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THIS WEEK

ANALYSIS

COVER STORY

1 Cancer grows on SOD1
Researchers from Attenuon have found that SOD1 is a master regulatory switch for kinase phosphorylation involved in angiogenesis and cell proliferation. SOD1 thus is a potential target for a variety of cancers and might have some utility in degenerative diseases as well.

TARGETS & MECHANISMS

5 FivePrime's time
Researchers from FivePrime have published proof of concept for the company's secreted protein discovery engine, which was used to identify IL-34. The previously unknown protein is involved in monocyte proliferation, but its functional role in a host of potential diseases now needs to be elucidated.

6 Moving upstream of diabetes
With no approved treatments for metabolic syndrome, two papers in *PNAS* point to a trio of targets for treating two of the syndrome's key features—obesity and insulin resistance. More animal work will determine the best choice of the three targets: a TGF-β receptor called ALK-7 or either of its two ligands, activin B and GDF-3.

8 Swell effect on glioma
Although chemo- and radiotherapy directly attack gliomas, they do not address the neurodegeneration and edema that result from the tumor's invasion. A paper in *Nature Medicine* suggests both effects can be addressed by hitting the same target—the glutamate transporter xCT.

THE DISTILLERY

10 This week in therapeutics
Antagonizing ADRA2 to help with depression; treating cardiomyopathies with sildenafil; targeting IL-2 to treat type 1 diabetes; predicting CLL with an MDM2 SNP; targeting paclitaxel-resistant cancers with taxane derivatives; and more…

14 This week in techniques
Artificial, self-assembling viruses for drug delivery; high throughput protein microarrays; 3D fluorescence microscopy of subcellular processes; and more…

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Cancer grows on SOD1

By Michael J. Haas, Senior Writer

A report in the *Proceedings of the National Academy of Sciences* shows how superoxide dismutase 1 acts as a master regulatory switch for kinase phosphorylation in angiogenesis and cell proliferation, making it a potential target to treat a variety of cancers.[1] Although some mechanistic details remain to be elucidated, superoxide dismutase 1 inhibition could be used in combination with other cancer treatments and might have utility in some degenerative diseases as well.

Superoxide dismutase 1 (SOD1) is one of three SOD enzymes that catalyze the conversion of intracellular superoxide to hydrogen peroxide. Intracellular superoxide is produced when a growth factor binds to its receptor on the cell surface and induces receptor phosphorylation (*see* **Figure 1, "Superoxide dismutase 1 in cancer"**).

Recently, SOD1 was identified as the target of tetrathiomolybdate (TTM),[2] a compound that has antiangiogenic and antitumor activity in mice,[3–5] but whose mechanism of action remained unclear.

In the *PNAS* paper, short interfering RNA and ATN-224, a second-generation TTM from **Attenuon LLC**, were used to study SOD1 inhibition in human umbilical vein endothelial cells (HUVECs) and multiple myeloma (MM) tumor cells.

The research team was led by Fernando Doñate while he was associate director of biology at Attenuon and included scientists from **Cold Spring Harbor Laboratory** and **D.E. Shaw Research**. Doñate is presently director of preclinical R&D at **Proacta Inc.**

The researchers found that in proliferating cells, hydrogen peroxide oxidizes protein tyrosine phosphatases (PTPs)—such as PTP-1B—thus blocking their dephosphorylation activity. PTP inactivation in turn upregulates the kinase cascade, which ultimately drives phosphorylation of MAP kinase ERK-1 and MAP kinase ERK-2, both involved in angiogenesis and cell growth.

When SOD1 was inhibited, hydrogen peroxide levels decreased and PTPs remained active, resulting in reduced phosphorylation of ERK-1 and ERK-2.

"The kinases are still working, but the phosphatases win the battle," Doñate said. "This results in attenuation—not complete shutdown—of the phosphorylating kinase pathways."

Complete inhibition of SOD1 with ATN-224 induced apoptosis in most cell lines the team tested, but Doñate said they have not yet determined how this occurred.

