldmann@mpi-dortmund.mpg.de</a>
<b>Transplantation</b>				
Graft rejection	Complement 3 (C3); C5a	Mouse studies suggest a combination of C3 and C5a inhibition could be useful for preventing graft rejection. In a mouse model for tracheal transplant, C3 knockout animals treated with NOX-D19, an aptamer antagonist of C5a, had decreased thrombin activation, vascular abnormalities and fibrosis and increased oxygenation and blood perfusion to engrafted tissue compared with wild-type or untreated controls. Next steps could include preclinical optimization of C3 and C5a inhibitors. Noxxon Pharma AG's NOX-D19 is in preclinical development for liver and kidney failure. AstraZeneca plc's MEDI-7841, a mAb against C5a and C5, is in Phase I testing for chronic obstructive pulmonary disease (COPD). Novo Nordisk A/S's anti-C5aR-151 (NN8209), an anti-C5a mAb, is in Phase I testing for rheumatoid arthritis (RA). Potentia Pharmaceuticals Inc. and partner Novartis AG are developing compstatin (APL-1; POT-4), a C3 inhibitor that is in Phase II testing for age-related macular degeneration (AMD).  <b>SciBX 6(18); doi:10.1038/scibx.2013.443</b> <b>Published online May 9, 2013</b>	NOX-D19 is patented by Noxxon Pharma; licensing status undisclosed	Khan, M.A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 25, 2013; doi:10.1073/pnas.1217991110 <b>Contact:</b> Mark R. Nicolls, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:mnnicolls@stanford.edu">mnnicolls@stanford.edu</a>

## SciBX

**SciBX: Science–Business eXchange**—transform your ability to efficiently identify and evaluate new developments in science and technology that have commercial and investment potential within the biotechnology and pharmaceutical arena.

Subscribe today at [scibx.com](http://scibx.com)

