State of HSP Research: The Promise and the Reality

by Allen Bernard

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Author's note: This article is not intended to teach cell biology in any way. The cellular functions I talk about here are vastly oversimplified. Entire text books are devoted to some of the functions I attempt to describe with a single sentence. But you cannot talk about HSP research without talking about cell biology, so I do my best to describe the areas of the cell that researchers are targeting for potential treatments.

As a writer, I hate using clichés but, in this instance, borrowing Charles Dickens' most famous line is appropriate: "It was the best of times, and it was the worst of times ... ". Or, put in more modern terms, this is a "good news/bad news" story. It's just a matter of perspective.

First the good news. Researchers working on hereditary spastic paraplegia, better known as HSP, know more today than ever before. They are uncovering new linkages between the proteins that are at the heart of the disorder all the time. This is good because the more common themes you can discover in a disease as complex and mysterious as HSP, the better. These themes, or nodes as they are also called, help cell biologists map the disease and understand why so many different variants -- SPG3A, SPG4, SPG31, etc. -- cause the same common problem: lower limb spasticity and high muscle tone.

This phenotype, or what you and I would call symptoms, cuts across all forms of HSP, both pure and complex. And it is this common phenotype that has led researchers to look for a common cause to the disease -- even though, underneath it all, at least 48 different malfunctioning genes are thought to lie at the heart of the disorder. This is important. From a biological point of view, you would think that so many different genes, which are part of your DNA and provide the instructions the cell needs to make proteins, would cause very different diseases but that's not how the body works.

This is because proteins work together along complex pathways inside the cell to create energy, remove waste, generate electrical signals, create copies of themselves -- basically, to do everything we need to live, move, breathe, eat, sleep, drive a car ... whatever. Now, most cells are extremely small complex structures (there are over four trillion of them that make up the human body) that are only now starting to be well understood.

With HSP, researchers and doctors are dealing with one of the most complex and least understood cell types in the body: motor neurons. These cells are found in the motor cortex of the brain. This is where movement begins. These motor neurons have long tails called axons that start, basically, at the top of your head and end at the base of your spine and make up part of your spinal cord. They are one of the longest cells in nature and yet the structures inside these cells are measured in nanometers. To give you some perspective on this, it takes between five and 10 *atoms* to make one nanometer.

Because of these two vastly different scales – small diameter yet long length – motor neurons are hard to study. You can't just open them up and look at them. They are too small and too intertwined with other parts of the body to put them under a microscope and see what's going on. What this means to folks with HSP (and, just so you know, my four year old daughter Brianna is one of them), is this makes HSP incredibly hard to understand and, therefore, to treat ... at least for now.

So, for folks hoping for something just around the corner, that's the bad news. There are currently no known drugs that you can take to treat the cause of HSP and, I'm sorry to say, none on the horizon. There are, of course, drugs for treating the symptoms like Botox and baclofen but they do nothing to reverse the underlying problem.

Still, I believe, there is more good news than bad to tell in this story.

If you rewind the clock just five years, almost nothing was known about the proteins involved in HSP, how they interacted, what they did or why they did

it. Since then much has been learned. If you go back 10 years, some of the proteins involved where just being uncovered. Go back 15 and HSP was almost a complete mystery. That may sound like a long time, but it's not -- at least not in scientific terms. It helps to remember that for most of human history it was thought that disease was caused by night vapors or angry gods, not bacteria, viruses and, now, our genes.

The best and brightest

So that brings us to today. What do we know now that will lead to a treatment sooner rather than later? The answer is a lot but, full disclosure here, a lot still needs to be discovered and many tests need to be run and many questions need to be answered before you head to the pharmacy to refill your prescription.

To create this article I talked at length with five of the world's leading HSP researchers:

- Dr. Craig Blackstone at the National Institutes of Health in Bethesda, Maryland;
- Dr. Evan Reid at the University of Cambridge in the UK;
- Dr. Gerardo Morfini at the University of Illinois, Chicago;
- Dr. Joanna Bakowska at Loyola University, Chicago; and
- Dr. Michael Hanna at the Texas A&M University, Commerce.

Fortunately for us, there are many, many other equally qualified researchers around the world looking at the HSPs with whom these five interact, share knowledge, and learn from.

Each of these five researchers is working on different variations of HSP based on the gene involved. Dr. Hanna is focused on SPG 21, for example, while Dr. Blackstone is working on SPG3A, but they are all finding relationships and interaction between the HSP proteins these genes code for. And, although not

all of these researchers are in complete agreement on this point, the majority view is the points at which these proteins come together are extremely important to discovering a single compound, or group of compounds, that could treat many forms of HSP.

