

## Lab Reports

### Brain Protein May Suggest New Epilepsy Treatment Strategy

A protein produced within the brain acts like antiepileptic drugs, report researchers from Stanford University School of Medicine in Stanford, California (Christian CA et al. *Neuron*. doi:10.1016/j.neuron.2013.04.026 [published online May 30, 2013]). In addition to being an intracellular transporter of a metabolite called acyl-CoA, the protein, diazepam binding inhibitor (DBI), binds to receptors on nerve cells that are responsive to the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>).

Using single nerve cell-recording techniques, the researchers showed that within the brain's thalamic reticular nucleus, DBI has the same inhibition-boosting effect on GABA<sub>A</sub> receptors as do benzodiazepines. Diazepam binding inhibitor lost its effect in bioengineered mice with GABA<sub>A</sub> receptors that had a defective benzodiazepine-binding site, which made the mice seizure-prone. In normal mice, a compound known to block the benzodiazepine-binding site weakened these same receptors' inhibitory activity in the thalamic reticular nucleus.

Mice lacking the gene for DBI were also seizure-prone and had diminished activity of benzodiazepine-responsive GABA<sub>A</sub> receptors. When the gene was reintroduced, the strength of GABA<sub>A</sub> receptor-induced inhibition was restored.

The findings suggest that enhanced DBI signaling could represent a new therapeutic strategy to treat epilepsy and other neurological disorders.

### New Clues, Potential Solution to Cancer Drug's Cardiotoxicity

The anticancer drug sunitinib, which is known to damage heart muscle, destroys cells called pericytes that wrap around blood vessels and are essential to their function, report scientists from Amgen, in South San Francisco, California, in collaboration with investigators at the University of Texas and Baylor College of Medicine, in Houston (Chintalgattu V et al. *Sci Transl Med*. 2013; 5[187]:187ra69).

Pericytes are dependent on signaling by platelet-derived growth factor receptor

(PDGFR), a protein targeted by sunitinib. By using the PDGFR inhibitor CP-673451, the researchers were able to recapitulate the kind of cardiotoxicity that sunitinib produces.

Also, mice that were treated with sunitinib developed cardiac and coronary microvascular dysfunction and demonstrated an impaired cardiac response to stress that was accompanied by a substantial depletion of pericytes.

Treatment with thalidomide, which is known to exert beneficial effects on pericyte survival and function, prevented sunitinib-induced pericyte cell death in vitro and prevented sunitinib-induced cardiotoxicity in a mouse model without appearing to affect sunitinib's anticancer potency.

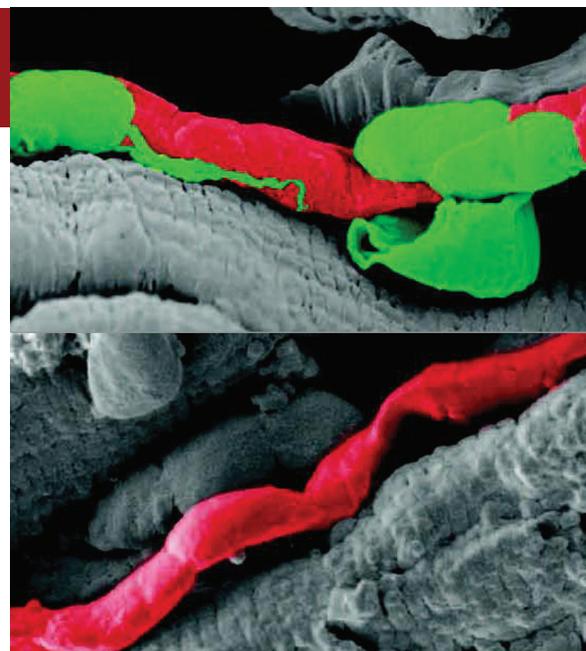
In addition to identifying pericytes as the primary cellular target of sunitinib-induced cardiotoxicity, the findings provide preliminary evidence that thalidomide may be able to help protect the heart health of patients treated with sunitinib.

### Newly Designed Protein Augments Efficacy of Anticancer Antibodies

Some tumor cells express a protein called CD47 that signals macrophage immune cells not to engulf and destroy them. Now researchers from Stanford University Medical Center have created variants of the receptor for CD47 that act as antagonists of CD47 and boost the effectiveness of antitumor antibodies (Weiskopf K et al. *Science*. doi:10.1126/science.1238856 [published online May 30, 2013]). The new variants had approximately 50 000-fold increased binding affinity for human CD47 relative to the wild-type receptor.

Although the antagonists blocked CD47 in tumor-bearing mice, they still had to be paired with any of a number of antitumor antibodies to effectively induce macrophages to engulf the tumor cells. Mice receiving both therapies had augmented responses compared with those that received either therapy alone. A toxicity study in cynomolgus macaques suggested that the strategy may be safe in humans.

This "one-two punch" directs immune responses against tumor cells while lowering the threshold for activation of macro-



The loss of pericytes that surround blood vessels appears to cause the cardiotoxicity of the anticancer drug sunitinib. Studies revealed that pericytes (green) seen in control mice (top) are absent in sunitinib-treated mice (bottom).

phages, according to the authors. They suggested that the approach may provide a universal method for increasing the efficacy of anticancer antibodies that are currently available or are under investigation.

### Potential Targets Found for Neurodegenerative Disease

Using cross-species genetic screening in *Drosophila*, human cells, and a mouse model, researchers have identified proteins that modulate levels of the mutant ataxin 1 (ATXN1) protein that accumulates in the neurodegenerative disease spinocerebellar ataxia type 1 (SCA1). The proteins, components of the RAS-MAPK-MSK1 pathway, are potential therapeutic targets for the disorder, they said (Park J. *Neuron*. doi:10.1038/nature12204 [published online May 29, 2013]).

Because the pathway is involved in the early stages of SCA1, targeting it could potentially delay disease development. Indeed, drugs that inhibit different components in the pathway reduced ATXN1 levels and suppressed neurodegeneration in *Drosophila* and mice.

Similar screening techniques might be used to identify drug targets for other neurodegenerative diseases, according to the authors.—Tracy Hampton, PhD