## 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
<b>Assays &amp; screens</b>			
T2 magnetic resonance (T2MR) nanoparticle diagnostic for systemic <i>Candida</i> infection	A T2MR diagnostic method could be used to detect systemic <i>Candida</i> infection in whole blood samples. The T2MR method uses <i>Candida</i> cell lysis, PCR amplification and nanoparticles that can detect the amplified product in whole blood. In whole blood samples taken from healthy donors and then spiked with various species of the <i>Candida</i> fungus, T2MR detection showed a 98% positive agreement and 100% negative agreement with standard blood culture diagnostics. T2MR detected <i>Candida</i> in blinded whole blood samples from patients in about 2 hours, whereas standard blood culture diagnostics took an average of 48 hours. Next steps include clinical testing.	T2 Biosystems Inc. has 10 U.S. patents and 10 international patents covering the T2MR method; available for partnering	Neely, L.A. <i>et al. Sci. Transl. Med.</i> ; published online April 24, 2013; doi:10.1126/scitranslmed.3005377 <b>Contact:</b> Thomas J. Lowery, T2 Biosystems Inc., Lexington, Mass. e-mail: <a href="mailto:tlowery@t2biosystems.com">tlowery@t2biosystems.com</a>
<b>Computational models</b>			
Community-developed computational model for breast cancer progression	A computational model for breast cancer progression developed through an open innovation challenge could lead to better prognostic tests for the disease and help guide the development of future computational models. An online server was used to host user-submitted computational algorithms for predicting disease progression based on a dataset containing expression, copy number and clinical data from about 2,000 breast cancer samples. The winning model predicted progression on a validation data set of 184 samples with higher accuracy than that of previously reported prognostic models for breast cancer. Next steps include studying the biology underlying predictive features of the model and running additional challenges in other disease areas using this framework. Oncotype DX from Genomic Health Inc. and MammaPrint from Agendia B.V. are prognostic gene expression tests marketed for breast cancer ( <i>see DREAM team, page 4</i> ).	Findings unpatented for both studies; licensing status not applicable	Margolin, A.A. <i>et al. Sci. Transl. Med.</i> ; published online April 17, 2013; doi:10.1126/scitranslmed.3006112 <b>Contact:</b> Stephen H. Friend, Sage Bionetworks, Seattle, Wash. e-mail: <a href="mailto:friend@sagebase.org">friend@sagebase.org</a> <b>Contact:</b> Adam A. Margolin, same affiliation as above e-mail: <a href="mailto:margolin@sagebase.org">margolin@sagebase.org</a>  Cheng, W.-Y. <i>et al. Sci. Transl. Med.</i> ; published online April 17, 2013; doi:10.1126/scitranslmed.3005974 <b>Contact:</b> Dimitris Anastassiou, Columbia University, New York, N.Y. e-mail: <a href="mailto:da8@columbia.edu">da8@columbia.edu</a>
Gene regulatory network mapping in late-onset Alzheimer's disease (AD)	A gene regulatory network map of late-onset AD could help identify and prioritize pathways and therapeutic targets in the disease. A bioinformatics analysis of gene expression data from 1,647 postmortem brain tissue samples from patients with late-onset AD was used to create a gene regulatory network of the condition. Analysis of the network found that a set of immunity- and microglia-specific genes had the strongest association with disease pathophysiology. The analysis also showed that TYRO protein tyrosine kinase binding protein (TYROBP) is upregulated in late-onset AD and acts as a key regulator in the network. Next steps include continuing functional studies in mouse models and in microglia and carrying out genetic tests to identify modules with effects on brain atrophy and dementia.	Unpatented; licensing status not applicable	Zhang, B. <i>et al. Cell</i> ; published online April 25, 2013; doi:10.1016/j.cell.2013.03.030 <b>Contact:</b> Valur Emilsson, Icelandic Heart Association and University of Iceland, Kopavogur, Iceland e-mail: <a href="mailto:valur@hjarta.is">valur@hjarta.is</a> <b>Contact:</b> Bin Zhang, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: <a href="mailto:bin.zhang@mssm.edu">bin.zhang@mssm.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug delivery</b>			
Cell-penetrating peptides for prostate cancer	Cell culture studies suggest engineered, cell-penetrating peptides could be useful for delivering therapeutics into tumor cells. In cultured prostate cancer cells, phage-display selection identified 12-mer engineered peptides that penetrated into the cytoplasm at low picomolar concentrations. The best of these peptides had high selectivity for the chosen cell line but not for other tumor types. When coupled in multiple copies to green fluorescent protein (GFP), the best peptides induced higher intracellular fluorescence than previously described cell-penetrating peptides. Next steps include testing delivery of therapeutic cargoes coupled to the peptide in animals.  <b>SciBX 6(18); doi:10.1038/scibx.2013.447</b> <b>Published online May 9, 2013</b>	Patent pending; available for licensing	DePorter, S.M. <i>et al. Chem. Biol.</i> ; published online March 21, 2013; doi:10.1016/j.chembiol.2013.01.015 <b>Contact:</b> Brian R. McNaughton, Colorado State University, Fort Collins, Colo. e-mail: <a href="mailto:brian.mcnaughton@colostate.edu">brian.mcnaughton@colostate.edu</a>
<b>Drug platforms</b>			