Okay, now we're going to need a quick bit of science here so we can move on. Genes are basically a set of instructions that tell the cell how to manufacture a protein. Proteins do the work inside of the cell: making energy, removing waste, etc. There are somewhere in the neighborhood of 20,000 to 30,000 proteins that carry out these and all the other functions of life but we are only concerned with a very small number of them.

Depending on the form of HSP, the instructions those genes are putting out are wrong. What this amounts to is you have too much or not enough of a given protein, or you have the right amount of protein but it doesn't work right. In the end, the result is the same: The cell doesn't function properly.

One of the other things that makes HSP so difficult to treat and study is, even though HSP is often caused by a single malfunctioning protein, that protein often serves more than one function in the cell; kind of like the cellular equivalent of multi-tasking.

Now, this is a vastly over-simplified explanation given that whole books are written on the subject, but you don't need to understand cell biology to understand what it means: that you have HSP.

Okay, so back to the findings. As I mentioned, researchers keep finding connections between all the different proteins implicated in HSP. The nodes I referred to earlier. Many of you will be all too familiar with the names: atlastin, spastin, maspardin, REEP1, NIPA1, etc. but the vast majority of cases are caused by just three malfunctioning genes: SPG4, SPG3A and SPG31, which code for spastin, atlastin, and REEP1 respectively. Like all HSP genes, these three are very old, having been found in very simple and very ancient life

forms, and account for as many as 60 percent of all HSPs. This is actually good news from a cell biology point of view. Here's why.

Fundamental to us all

One of things that HSP has going for it from a treatment point of view is the proteins like atlastin are fundamental to how cells work. Because of this, cell biologists are becoming increasingly interested in studying them so they can increase their knowledge of basic biology. This greatly expands the base of very smart people exploring what these proteins do and how they do it.

For a very rare disease like HSP, this is like hitting a walk-off homerun because it opens the door to unlooked-for-discoveries by researchers outside of the HSP field that could lead to significant breakthroughs in how HSP is understood and treated.

The bottom line here is more interest equals more knowledge and more knowledge is what will lead to a treatment. Unfortunately, right now, today, there just isn't enough basic knowledge of what HSP proteins do to begin testing compounds to counteract the disease. But this is changing quickly.

BMP signaling

One of the more promising areas of research is being pursued by Dr. Reid at the University of Cambridge. He and his team are looking at something called the BMP signaling. While BMP stands for bone morphogenic protein, what's really important is it appears that atlastin (SPG3A), spastin (SPG4), maspardin (SPG21), spartin (SPG20), and NIPA1 (SPG6) are all part of the same functional pathway within the motor neuron.

BMP signaling appears to play a key role in how axons grow and what they look like as they branch out into synapses. It is this distal end of the axon, the one at the base of the spine, that connects the neurons in your motor cortex to your legs. If BMP signaling causes HSP's symptoms, then you have a target to

go after with drugs. Dr. Reid strongly believes this could be the case but more research needs to be done; particularly in animals; especially in mammals.

From a treatment perspective, this pathway tells researchers that all of these proteins are involved in the same cellular function and, if you can influence one of these proteins, maybe you can influence all of them. In other words, if you fix spastin or atlastin, that may be enough to fix the pathway and arrest the disease.

Dr. Reid likens this treatment approach to a car's engine: If you pull out one spark plug, loosen a belt, clog the air filter, and put water in the gas it will still run, just not very well. The same holds true if you, say, install Ford parts into a Chevy. The engine may run but, again, just not very well. As you start to reverse these problems, you will get a better running engine.

With cells, it's kind of the same thing only you may not have to actually fix anything 100 percent like you would in the car. By fixing or tweaking some of the other parts of the cell the HSP protein interacts with, for example, it may be that you can influence the defective protein just enough that you can restore the cell to more or less normal function. Since this holds true for other diseases, it probably holds true for HSP, as well.

There is an experimental drug, DMH-1, for example, that can reverse BMP signaling issues in small critters like zebra fish and fruit flies but this chemical is so toxic it cannot be taken daily. Also, as I mentioned, since many of these proteins do more than one thing in human cells it isn't a matter of just turning one on or turning one off; what you might think of as gene therapy. The downstream implications could be worse than the disease.

So much more needs to be understood before a drug will find its way to market. But what is encouraging is researchers are now able to identify specific molecular targets and affect them with chemicals. This is a long, long way from where they were even a few years ago.

The ER (no, not that one ...)

