KATERINA AKASSOGLOU LAB

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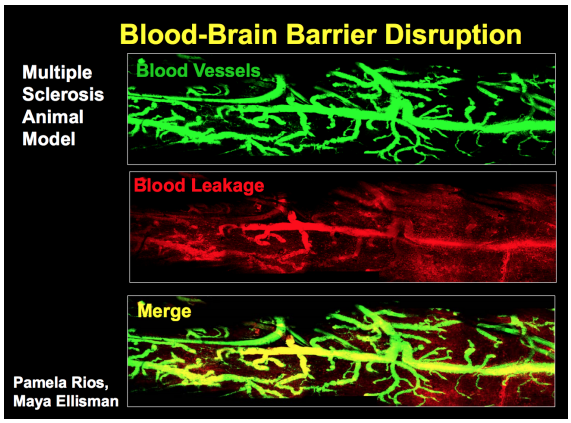
One paralyzed mouse. The road to new ways of thinking about what causes neurological degenerative diseases and how to diagnose, track, and treat them—as well as the means to visualize their development in real time—all started with a single mouse.

AN UNEXPECTED DISCOVERY

In the mid 1990s, Katerina Akassoglou (pronounced ah-KAH-so-gloo) was working on her PhD in a lab studying systemic inflammation in arthritis. To test theories about a cell-signalling factor associated with the disease, the lab's scientists had genetically designed mice to produce constant quantities of that protein. But one mouse hadn't developed arthritis; instead it was paralyzed, with symptoms resembling those of multiple sclerosis (MS). Given the job of figuring out why, Dr Akassoglou made an unexpected discovery: In the paralyzed mouse, the immune factor had opened holes in the brain's blood vessels, spilling proteins into its brain.

This finding ultimately led not only to the development of a new mouse model of MS, but also to the realization that a disease like MS, which is primarily characterized as an autoimmune disease, could potentially be triggered by the failure of a different system—in this case, by blood breaching the blood-brain barrier.

INVESTIGATING THE CAUSES OF NEURODEGENERATION



The presence of inflammation and blood in the brain of patients with MS was first observed more than 150 years ago. Since then, the presence of blood in the brain and its correlation with neuron cell damage and death has been established as a hallmark not just of MS but *every* neurological disease, including Alzheimer's, brain traumas, spinal cord injuries, and different forms of epilepsy. The question was, was the presence of inflammation and blood the result of MS, or part of its cause?

It took the cross-disciplinary mindset of Dr Akassoglou, whose training is not only in neuroscience but vascular biology and immunology as well, to ask—and start answering—that question.

A THREE-PRONGED ATTACK

Observing that there was significant damage and death of neuron cells in the areas surrounding the blood leakage, Dr Akassoglou began investigating whether blood could activate immune processes that would cause neurodegeneration.

Within X years, she and her team determined that when blood leaks into the brain, it does damage in three ways, causing inflammation, creating a toxic environment that kills neurons, and stopping the brain's progenitor stem cells from carrying out their normal repair processes. Further research has shown that in addition to halting healing, the presence of blood actually causes the brain's stem cells to turn into cells that further contribute to the damage.

Now sure that the presence of blood was not just a byproduct of neurological disease but a large contributor to its development, Dr Akassoglou and her lab worked to identify which of the many proteins carried in blood might be causing the inflammation and associated damage in patients with MS. To do so, they developed specialized imaging tools and techniques (see sidebar).

