

The good, the bad, and the ugly of the blood-brain barrier

By Jordan St Charles

In his Big Picture, Small Talk seminar Dec. 9, David Miller, Ph.D., deputy chief of the Signal Transduction Laboratory, described how therapeutic drugs and other foreign chemicals move around the body.

A new seminar series

Big Picture, Small Talk is a new series organized by Abee Boyles, Ph.D., of the National Toxicology Program, and by a cross-divisional organizing committee with the goal of presenting NIEHS research in a format that is more accessible to nonspecialists. Previous talks were given by [John Schelp](#), Geoffrey Mueller, Ph.D., and [Richard Kwok](#), Ph.D., with topics ranging from allergies to epidemiology.

“Feedback from participants has been positive, with people consistently commenting that the talks increase their knowledge of the topic, and that they enjoy learning more about research conducted at the institute,” said Boyles.

How drugs travel through the body

Miller began his talk by defining pharmacology, the science of how drugs interact with the body. He explained that drugs move through the body using the circulatory system.

Ingested drugs enter the circulatory system through the small intestine, then travel to the liver, where they can be metabolized into different forms. “From the liver, many of these metabolites get dumped into the blood and distributed throughout the body,” said Miller.

The blood-brain barrier and research in the Intracellular Regulation Group

Certain tissues, such as the brain, placenta, and testes, have additional barriers to drugs. The brain is protected by a feature known as the blood-brain barrier. Blood entering the brain moves into small capillaries lined with endothelial cells, which Miller compared to a brick wall. There are plugs, called tight junctions, between the endothelial cells and transporters on the cell membranes. Efflux transporters recognize and block foreign chemicals.

Miller explained that in addition to keeping out dangerous chemicals, the blood-brain barrier may also keep out helpful drugs, such as chemotherapeutics. Research in Miller’s lab focuses on finding ways to move drugs that have been shown to be effective in the test tube past the blood-brain barrier, so they can be effective in treating tumors in the brain.

He showed several experiments featuring his favorite transporter, p-glycoprotein. In one experiment, the transporter was blocked with a drug called cyclosporine, which allowed chemotherapeutics to get across the barrier. Unfortunately, this method was only effective with levels of cyclosporine high enough to cause side effects.

To avoid these side effects, Miller’s lab focuses on finding ways past the transporters by using cell-signaling molecules that would turn off the transporter. Patients would be treated with both a drug that signals the transporter to be turned off and a therapeutic drug, such as Taxol. “So by manipulating the dose and timing of the drug, I could create a time window when Taxol would go in, since the transporter is not working. But then the window would close, and the transporter would be there to protect the brain against other nasty things,” he said, demonstrating the complexity of the challenges researchers face.

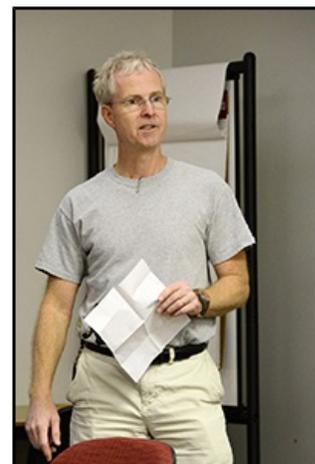
(Jordan St Charles, Ph.D., is an Intramural Research and Training Award fellow in the DNA Replication Fidelity Group at NIEHS.)

Upcoming Big Picture, Small Talk

Big Spill, Small Talk: What Was in the Elk River Spill?

Scott Auerbach, Ph.D.,
National Toxicology Program

Tuesday, Jan. 20, 2015
1:00 – 2:00 p.m., Keystone
1003



Gary Bird, Ph.D., of the Signal Transduction Laboratory, introduced Miller, who joined NIEHS in 1985. (Photo courtesy of Steve McCaw)



Geoff Mueller, Ph.D., left, and Lars Pedersen, Ph.D., both of the Genome Integrity and Structural Biology Laboratory, pondered the difficulties of the blood-brain barrier. (Photo courtesy of Steve McCaw)



Miller spoke about pharmacology using many metaphors, including comparing his research to the movie “The Good, the Bad, and the Ugly.” (Photo courtesy of Steve McCaw)

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