Medial ganglionic eminence (MGE)-like progenitor cell transplantation to treat memory and learning deficits	Cell culture and mouse studies suggest transplantation of MGE-like progenitor cells could help treat learning and memory deficits. Human embryonic stem cells were induced into MGE-like progenitor cells that could differentiate into basal forebrain cholinergic neurons and $\gamma$ -aminobutyric acid (GABA) interneurons. In mice with immunotoxin-mediated destruction of hippocampal basal forebrain cholinergic neurons and GABA neurons, hippocampal transplantation of the human MGE progenitor cells increased memory, learning and spatial cognition compared with transplantation of human spinal progenitor cells. Next steps could include testing the procedure in animal models for neurodegeneration or neurological disease.  <b>SciBX 6(18); doi:10.1038/scibx.2013.448</b> <b>Published online May 9, 2013</b>	Patent and licensing status unavailable	Liu, Y. <i>et al. Nat. Biotechnol.</i> ; published online April 21, 2013; doi:10.1038/nbt.2565 <b>Contact:</b> Su-Chun Zhang, University of Wisconsin–Madison, Madison, Wis. e-mail: <a href="mailto:zhang@waisman.wisc.edu">zhang@waisman.wisc.edu</a>
Self-mineralizing viruses for improved efficacy and storage stability	Cell culture and mouse studies suggest self-mineralizing vaccines could have better efficacy and stability than conventional vaccines. Human enterovirus type 71 engineered to express genes that encode calcium- and phosphate-chelating agents formed a self-mineralized calcium phosphate shell when cultured in calcium-enriched medium. In mice, the engineered virus induced almost twofold higher titers of neutralizing antibodies than the native virus. The mineralized virus was stored for 7 days at 37 °C and for 9 days at 26 °C. Next steps include further improving the vaccine's thermal stability.  <b>SciBX 6(18); doi:10.1038/scibx.2013.449</b> <b>Published online May 9, 2013</b>	Patent application filed; unavailable for licensing	Wang, G. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 15, 2013; doi:10.1073/pnas.1300233110 <b>Contact:</b> Cheng-Feng Qin, Beijing Institute of Microbiology and Epidemiology, Beijing, China e-mail: <a href="mailto:qincf@bmi.ac.cn">qincf@bmi.ac.cn</a> <b>Contact:</b> Ruikang Tang, Zhejiang University, Hangzhou, China e-mail: <a href="mailto:rtang@zju.edu.cn">rtang@zju.edu.cn</a>
<b>Markers</b>			
CD44, CD47, c-Met proto-oncogene (MET; HGFR) and epithelial cell adhesion molecule (EpCAM) as a signature for metastasis-initiating circulating tumor cells (CTCs) in breast cancer	A protein signature specific to EpCAM <sup>+</sup> CTCs associated with brain metastases could be used for diagnosis of metastatic breast cancer. EpCAM <sup>+</sup> CTCs isolated from individuals with progressive metastatic breast cancer expressed CD44, CD47 and MET. In immunodeficient mice, injection of that subset of CTCs resulted in metastasis to the bone. In blood samples from patients with cancer, increased levels of EpCAM <sup>+</sup> CTCs expressing CD44, CD47 and MET correlated with shorter overall survival. Next steps include genetically examining whether MET and CD47 are essential for survival and function of metastasis-initiating cells in hormone receptor-positive breast cancers and testing several MET and CD47 inhibitors on the newly established CTC lines.  <b>SciBX 6(18); doi:10.1038/scibx.2013.450</b> <b>Published online May 9, 2013</b>	Patent application pending; available for licensing	Baccelli, I. <i>et al. Nat. Biotechnol.</i> ; published online April 21, 2013; doi:10.1038/nbt.2576 <b>Contact:</b> Andreas Trumpp, Heidelberg Institute for Stem Cell Technology and Experimental Medicine GmbH, Heidelberg, Germany e-mail: <a href="mailto:a.trumpp@dkfz-heidelberg.de">a.trumpp@dkfz-heidelberg.de</a> or <a href="mailto:andreas.trumpp@hi-stem.de">andreas.trumpp@hi-stem.de</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Colorectal cancer (CRC) classification system that correlates cellular phenotype to clinical outcome	Computational analysis of drug-induced gene expression profiles in CRC provides a classification system that could be used to guide treatment decisions. Gene expression data from 1,290 CRC tumors were analyzed and mapped to a data set of clinical responses to the epidermal growth factor receptor (EGFR) inhibitor Erbitux cetuximab in 80 patients. Six subgroups were identified that corresponded to different levels of disease-free survival. For each subgroup, gene expression and protein biomarkers were identified that could be used to propose subtype-specific therapeutic strategies. Next steps include refining the quantitative gene expression approach and further validating the CRC subtype-specific signatures using additional retrospective sample sets. Eli Lilly and Co. and partners Bristol-Myers Squibb Co. and Merck KGaA market Erbitux to treat CRC and head and neck cancer.  <b>SciBX 6(18); doi:10.1038/scibx.2013.451</b> <b>Published online May 9, 2013</b>	Patent status undisclosed; available for licensing	Sadanandam, A. <i>et al. Nat. Med.</i> ; published online April 14, 2013; doi:10.1038/nm.3175 <b>Contact:</b> Douglas Hanahan, Swiss Institute of Bioinformatics, Lausanne, Switzerland e-mail: <a href="mailto:douglas.hanahan@epfl.ch">douglas.hanahan@epfl.ch</a> <b>Contact:</b> Joe W. Gray, Oregon Health & Science University, Portland, Oregon e-mail: <a href="mailto:grayjo@oshu.edu">grayjo@oshu.edu</a>
Gene expression signature as a prostate cancer prognostic	A 32-gene expression signature could help guide the choice of postoperative treatment for prostate cancer. Bioinformatic analysis of the expression of 1,536 genes in malignant prostate tissue isolated from patients with prostate cancer following radical prostatectomy identified a 32-gene expression signature that correlated with outcome. The signature was validated in a blinded cohort of 270 patients, in which it had greater prognostic value than existing clinical markers. Next steps include looking prospectively to test whether the expression signature predicts disease progression. The work was carried out in collaboration with the bioTheranostics Inc. subsidiary of bioMerieux S.A.  <b>SciBX 6(18); doi:10.1038/scibx.2013.452</b> <b>Published online May 9, 2013</b>	Patented; unavailable for licensing	Wu, C.-L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 26, 2013; doi:10.1073/pnas.1215870110 <b>Contact:</b> W. Scott McDougal, Massachusetts General Hospital, Boston, Mass. e-mail: <a href="mailto:wmcdougal@partners.org">wmcdougal@partners.org</a>