Taken together, he said the results indicate ATN-224 could be complementary to tyrosine kinase inhibitor therapy for cancer. Such

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 38 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
Computational model for predicting drug toxicity	A predictive model for identifying compounds with off-target activity against the membrane transporter protein multidrug resistance–associated protein 2 (MRP2) could help exclude potentially toxic drug candidates from the early stages of drug discovery. Inhibition of MRP2 can disrupt hepatic lipid homeostasis and cause liver toxicity. The computational model discriminated inhibitors from noninhibitors based solely on molecular structure, with predictive powers of 86% and 72% for two different sets of compounds. MRP2 inhibitors were generally larger and more hydrophobic, and they had higher aromaticity and better hydrogen binding capacity than noninhibitors. Next steps include comparing modes of MRP2 inhibition with those of other membrane transporters.	Not patented; unlicensed	Pedersen, J.M. *et al. J. Med. Chem.*; published online May 6, 2008; doi:10.1021/jm7015683 **Contact:** Per Artursson, Uppsala University, Uppsala, Sweden e-mail: per.artursson@farmaci.uu.se
Fluorescence microscopy for 3D imaging of cells	Biplane fluorescence photoactivation localization microscopy (BP FPALM) could be useful for detecting subcellular disease-associated processes that were previously detectable only by electron tomography (sectional imaging). The method imaged layers of 40 nm diameter fluorescent beads at a resolution of about 30 nm laterally and 75 nm axially, which is superior to the 100 nm resolution of 3D light microscopy. The BP FPALM technology is compatible with live-cell imaging. Next steps include developing photosensitive imaging markers and probes.	Two patent applications filed for 3D FPALM; available for licensing from The Jackson Laboratory	Juette, M.F. *et al. Nat. Methods*; published online May 11, 2008; doi:10.1038/nmeth.1211 **Contact:** Joerg Bewersdorf, The Jackson Laboratory, Bar Harbor, Maine e-mail: joerg.bewersdorf@jax.org
High throughput protein microarray	*In vitro* studies suggest that a nucleic acid programmable protein array (NAPPA) could be useful for identifying therapeutic targets in multiple diseases. The method allowed for functional proteins to be synthesized directly from printed complementary DNAs, resulting in high-density arrays of hundreds of gene products. Protein displays were reproducible between replicates within an array and between duplicate arrays. Next steps include evaluating the utility of the method for detecting protein-protein interactions, screening enzyme substrates and measuring small molecule binding kinetics.	NAPPA technology has multiple patents; available for licensing through Auguron Biosciences Inc.	Ramachandran, N. *et al. Nat. Methods*; published online May 11, 2008; doi:10.1038/nmeth.1210 **Contact:** Joshua LaBaer, Harvard Medical School, Cambridge, Mass. e-mail: joshua_labaer@hms.harvard.edu
Nanoparticle drug delivery of chemotherapeutics	Studies *in vitro* and in xenograft mice suggest that nanoparticle-mediated delivery of paclitaxel prodrugs could offer improved activity over commercial formulations of paclitaxel. The prodrugs were formulated in polymer-stabilized nanoparticles, and the rate of prodrug release could be adjusted by varying the hydrophobicity of the prodrug's lipid anchor. Next steps include toxicology studies of the nanoparticle prodrugs. Paclitaxel is a generic chemotherapeutic that is marketed to treat multiple types of cancer. No fewer than 24 companies have paclitaxel-based compounds and delivery devices in development stages ranging from preclinical to marketed.	Patent applications filed for the nanoparticle technology; available for licensing	Ansell, S. *et al. J. Med. Chem.*; published online May 9, 2008; doi:10.1021/jm800002y **Contact:** Steven M. Ansell, Celator Pharmaceuticals Corporation, Vancouver, British Columbia, Canada e-mail: sansell@celatorpharma.com
Self-assembled artificial viruses for drug delivery	An artificial filamentous viral assembly could offer improved bioavailability compared with that of conventional carriers for delivery of gene therapy or encapsulated molecules. As proof of concept, the viral assembly transfected HeLa cells with GFP short interfering RNA with efficiency comparable to that of Lipofectamine 2000 (LF2000), an RNA transfection reagent marketed by Invitrogen Corp. The viral assembly also delivered molecules of the dye Nile red to both the cytoplasm and nucleus of the HeLa cells. Next steps include refining the technique to incorporate additional functional properties of natural virions into the artificial ones, such as endosome escape, efficient cell binding, nucleus localization and tissue targeting.	Not patented; licensing status not applicable	Lim, Y.-B. *et al. Angew. Chem. Int. Ed.*; published online May 7, 2008; doi:10.1002/anie.200800266 **Contact:** Myongsoo Lee, Yonsei University, Seoul, Korea e-mail: mslee@yonsei.ac.kr