Why fund ALS research?

The following are excerpts from our interview and an article written by and about the research done by Carol Milligan, Ph.D. Director of the ALS Center Translational Science Unit, Director at Wake Forest School of Medicine– a program funded by the Blazeman Foundation's warriors, donors and supporters. Your donations at work!

Over the course of the past few months with the craze about the "Ice Bucket Challenge" the question of why do so much for ALS research as opposed to diseases that affect a larger number of people. The answer is simple- because we have nothing to offer ALS patients. While it is true that the quality of care has improved significantly since the time of Lou Gehrig, the fact is that the average lifespan from time of diagnosis to death has not changed. The only way to begin to understand the disease and ultimately develop an effective therapeutic will be through roll-up your sleeves and work hard basic science research. This is not easy, it take time, effort and yes, money.

Tell us about the project that the Blazeman Foundation is currently funding?
Our research project on Heat Shock Protein 70 or Hsp70 is a perfect example of "bench to bedside" research. It is also a good example of the time involved in this type of project. In 1981, a colleague in our department, Dr. Mike Tytell published a paper that demonstrated that supporting cells that surround the squid giant axon made proteins and then transferred those proteins to the axon. One of the proteins was heat shock protein 70.

What is heat shock protein 70?
The protein is called "heat shock protein" because it is one of a series of proteins that cells make more of at times of stress, such as "heat shock." Hsp70 is a "chaperone" protein. It helps to transport other proteins between the different parts of the cells. It is also important because it protects proteins during time of stress when they can be damaged.

Can you move toward a clinical trial?
Recently, our project was "dead in the water." I say this because we simply could not move forward. We had been purchasing the recombinant protein for our studies. For the 2007 study the company that made Hsp70, Stressgen gave us an 85% discount so we could purchase enough for the study. Stressgen was sold to a company that was then sold to another company and for the 2012 study we were getting a 15-20% discount. We simply could not afford to purchase enough protein to move forward. We also found that the quality of the protein started to vary between batches making it hard to interpret results of our studies. If we could not do this to conduct a few experiments, obtaining the protein in sufficient quantity and purity for a clinical trial was out of the question.

But couldn't you get funding to help move the study along?
That was the problem. Nobody wanted to pay for us to make a protein. This is understandable. Funding agencies want you to provide answers not a product. But, if we could not make the protein, we could not do additional studies for get answers. This was very frustrating and we were accepting that the project would just stop.

What changed?
The Blazeman Foundation! I had had a conversation with Bob and Mary Ann about the different projects we had going on in the lab. Around the same time, a fellow from our "innovations" group learned about our results with Hsp70 and thought they might be able to help move it forward toward clinical trial. With the conversations between Bob and Mary Ann and Innovations, the Department of Neurology also go on board. Another key piece of this was that Mac Robinson, a former student in my lab was completing his postdoc. Mac had done the initial work on Hsp70 on the chick motor neurons. He also began to make the recombinant protein. It is a tricky protein to make because it is rather big, but Mac has a good protocol started. That was about the time he finished his PhD work. He went onto to do work in our Genomics Group and got his Masters in Public Health Science. But he realized that of all the disorders to devote his efforts to, ALS was the one most in need. So with the momentum generated by the Blazeman Foundation, Mac joined our department as a junior faculty member in our ALS group.

And how is the project going?
I think we are making progress and pretty much are on schedule. We started with Mac's original protein and purification protocol. The big problem was being able to make enough of the protein and to be able to get it purified. Mac has achieved that much. He is getting very good yields of protein. By our analysis, it looks to be fairly pure. We have just begun testing it in animals.

So you are well on your way?
Well, we are on the right track. We are at a crossroads right now that is both very exciting and a bit scary. We have to decide if we should continue to improve the purification process or do we move toward having the protein be made in a GMP facility. GMP means "good manufacturing process" and this is the standard for all clinical agents. We have begun discussions about this, and the folks at one GMP facility think we have it to a point where they can take over. This will be an expensive endeavor- with an estimate of about $200K to make enough protein for an initial phase 1 safety trial. As a scientist I do not want to hand this over until we get the results from our animal studies confirming that the protein is working as we expect. I think we are looking at least another six-ten months before we know this for sure. We also need to complete a dose response study that will give us a better idea of the appropriate starting dose. Our initial studies used only one dose- simply because we could not afford to do more. But if we are seriously thinking of going into patients, then we need to do this right and get a dose response. I think if we get confirmation that we can repeat our original results with our protein, we could have a GMP facility start production while we work out the dose response. We will want an independent lab to test that GMP-made protein, and I have a colleague who is interested in doing this.

And, with discussions of going into patients- we have more questions to answer as well. For example, we need to demonstrate that we can detect the protein we inject into patients, and that

it is getting to the area we expect it to be - to the muscle. We are working with our ALS clinicians to figure out the best way to do this. This is not as easy as it might sound because the body already makes Hsp70, so we need to be able to distinguish what we inject versus what the patient makes. We have some ideas of how to do this though. But, the clinicians are starting to think about the best way to do the first safety trial.

We of course, also have to start thinking about going to the FDA. While getting FDA approval is challenging, we do have a few advantages, the biggest being that unlike a virus or new drug, we are treating with a human protein that is normally present in the body. Our first step will be to show that by giving more of that protein, we do not harm the patient. Fortunately, so far we have not seen any adverse effects in our mice. This is all encouraging.

When do you think you will start testing in patients?
I think if we stay on tract, we should be in a Phase 1 trial in 3-5 years. Maybe sooner, but I think this is a good estimate. If course, that is only phase 1 and will only test safety. It will be the Phase 2 and 3 trials that will look for effect.

So bench to bedside?
Yes, we started in the early 2000's with cells in a dish. Actually, in 1981 if you trace back to Mike's original study. And, after all this, there is still no guarantee that it will work. This is really the hard part. When I start to think about how much we have done, and how much we have to still do- and how much it is going to cost- it is unnerving. No one else is doing this. But it's times like this when I go look at the Blazeman Website ; "Decision must be instant- Commitment must be total."