The Robert Packard Center for ALS Research Projects Funded by MDA's Wings Over Wall Street® 2009-10

Scientists with the Packard Center for ALS Research at Johns Hopkins continue to make vital discoveries about ALS — to shed light on its cause, to explain the course of the disease at a molecular level, and to find and study the genes that either cause it outright or make people susceptible to it. All this, of course, drives Packard's single-minded goal: Find therapies to beat the disease.

Our scientists, for example, first explained one of the main reasons for cell death in ALS. That find formed the basis for a decade of drug discovery leading to Riluzole, the only FDA-approved drug for ALS.

Scientific work at Packard is not about throwing darts at a board, hoping for a bulls-eye, but rather about taking deeply thoughtful, tailored approaches based on the cumulative understanding of ALS from the world's leading scientists. This past year, thanks to the generous funding from MDA's Wings Over Wall Street®, more than **30** outstanding researchers collaborated in our performance-driven model.

In addition, the projects our Center scientists share with other organizations widen the chances of discovery and shorten the path to therapy. Our strong ties with P²ALS, for example, a tight group of top researchers from Packard and Project A.L.S., has advanced gene-silencing as a therapy for familial ALS. The collaboration is also on the verge of making a plentiful supply of *human* ALS cells a reality. Having actual human ALS cells or tissues to study has been a holy grail of ALS research. They can reveal errors in the true disease; they can be our closest models for drug-testing.

The solid discoveries that your support made possible this year include the following:

<u>ALS Genetics</u>

- Scanning DNA data from European families, Bryan Traynor uncovered VCP, a new ALS gene, using a brand-new, sophisticated way of surveying DNA.

- Aaron Gitler discovered the Ataxin-2 gene, which stands out as the first susceptibility gene for ALS. The work to understand why that gene increases risk has revealed a new target to investigate for therapy.

<u>New Animal Models</u>

- Phil Wong's mouse model that carries the mutant TDP-43 gene (it's in *both* familial and sporadic patients) mirrors human ALS in important new ways, including paralleling the time course of the disease.

- J. Paul Taylor has created a fruit fly model of the new VCP gene. The model lets him map the gene's most likely effects and is helping solidify the idea of what events are most crucial — and targetable for therapy — in ALS's beginnings.

- The inexpensive, efficient roundworm model of ALS that Jiou Wang engineered features the TDP-43 gene now under such intense study. Already, his model has shown an unsuspected connection to the aging process and a new potential therapeutic target worth investigating.

Basic Science

- Dwight Bergles' discovery that ALS trips a huge outpouring of oligodendrocytes (one type of nervous system cell) in both animal models and patients, from a type of stem cell that he uncovered earlier is a major find. Understanding why this outpouring occurs is the next step, and one that offers a plausible reason for the death of nerve cells in ALS.

- Mitochondria, the tiny organs within cells that produce most of the energy for life, are vulnerable in ALS. This year, Packard-associated scientists Piera Pasinelli and Don Cleveland separately showed specific ways that they go wrong. Screening drugs for something that could "heal" mitochondria could produce one that changes the course of ALS.

- Work by Jonathan Glass has strengthened the case that ALS is, in part, a disease of the axons that extend from a motor neuron's cell body to muscle. He's shown that a normal supply of a common (SOD1) antioxidant enzyme is necessary for healthy axons, that the lack of it mimics ALS.

- Jack Griffin and Mohamed Farah singled out an agent originally tested to damp down a protein that builds up in Alzheimer's-damaged brains. They discovered it makes injured nerve endings grow back significantly faster.

Also, the two scientists created a new way to follow disease in whole nerves of ALS models—in real time—as well as, potentially, the effects of potential therapies.

Drug Discovery

- Rita Sattler has streamlined assays to tell if the experimental drug ceftriaxone—now in Phase III trials—is working or if other offshoot drugs would be better. She's testing drugs that have the same target but which may have better penetration and staying power.

- As part of a P^2ALS project, Nicholas Maragakis is testing glial-restricted precursors (GRPs) to protect the nervous system from ALS. Earlier, he showed that adding rodent GRPs extends life and lessens damage in ALS rats. Now he's testing *human* GRPs in animal models of ALS for therapy potential.