

Fast ForwardSM

Accelerating Innovation Fund

This project is funded through a collaboration between Fast Forward, LLC, established by the National MS Society to speed potential therapies into drug development and clinical trials, and EMD Serono, Inc., an affiliate of Merck KGaA, Darmstadt, Germany. Fast Forward and EMD Serono committed \$3 million in 2009 to support innovative early-stage projects directed towards the development of therapies to prevent, treat, or reverse nervous system damage in MS. This Request for Proposals (RFP) issued under the auspices of a multi-year collaboration between Fast Forward and EMD Serono to accelerate innovation and commercial development of MS therapies. Merck KGaA, the parent corporation of EMD Serono, Inc., will provide up to \$19 million in total funding for the collaboration.

<i>Primary Investigator</i>	<i>Project Title</i>	<i>Amount to be Committed</i>
Katerina Akassoglou, PhD The J. David Gladstone Institutes University of California, San Francisco, CA	Small Molecule Inhibitors of Microglial Activation	\$300,000 Term – 12 months

About the Investigator

Katerina Akassoglou, PhD, is an Associate Professor at the Department of Neurology at University of California, San Francisco and an Associate Investigator at the Gladstone Institute of Neurological Disease. She has been working in the field of neuroinflammation and MS for the past 16 years. She earned her PhD in neurobiology at the University of Athens in Greece and also trained at the University of Vienna in Austria under the supervision of Hans Lassmann, where she developed a novel transgenic animal model for MS. As a recipient of the Human Frontier Science Program postdoctoral fellowship and the Young Investigator Award from the Wadsworth Foundation, she performed her postdoctoral studies at the Rockefeller University and New York University. Her research on interactions of the blood protein fibrinogen with the nervous system identified fibrinogen as a potential therapeutic target in MS. For this work, Dr. Akassoglou received the Presidential Early Career Award for Scientists and Engineers awarded by The White House and the John J. Abel Award in Pharmacology awarded by the American Society of Pharmacology and Experimental Therapeutics (ASPET) and Eli Lilly.



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Project Background & Goals

In a healthy immune system, brain cells known as “microglia” help to keep the brain and spinal cord safe from infectious agents. The immune system proteins that protect the rest of the body are too large to cross the blood-brain barrier (BBB, the lining of cells that protects the brain) so it is microglia that must recognize invaders and initiate the immune defense.

Unfortunately, many immune system defenders switch to the offense in the immune attack in MS. In MS lab models, it is believed that microglia get involved early, acting as “antigen-presenting cells”— the cells that serve up triggering molecules to immune T cells and spur on the attack.

Katerina Akassoglou, PhD (University of California, San Francisco) and colleagues have uncovered evidence that a molecule called fibrinogen, known as a blood clotting factor, directly activates microglia. They have developed a method of inhibiting fibrinogen in mice without compromising its clotting capabilities. By inhibiting fibrinogen in mice with EAE after the first attack, they were able to decrease the activation of microglia, and this dramatically diminished subsequent damage to nerve fiber-ensheathing myelin (a main target of the MS attack). The treated mice recovered faster as well, and didn’t experience further relapses.

This team has also shown that inhibiting fibrinogen specifically from interacting with a molecule called CD11b protected mice from myelin damage, nerve fiber damage (which contributes to long-term disability in people with MS) and it also diminished T cell infiltration into the brain and spinal cord.

Now this team is using cutting-edge technology to identify compounds that can stop fibrinogen from interacting with CD11b to prevent the activation of microglia in MS. In collaboration with the UCSF Small Molecule Discovery Center they are using two methods for testing numerous molecules simultaneously. One method will capture molecules that can inhibit fibrinogen from linking to CD11b, and one will pinpoint molecules that can affect the signaling pathways that this interaction sets off.

Results from this study have the potential to reveal novel compounds that may stop the MS attack in its tracks.