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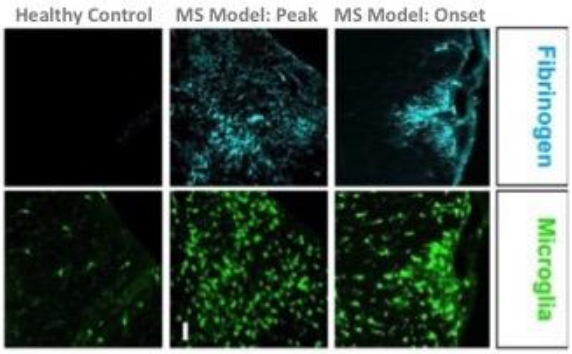
Ultimately, Dr Akassoglou's lab identified fibrinogen as the key protein in the blood that binds to brain cells and subsequently induces inflammation, neuron damage, and scar formation. It is active in brains of people and animals with diseases of the peripheral and central nervous systems, such as MS, traumatic brain injury, and Alzheimer's. And when Dr Akassoglou's team developed animal models in which fibrinogen's component fribin was depleted, they observed improved healing.

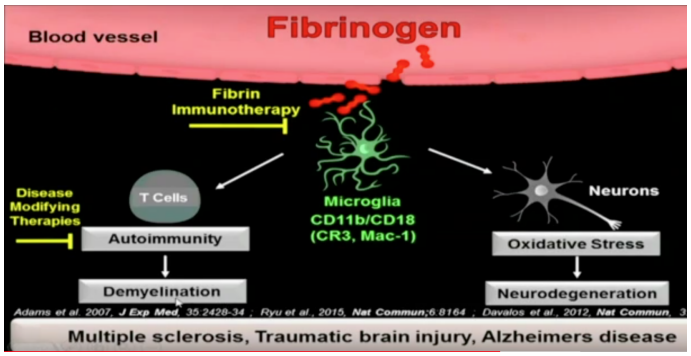
However, fibrinogen is also an important part of the body's natural inflammation and wound-healing cascade—fibrinogen is converted to fibrin for blood clotting—and thus the team developed a monoclonal antibody, 5B8, that stops fibrinogen from damaging the brain while maintaining its beneficial coagulation effects outside of the brain.

[SIDEBAR: NEW INVESTIGATIVE TOOLS
Dr Akassoglou's team has developed several techniques—using powerful lasers, multi-photon microscopes, 3D imaging, and specially designed molecular probes—that have enabled them to observe, in real time, what happens in the brains and spinal cords of mice. Their techniques generate raw video imaging that needs no additional processing and can be used immediately for analysis.]



Other MS treatments have targeted processes that occur after the blood leakage, such as the autoimmune activity of T cells. But the 5B8 monoclonal antibody targets processes upstream, giving it the potential to not just stop the autoimmune activities of T cells but also prevent neuronal damage, oxidative stress, and neurodegeneration.

Several years of preclincial testing in MS and Alzheimer's disease animal models have shown that 5B8:



- Preferentially binds to fibrin rather fibrinogen (thereby helping preserve the positive effects of fibrinogen)
- Does not affect anticoagulation or other immune pathways that help fight infection
- Inhibits the activation of microglia, a sign of inflammation
- Reduces the recruitment of peripheral macrophages
- Inhibits proinflammatory gene expression
- Reduces demyelination, axonal damage, and oxidative stress
- Reduces symptoms of MS, such as relapse and paralysis

FUTURE STEPS

Dr Akassoglou believes that fibrinogen may be able to serve as a valuable biomarker for diagnosing and tracking the progression of neurological diseases. Further, she and her team have found that there are bidirectional molecular communication mechanisms between the blood and brain that may affect the degree of damage and the ability of tissues to regenerate, both in and outside of the nervous system. Using their advanced imaging techniques, the members of the Akassouglou lab are continuing their work in these many avenues of research, with its potentially far-reaching ramifications for millions of people worldwide.

However, Dr Akassoglou and her team of scientists cannot do this work alone. They need prescient philanthropists who realize that supporting highly innovative translational initiatives is the best way to develop real solutions for devastating brain diseases. They need the backing of individuals who understand that good science is not just the result of many scientists carrying out studies carefully designed to test theories without ambiguity, but it is also exemplified by a desire—and the latitude—to explore unanticipated byways...such as the fate of a single mouse.
Join Gladstone in helping science overcome disease.