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United Against ALS

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By Christie Rizk

Collaborations can be a bit of a crapshoot. Those involved can never really be sure whether anything will come out of their efforts. Sometimes, though, even if the study falls apart, the experience of working together can be valuable enough. That was the case for Benjamin Wolozin, from the Boston University School of Medicine, and Marcie Glicksman, co-director of the Harvard Neurodiscovery Center's Laboratory for Drug Discovery in Neurodegeneration. When Wolozin and Glicksman worked together on a study searching for LRRK2 inhibitors, they didn't get the results they were hoping for, and the project ended. But when Glicksman's center sent out another request for collaborators on a study to find therapeutics for amyotrophic lateral sclerosis, Wolozin was quick to respond.

Glicksman's LDDN is a "one-stop shop" for high-throughput drug discovery, Wolozin says. At any given time, the center is in the midst of 15 to 20 projects, all in various stages of development, and all of "The whole idea is that we provide the drug them with collaborators. discovery expertise, having come from industry and been involved in multiple drug discovery projects," Glicksman says. "Each of our collaborators brings the science and we work with them on how to convert their science into a drug discovery project. It's very complementary."

"They have the robotics and the medicinal chemistry in place, so you don't really have to go too far," Wolozin adds. "It's easy to see how to move things forward, instead of trying to figure it out at every step." Boston University is working on building a setup much like LDDN's, Wolozin says, but currently doesn't have the kinds of resources to do the robotic screening and high-content or high-throughput assays for these types of studies, nor the personnel to help carry them out.

But beyond that, the two collaborators say, they simply enjoy working with each other. "I find it really easy to work with Marcie," Wolozin says. "I like it."

Glicksman agrees. "Ben is a great collaborator."

Stop the aggregation

The ALS project itself is still in the early stages. The disease is characterized by an abnormal accumulation in motor neurons of insoluble and misshapen proteins, the major component being Tar DNA-binding protein 43. In 2006, researchers at the University of Pennsylvania first identified TDP-43 as the largest component of the inclusions found in the neurons of many ALS patients. It is thought that inhibiting the accumulation of TDP-

43 might also prevent these inclusions from developing — and slow down the process of neuro-degeneration.

According to Wolozin, the researchers are currently using cell-based assays and high-throughput screening to slog through LDDN's collection of 150,000 compounds to find molecules that inhibit the aggregation of TDP-43 and the formation of inclusions that cause not only ALS, but fronto-temporal dementia as well. Using a neuronal cell line that stably expresses GFP-tagged TDP-43, Wolozin says, the team will test hits to determine whether they inhibit stress granule-formation, which is linked to TDP-43 aggregation.

"We have a couple of compounds that are giving an interesting phenotype, which we're looking at in more detail," Glicksman says. The team will most likely take the next three or four months to test about half of the compounds in LDDN's library and then do characterizations of the hits they see. Glicksman says they're also performing an assay optimization in tandem with the study.
Wolozin says he actually started with the US Food and Drug Administration's library of compounds — but didn't get any promising hits — before moving to LDDN's library. With LDDN's compounds, he has identified molecules that actually stimulate inclusion formation instead of inhibiting it.

"One of the benefits, and the drawbacks, of the high-content screening is that the compounds we're looking at might act by directly interfacing with TDP-43 and they could also act on the biochemical processes that regulate TDP-43 inclusion formation, so there's a lot of ways of interfacing there," Wolozin says.

But even the identification of the compounds that do the exact opposite of what the researchers want them to do is valuable information, he adds. Those compounds have proven to be "biologically interesting" and could provide clues as to which compounds will work to reduce inclusions. Some of the compounds that they have tested have shown a small reduction in inclusions, some up to 50 percent, but the researchers are looking for "much better than that," Wolozin says. The researchers are keeping their options open, in case they don't find what they're looking for. "We can either mix and match or use medicinal chemistry" to combine compounds with less than 100 percent effectiveness, Wolozin says.

Though they are not far enough along to reach any conclusions, "I really think we're going to find what we want," he says. "I would be surprised if we didn't come up with some hits."

Glicksman is also hopeful. "Often what we look for is a pretty novel approach, so it's fairly high risk and there's going to be a certain drop-off," she says, much like the first collaboration between Wolozin and LDDN. However, "this one is going well so far," Glicksman adds.

Money, money

The study has already run for longer than the original funding anticipated. The support for this particular project comes from the ALS Therapy Alliance and Project ALS, Glicksman says, and LDDN has support for the study for two years. During the first year, Wolozin's postdoc Peter Lee's salary was covered by the money from the ALS foundations. Now, says Wolozin, "I'm funding him myself."

Wolozin and Glicksman are continuing to collaborate outside the lab and are coming up with ideas to find more money to continue the study, which may have an impact beyond the treatment of ALS. Depending on the compounds they find and the mechanism of the compound's action again TDP-43 aggregation, the research has implications for treatment of multiple neuro-degenerative diseases, a possibility that is "certainly on our minds," he adds.

"Additional fundraising is continuing to keep this going and we will likely apply for NIH grants with Ben to get additional funding," Glicksman says. "A project continues if it meets specific criteria to move forward … so a time limit is not imposed as long as the project progresses."

The Breakdown

Members: Boston University
School of Medicine and Harvard Neurodiscovery Center Laboratory for Drug Discovery in Neurodegeneration

Funding Source: Project ALS and the ALS Therapy Alliance through LDDN's Collaborative ALS Drug Discovery Initiative. The collaborators are searching for additional support.

Time frame: One year has elapsed so far, but the project is continuing.