Dr. Blackstone's work has led to the realization that spastin, atlastin, REEP1, reticulon2 and possibly NIPA1 are all involved in shaping a very important organelle inside the cell called endoplasmic reticulum (ER). And this is extremely important from a cell biology point of view because the ER sits at the heart of cell function and is believed to run the length of the axon.

Indeed, before the discovery of atlastin, no one really understood why the ER looked the way it did. Now, HSP has opened a window into this most essential part of the cell. A gateway, if you will, to this and many other areas of cellular function that are now better understood because of HSP.

You may notice that some of these proteins overlap but it isn't clear if ER shaping and BMP signaling are related. Still, this is yet another common point of interaction between two ideas on what is causing HSP. In other words, it gives researchers another place to look for clues that will unravel more of the mystery and teaches them more about how, in this case, the ER is formed, and therefore what is does and, potentially, how to affect it.

Casein kinase 2 (CK2)

Working together, the research teams of Dr. Morfini and Dr. Peter Baas at Drexel University in Philadelphia have found a potential target for a treatment of SPG4, spastin. Like Dr. Reid, their findings are preliminary but, if they pan out, they might provide a new framework for the development of treatments that may help prevent motor neuron degeneration in HSP.

Their findings indicate that the protein kinase CK2, which regulates the activity of other proteins, is abnormally activated by mutant forms of spastin. Abnormally activated CK2, in turn, negatively affects yet other proteins that are involved in the movement of materials along the axons in an important cellular process referred to as “axonal transport” (more on that in a minute).

Like many other protein kinases, CK2 is a drugable target. What's exciting about Drs. Morfini's and Baas's work is that CK2 has been studied for decades, so it is very well understood and there are currently cancer drugs in Phase I of the FDA approval process today to regulate it.

This same holds true for Dr. Reid's work. Signaling pathways have been implicated in certain cancers over the years so much is known about them from prior research. If BMP signaling turns out to a drugable target, then there is a lot of basic research to work with; potentially short-circuiting the time it will take to get a drug to market.

Dr. Morfini is quick to point out that this is all very promising but preliminary data. CK2 has yet to be looked at in living organisms (in vivo, as it is called in the scientific community) and this step is absolutely essential to validate his observations and move the research forward -- which also brings us to one of the biggest stumbling blocks to finding a treatment: inadequate animal models. More on that in a minute.

Reality check

These are but a few good examples of what researchers are finding. There is more but to talk about it goes well beyond the scope of this article. The important take away here is researchers are finding more and more targets -- functions like axonal transport and structures called microtubules, for example -- to focus on for potential treatments. If just one of these targets proves to be the key to a bona fide treatment, then that is all it takes.

Now, just to be clear, HSP is a *very* complicated disease with many different forms and no two individuals are affected in exactly the same way so the chances of finding just one pill that cures everyone is remote. But, if 4, 3A and 31 are found to be treatable as a group because of how closely related they are, that would benefit the majority of sufferers.

The squishy side of science

To find this one wonder drug, you might think that money is the end all, be all but it's not. Don't get me wrong on this point, however, more money is definitely better and needed, but perhaps the biggest inhibitor to finding a treatment is lack of good animal models.

While HSP-like symptoms can be created in mice, for example, the phenotype that mice exhibit is less severe than in people and, therefore, harder to measure. Also, mice are just a few inches from head to tail while the cells involved in human HSP are up to a meter long. Mice also take a long time to mature. So when you work with mice, it can take up to a year or more for symptoms to show.

That is why researchers often turn to fruit flies, which share the majority of their genes with humans (they just have fewer variations of them) and they reproduce very quickly so you can see results much sooner. But, fruit flies are not people. They can point you in the right direction; give you an idea of what to look for or what questions to ask but they won't serve as a stand in for us.

Researchers like Dr. Morfini also work with squid since their axons can be removed, viewed under a microscope, and react to HSP similarly to our own. Squid have long been used to study other central nervous system (CNS) diseases like ALS and Parkinson's so a lot is known about their basic structure.

This makes squid an important source of information since 99 percent of a motor neuron cell is actually made up of its axon. So axonal transport, or the movement of molecules and proteins up and down the long thin tube that is the axon, is also considered by many in the field to be an good place to look for a cause of HSP. Any disruption of this very finely tuned architecture could result in disease.

Dr. Reid is working to overcome the limitations mice present by employing a new tool called a DigiGait to get better measurements. If he and his team are successful, then the mice models available today may be good enough to start

testing compounds against. That would be an exciting development and one we could know the results of before year's end.

Animal models are also expensive to make and house. This is often one of the biggest expenses researchers face and where a lot of money gets spent in the pursuit of a treatment. This challenge can greatly limit a researchers' ability to try new ideas.