## Can You Afford Not to Read SciBX?

According to MEDLINE®, the U.S. National Library of Medicine's® premier bibliographic database of articles in life sciences, over 775,000 articles were added to the database in 2009 alone—an average of almost 15,000 new articles every week.

Can you afford to miss investment opportunities?

Can you afford to miss emerging competition?

SciBX is the single source for scientific context, commercial impact and the critical next steps.

Visit [scibx.com](http://scibx.com) for details on how to subscribe to SciBX

**SciBX: Science–Business eXchange**

**Erratum: Analysis: Targets & Mechanisms**

Haas, M.J. *SciBX* 6(17); doi:10.1038/scibx.2013.407  
Published online May 2, 2013

The Analysis item “Add radioactivity to the *Listeria*” misstated the indication for CRS-207 (ANZ-207) and erroneously mentioned a second compound. CRS-207 is in Phase I testing to treat malignant pleural mesothelioma, and the second compound name has been removed from the story.

**Erratum: The Distillery: cancer: pancreatic cancer**

*SciBX* 6(17); doi:10.1038/scibx.2013.413  
Published online May 2, 2013

A Therapeutics item on cancer, highlighting an article by Quispe-Tintaya *et al.*, misstated the order of one compound name and its indications and erroneously mentioned a second compound. The correct order for the compound name is CRS-207 (ANZ-207), which is in Phase I testing to treat malignant pleural mesothelioma, and the second compound name has been removed from the item.

## INDEXES

**Company and institution index****A**

AC Immune S.A.	8
Affiris AG	8
Agendia B.V.	4,14
Aragon Pharmaceuticals Inc.	2,12
Astellas Pharma Inc.	11,12
AstraZeneca plc	3,13

**B**

Baxter International Inc.	8
Bill & Melinda Gates Foundation	6
bioMerieux S.A.	16
Brigham and Women's Hospital	8
Bristol-Myers Squibb Co.	11,16

**C**

Center for Structural Genomics of Infectious Diseases	6
Chugai Pharmaceutical Co. Ltd.	11
Columbia University	4
Cytos Biotechnology AG	8

**D**

DREAM Project	4
---------------	---

**E**

Elan Corp. plc	8
Eli Lilly and Co.	8,11,16
European Medicines Agency	1
Evotec AG	12

**F**

Fondazione Telethon	13
Food and Drug Administration	1

**G**

Genomic Health Inc.	5,14
GlaxoSmithKline plc	8
Global Alliance for TB Drug Development	6

**H**

Harvard Medical School	8
Heritage Provider Network Inc.	5
Howard Hughes Medical Institute	1

