Meet Dr. James Shorter: ALS Researcher Dedicated to Understanding What Causes ALS

Meet Dr. James Shorter, professor of Biochemistry and Biophysics at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. He and his team work tirelessly in the lab to better understand the causes of ALS, so those causes can be translated into potential therapeutic targets. The ALS Association has proudly funded him since 2014.

Dr. Shorter's work focuses on protein homeostasis, which is how proteins in the cells of the body fold into specialized structures to perform specific functions. Sometimes protein misfolding occurs, which allows the formation of protein aggregates (clumps of protein).

When protein aggregates are in the form of fibrils and oligomers, they can be harmful to cells. Dr. Shorter and his team's goal is to understand how protein misfolding occurs and how cells can prevent it from happening.

In ALS disease, it is known that certain RNA-binding proteins, such as TDP-43, FUS, hnRNPA1, and hnRNPA2, mis-localize from the cell's nucleus into the cytoplasm and accumulate in cytoplasmic aggregates (protein clumps). Mutations in a specific area of these proteins, called prion-like domains, play a part in accelerating fibrillization that causes toxicity in cells.

In the last few months, Dr. Shorter and his team have published two papers in high-impact journals, *Cell* and *Molecular Cell*, that help get to the core of how mechanisms in the cell can prevent toxic aggregation. These newly defined prevention methods represent potential therapeutic targets that could prevent neurodegeneration.

We sat down with Dr. Shorter to learn more about how he and his team worked together to learn more about preventing the toxic aggregation of proteins.

Congratulations on your recent publications! We're excited to learn more about your work and your motivations to work in the ALS space. First, why do you like working in ALS research and what motivates you?
Thank you! We're excited to try and understand the basic processes that go awry in people with ALS, so that we can develop methods to put these things right and intervene therapeutically. In particular, we're motivated to find therapeutic solutions for ALS that eliminate cytoplasmic clumps of RNA-binding proteins, like TDP-43, and restore them to the nucleus.

What are the major takeaway messages from these papers?
In the first paper, an exciting collaboration with Dr. J. Paul Taylor at St. Jude and several others that was published in *Cell*, we discovered that a class of protein called nuclear-import receptors (NIRs) can break up cytoplasmic clumps of RNA-binding proteins like TDP-43 and FUS.
Not only did the NIRs break up these clumps, they also returned the RNA-binding proteins to the nucleus where they could perform their important functions. In this way, NIRs could rescue neurodegeneration in fly models of ALS.

In the second paper, an exciting collaboration with Dr. Nancy Bonini at Penn that was published in *Molecular Cell*, we discovered that a type of polymer found in cells, called poly(ADP-ribose) or PAR, binds to the major ALS protein, TDP-43, and prevents TDP-43 from forming pathological clumps in the cytoplasm.
We also found that inhibition of enzymes that make PAR polymers, called PARPs (PAR polymerases), helped to keep TDP-43 in the nucleus and prevented accumulation of TDP-43 in the cytoplasm. Importantly, reducing PARP levels rescued neurodegeneration in a fly model of ALS.

How do your findings bring us closer to new ALS therapeutics?
The first paper indicates that finding ways to elevate NIR expression, which can be reduced in people with ALS, may be therapeutic as it would combat aggregation and mislocalization of RNA-binding proteins connected to ALS.

We're excited to explore ways to deliver NIRs to mouse models of ALS in an effort to rescue them. We are also screening for small-molecule drugs able to get into the brain that increase NIR expression or activity, which could also be therapeutic leads for ALS.

The second paper, and a follow up paper published in *Acta Neuropathologica Commununications*, suggest that PARP inhibitors could be interesting candidates to develop into ALS therapeutics. This possibility is particularly exciting because PARP inhibitors are already FDA-approved drugs for various cancers. We're excited to partner with AstraZeneca to try and develop PARP inhibitors specifically for ALS.

Dr. Shorter and his team

How has funding from The ALS Association helped your research efforts?

Funding from The ALS Association to support our work has been extremely important. It has allowed us to pursue high-risk projects that could have large rewards. We're excited to build on our studies funded by The ALS Association to generate therapeutic leads for ALS.

We always enjoy getting to know the scientist away from the bench. What do you enjoy doing outside of the lab?

I'm a huge Philadelphia Eagles fan and enjoy hanging out with my wife and cat when not in lab.

Thank you, Dr. Shorter. We're thankful you and your team are working so hard to help us realize our vision of creating a world without ALS.

Paper citations:

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Link to open access paper: https://doi.org/10.1186/s40478-018-0586-1