I should also mention the rather sobering fact that once a compound is identified and a pharmaceutical company gets involved, it can (and often does) take about seven more years before that compound becomes a drug. Even then, because animals are not people, most of these promising compounds never make it through clinical trials.

But, what could short circuit and circumvent this particular problem is testing existing FDA approved drugs to see if they hold any benefit. Once a good animal model is developed or the measurement of existing models proves up to the task, then this type of work could begin sooner rather than later. There are some 15,000 generic drugs, for example, that, if one proved effective, could be made available comparatively cheaply and quickly.

Moving the needle

So, the question I'm sure many of you are asking is: "What needs to be done to get from where we are today to a treatment tomorrow?"

Well, while money is not a panacea, more is always needed. More money will buy more animals and hire more research assistants. It can provide seed money for young researchers just getting started and fund "blue sky" ideas that need fleshed out. But money can only do so much. Huntington's, a fatal CNS disease, is very well funded and yet no treatment has been found. Cancer is perhaps an even better example. It's got billions behind it and is still a killer.

Until then, Dr. Bakowska is calling for a concerted effort to create better models in creatures further down the food chain such as *C.elgans*, a small worm, that like fruit flies, tells us a lot about ourselves and is easier to work with. These models, unlike mice, are not made that often by researchers but could be used for fast screening of compounds to see which of the millions of known molecules would be worth studying further.

As I just mentioned, however, money could pay for the testing of FDA approved drugs -- provided the animal models exist. Money would be integral to that effort in fact so this is one area where it would make a big difference in the shortest possible time.

Dr. Reid would like to see each HSP protein singled out and explored individually so that more is known about what they do. Dr. Blackstone did this work with spastin, atlastin and REEP1 and that is what led to the discovery that they are all implicated in ER shaping.

Of course, the work of foundations around the world is essential to raising the profile of not only HSP but all rare diseases since more people have a rare disease in the U.S., for example, than any other type of condition. More awareness can lead to more interest. Parkinson's was given a big boost when Michael J. Fox revealed he was a sufferer, for example.

This work isn't sexy and doesn't provide for quick solutions but it is arguably the most important work that can be done to move the HSP research forward. Awareness equals interest and, because so many proteins that are fundamental to how you and I function are implicated in HSP now, Dr. Reid believes this will continue to pique the interest of major funding organizations like the National Institutes of Health in the U.S., and the Wellcome Trust in the UK. In the U.S., the NIH already supplies the lion's share of HSP research dollars.

And, of course, more on this front can always be done.

Every reason to hope

I once told Dr. Blackstone of a *Time Magazine* cover that I would like to see one day: "HSP: The Disease that Cured MS." I asked him if HSP could be such a disease, one that opens so many doors to understanding other CNS disorders that it will one day be looked upon as, what I like to call, a "Gateway Disease," a disease that leads to treatments and cures for some of today's most intractable illnesses. He said simply, "Yes."

I've alluded to the reason for this a few times now in this article. Namely, the proteins involved in HSP are old and integral to the proper functioning of not only motor neurons but many other cells in the body, as well. Atlastin, for example, is found in kidney, liver and skin cells as well as others. Even more interesting is if you have SPG3A HSP, atlastin is mutated in these other cells, and yet, they seem to function just fine. Why is that? No one knows yet.

There are other conditions like Charcot Marie Tooth Type 2b and some neuropathies (a loss of sensation in the feet and hands that can lead to amputations) that involve the same proteins as HSP and yet, on the outside, look completely different. This is the type of thing that gets researchers from other fields interested because there must be something very fundamental going on.

ALS and its cousin primary lateral sclerosis (PLS) also have something in common with HSP because of proteins. So, at some point in the future, a researcher in one of these fields or an HSP researcher could uncover a strong bond that could lead to a treatment for both. Multiple sclerosis (MS) is another disease where there appears to be some overlap but all of these connection need to be explored much more deeply.

The point is that there is ample reason to hope.

HSP is no longer an isolated rare disease with a handful of sufferers that people in the medical community only wonder about. If you take away nothing

else from this article, take away this: There are a lot of positive things happening today that weren't happening just a few short years ago that could one day rid us this disease.

From the better measurements of existing animal models to the fact that no new science needs to be invented to crack the riddle of HSP, there is more reason than ever to feel good that one day a drug will be found to eliminate or at least alleviate HSP's symptoms.

As the father of a little girl who really doesn't understand yet why she can't walk like everybody else, this gives me hope. I believe it should give you hope, as well. But, until the day we are free of this disease, life goes on. We smile and cry and persevere. And, in the end, that's what it's all about ... HSP or not.

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