**I**

IBM Corp.	4
InnoCentive Inc.	4
Intellect Neurosciences Inc.	8

**J**

Johnson & Johnson	8,12
-------------------	------

**M**

Medicines for Malaria Venture	6
Medivation Inc.	1,12
Memorial Sloan-Kettering Cancer Center	1
Mercia Pharma Inc.	8
Merck KGaA	11,16
Midwest Center for Structural Genomics	6

**N**

National Brain Tumor Society	5
National Cancer Institute	4
National Center for Advancing Translational Sciences	5
National Institute of Environmental Health Sciences	5
National Institutes of Health	4,6
Netherlands Cancer Institute	5

New York Academy of Sciences	4
Novartis AG	8,13
Novo Nordisk A/S	13
Noxxon Pharma AG	13

**O**

Oregon Health & Science University	5
------------------------------------	---

**P**

Pfizer Inc.	8
Potentia Pharmaceuticals Inc.	13

**R**

Roche	11
-------	----

**S**

Sage Bionetworks	4
Seattle Structural Genomics Center for Infectious Disease	6
Stanford University	5
Structural Genomics Consortium	6
Symphogen A/S	8

**T**

T2 Biosystems Inc.	14
TB Structural Genomics Consortium	6
Toyota Technological Institute at Chicago	2

**U**

University of Chicago	2
University of North Carolina at Chapel Hill	5
University of Texas MD Anderson Cancer Center	5

**Target and compound index**

AAB-001	8
A $\beta$	8

ACC-001	8
ACI-24	8
AD02	8
AD03	8
AN-1792	8
Androgen receptor	1,12
Anti-C5aR-151	13
APL-1	13
AR	1
ARN-509	2,12
ATP synthase	7
AURKA	10
Aurora-A	10
Aurora kinase A	10

**B**

$\beta$ -Amyloid	8
Betatrophin	12
Bicalutamide	3
Bisaryl-thiohydantoin	2
BRAF	10
Bapineuzumab	8

**C**

C3	13
C5	13
C5a	13
CAD106	8
Casodex	3
CD44	15
CD47	15
Cetuximab	11,16
Checkpoint kinase 1	10
Chk1	10
c-Met proto-oncogene	15
Complement 3	13
Compstatin	13

**D**

Diphtheria toxin	8
DNA gyrase B	7
Docetaxel	1
DR103	3

<b>E</b>		H3F3A	10	MAPK1	10	RNA polymerase	7
EGFR	11,16	H3 histone family 3A	10	MAPK3	10	RV-01	8
Enzalutamide	1,12	Hedgehog pathway	11	MAP kinase 1	10	<b>S</b>	
EpCAM	15	HGFR	15	MAS-1	8	Secoyohimbane	13
Epidermal growth factor receptor	11,16	Hydroxyflutamide	3	MEDI-7841	13	Solanezumab	8
Epithelial cell adhesion molecule	15	<b>I</b>		MER5101	8	<b>T</b>	
Erbix	11,16	IARS	13	MET	15	Tarceva	11
ERK-1	10	IgG2a	9	MicroRNA-146a	12	Tetanus toxoid	8
ERK-2	10	IgG2b	8	miR-146a	12	TFEB	13
Erlotinib	11	Insegia	8	MYCN	10	Transcription factor EB	13
<b>G</b>		IQGAP1	10	<b>N</b>		TYROBP	14
γ-Aminobutyric acid	15	IQ motif containing GTPase activating protein 1	10	NMYC	10	TYRO protein tyrosine kinase binding protein	14
G17DT	8	Isoleucyl tRNA synthetase	13	NN8209	13		
GABA	15	<b>L</b>		NOX-D19	13	<b>V</b>	
Gammagard Liquid 10%	8	LY2062430	8	<b>P</b>		V-myc myelocytomatosis viral related oncogene neuroblastoma derived	10
Gastrin-17	8	<b>M</b>		PF-5236806	8		
<b>H</b>		MammaPrint	4,14	POT-4	13	<b>X</b>	
H3.3A	10			<b>R</b>		Xtandi	1,12
				Rhynchophylline	13		