## Watching ALS mice walk

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that results in the progressive loss of motor neurons, voluntary muscle control, and the eventual death of those it afflicts. Though only a small percentage of ALS cases have a (known) genetic basis, transgenic mice have been important for understanding the disease. In 2009, Arthur Horwich and his lab at Yale developed a mouse model expressing the human SOD1 gene, responsible for about 20% of inherited human cases, along with a fluorescent YFP tag for monitoring gene expression. Most mice of this strain will become paralyzed and die by six months of age. Yet up until only a few days before paralysis, the mice move about with seemingly little difficulty.

Identifying the underlying changes to peripheral neural network function in the SOD1 model has been the focus of lab member Muhamed Hadzipasic. In a previous in vitro study involving spinal cord slices, Hadzipasic broadly categorized four classes

of motor neurons based on their firing speed and found that by four months, SOD1 mice will have lost all of the fastest spiking ones. The next step meant moving beyond tissue samples; his in vivo follow-up is reported in the Proceedings of the National Academy of Sciences (113, E7600-E7609; 2016).

Capturing movement was important to Hadzipasic because of the tangible connection between motor system output and motor neuron physiology. To record activity in awake, moving animals, he adapted and combined a head-fixed wheel platform with a spinal brace previously used for anesthetized imaging. With sugar water as a reward, the mice were trained to walk on the wheel while head- and lumbar spine-fixed, allowing highspeed video recording of gait as well as EMG and single-unit recordings of motor neurons.

Though stride length was maintained over much of the course of disease progression, the high-speed video showed increases in gait variability. EMGs revealed highly fractionated, "choppy" signals and overlapping



flexor and extensor muscle contractions. And single-cell recordings confirmed the in vitro observation that the fastest firing neurons are lost as the disease progresses, along with a lack of synchronization at the individual unit level.

Though exactly why the fast firing neurons die off first remains to be seen, both Hadzipasic and Horwich believe the results may point towards a broader understanding of motor system failure. According to Horwich, "We think ALS represents a multifaceted but common way that the motor system falls apart...if we can understand something about how it collapses, we might be able to generate some means to slow that down or even prevent it, regardless of what the primary triggering cause might be."

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## CHRONIC WEST NILE AND THE COLLABORATIVE CROSS

Inbred mice have been instrumental in biomedical research. Essentially clones of one another, they can offer researchers low variability between animals, increasing the power of their studies. Genetic diversity is not necessarily a bad thing though—it can help increase the predictive value of the models for human disease—but until recently it was challenging to control. The development of Collaborative Cross mice, in which multiple lines derived from both inbred and wild-type animals are interbred without losing track of their genotypes, is reintroducing genetic diversity in a controlled manner.

Collaborative Cross mouse lines are important tools in on-going immunogenetics project at the Fred Hutchinson Cancer Research Center to screen for emerging or extreme phenotypes prompted by different viral infections. As part of this effort, researchers working with West Nile Virus have identified a novel phenotype that models chronic infection (PLoS Pathog. 12, e1005996; 2016).

Most immunological work with West Nile Virus has been conducted in C57BL/6J inbred mice. Though infection in these mice is well characterized for acute symptoms, lead author Jessica Graham comments, "at the same time, there's a wide variety of symptoms and outcomes in humans that simply are not being observed in just one inbred strain," a common problem in classic models. Testing several Collaborative Cross mouse lines, the researchers identified a line in which viral RNA would persist, often with minimal symptoms, in the brain for several months. Looking more closely at immune responses in this model of chronic infection, the team observed changes in Regulatory T cells, responsible "for maintaining that balance of trying to clear the pathogen without doing too much damage and destroying neural tissue that can't be regenerated." In the chronic model, these cells appear to suppress immune responses enough that the virus can manage to linger on. Because the mice used have been genotyped, future work will look for potential genetic underpinnings as well as parallels to human infections.

The chronic infection discovered using this model is one example of multiple emerging phenotypes identified by the larger screening work, the results of which the researchers hope to share with the immunology community; the data itself is being uploaded to the NIH ImmPORT resource. Rather than having to undertake their own intensive (and expensive) screens, Graham explains, researchers looking for a particular phenotype can take advantage of the database to identify a smaller number of potential lines for testing with their own infectious diseases. All against a diverse but documented genotype, thanks to the Collaborative Cross.

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