

Intrabody Delivered with Adeno-Associated Virus Blocking Gene Dysregulation Offers Hope in Treating Huntington's Disease



Dr. Lee A. Henderson, Ph.D.
Chief Executive Officer

Vybion
www.vybion.com

Contact:
Lee A Henderson
607-227-2502
Lhenderson@vybion.com

Interview conducted by:
Lynn Fosse, Senior Editor
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- Dr. Lee A. Henderson, Ph.D.

CEOCFO: *Dr. Henderson, the tagline on the Vybion™ site is "Antibody Innovations". What are you working on today?*

Dr. Henderson: Our primary focus is on delivering Intrabodies (intracellular antibody fragments) for neurodegenerative diseases and specifically Huntington's disease. We have a drug product we call INT41, which we deliver with AAV (Adeno-Associated Virus). We have done animal studies that give us excellent improvement in cognitive capability as well as motor function in an animal model of Huntington's Disease. Then we worked out a mechanism of action so we understand its function within the cell. That is also leading to some insights on some of the drivers for Huntington's pathogenesis as well.

CEOCFO: *Could you tell us, in as close to laymen's terms as possible, what is the interaction in the body with the drug?*

Dr. Henderson: The Huntington protein, like any other protein, is synthesized by the cell, then goes through whatever function it has and then it is finally degraded. Unfortunately, in the terms of Huntington's there is not much known about function. However, in Huntington's once the mutant protein is degraded fragments containing very long repeats of positively charged glutamine amino acid residues are generated from the amino terminus of the protein and these are getting into the nucleus, binding to DNA and altering the expression of literally hundreds of genes. The product that we have binds to a region right next to this glutamine repeat. It stabilizes the protein and inhibits its binding to DNA and subsequently gene dysregulation. Gene dysregulation itself is driving the alteration of many metabolic processes, such as the function of mitochondria and intracellular signaling processes that ultimately lead to apoptosis or neuron death. One of the hallmarks of Huntington's disease is a loss of neurons in the striatum, which is in the central part of the brain. It is the region that controls executive function an essential

cognitive portion of the brain and also communicates and coordinates motor function.

CEOCFO: *How is the drug administered?*

Dr. Henderson: It is administered by a injection into the brain in a short surgical procedure. It is infused very slowly into the striatal region of the brain. It diffuses through this region. We are also exploring other delivery methods currently. The drug is actually part of the DNA of the Adeno-Associated Virus (AAV). The virus then will infect the cell, but is unable to replicate itself, so the virus does not persist beyond that. It essentially is used to deliver the DNA that encodes the drug INT41. Then that drug is made by the cell and serves its function achieving a steady state of concentration.

CEOCFO: *How have you decided how much to give? Does it depend on how extreme the condition is, the age, height or weight? What are the boundaries?*

Dr. Henderson: One of the things that is the most challenging with gene therapy is that you really have very little control over the amount of the product that is being made inside the cell, but gene promoters can regulate this within certain parameters and preclinical studies as well as toxicology establish safety. Therefore, what you are relying on is that the cell sees a foreign protein or a protein that is in this case a human protein and it degrades that protein just like it would deal with any other protein that is made inside the cell. That is in fact what we see; the drug is being made and then turned over by the cell just like any other protein. There are some technologies in the research stage that might allow you regulate the drug levels using promoters that can turn drug expression on and off, by taking an oral pill. This oral pill or small molecule would turn on production of the drug and you could modify the dose of the small molecule in order to regulate the expression of the product that you have delivered.

CEOCFO: *Have similar approaches been tried?*

Dr. Henderson: Yes, there has been quite a bit of success very early in Parkinson's disease. Voyager Therapeutics, for example, recently released announced some encouraging results as well as others in a range of other disorders like hemophilia. Gene therapy itself has been performed on dozens of patients at this point, without any evidence of any toxicity. Therefore, it appears to be relatively safe as far as we know at this point. There has been a lot of work done on human primates where it has been administered for more than a decade without any toxicity.

CEOCFO: *Where are you in the development process?*

Dr. Henderson: We are in the final stages of what is called preclinical development, where we have to complete a formal toxicology study in order to submit an investigational new drug application or IND to the FDA for approval to start human trials. We expect that to take about eighteen to twenty four months to complete those studies before we can get approval to administer in humans. However, we may also initiate these studies first in Europe.

CEOCFO: *Has the medical community been paying attention? Is it too early for any attention?*

Dr. Henderson: We have actually canvassed some neurologists and have talked to patients and academic groups. I think the key is early

education about what the drug is, what it does and what it does not do. We recently gave a webinar for patients and caregivers and I think we had a little over two hundred people sign up for that, which was quite a good number of people. That is the sort of thing that we are going to continue to do, not only with patients and caregivers, but also by reaching out to neurologists and explaining the technology and providing data, particularly as we walk through some of the preclinical stages before we get into humans.

CEOCFO: *How do you deal with the frustration of how long it takes to get a drug moving when you know you have got something that potentially can make such a difference?*

Dr. Henderson: Sometimes it is a little bit of like an acid drip, drip in your stomach, where you just wish you could move this faster! I have heard from any number of patients who have asked about, "Do you think there will be a drug for Huntington's any time soon? My son or my daughter or my wife or my husband has been recently diagnosed." When you hear those kinds of things you really wish you could get this process going much faster that it is." Therefore, it can be a little frustrating, but on the other hand you also want to be sure that you are not doing any harm to patients so safety is an important concern.

CEOCFO: *What have you learned so far as you have been working with the drug? What, if anything, has surprised you?*

Dr. Henderson: It kind of surprised me the way it was working. When we first started this work in 2011 we had a collaboration with the late Paul Patterson, at Caltech, who had developed a drug that was quite similar. We were originally trying to move that drug into the clinic and we discovered some problems with it along the way. Therefore, we used our proprietary platform to develop a whole series of very similar drugs that did not have the problems that the Caltech drug had. At that point the animals studies gave us really interesting data. We really had no idea what was happening. In other words, you are getting improvement in cognitive ability, but how is that really occurring. The first hint came from a publication in 2008 describing Huntingtin protein fragments binding to DNA. We were surprised that INT41 altered the binding of huntingtin protein fragments to DNA and inhibited gene dysregulation. We thought that those were possibilities, so we initially looked at gene dysregulation in cells. Then we started to look more closely at what was going on in different cellular sub compartments. While the mechanism was a bit surprising, there were some hints in the literature that this might be the case. However, you are never really certain of what you are going to find, so you are always a little bit surprised at the outcome.

CEOCFO: *How has prior experience about how to work on drug, how to eventually bring it to market and how to get it through regulatory issues, been helpful?*

Dr. Henderson: In a former life, we developed a dozen different biologic drugs from bench to IND, primarily the development of manufacturing processes. Therefore, we learned a lot of the do's and don'ts of not only making a product that was high quality, but also in what kinds of issues you need to be looking for in toxicology studies and we bring in the best scientists, regulatory experts and clinicians to advise us. I guess the things that we have seen many times is that a number of drugs that have failed because those studies were not done rigorously enough. It is interesting, if you look at some of the drugs that have been acquired from big pharma companies and then taken to market have been acquired

largely because the pharma company was having problems with toxicity or efficacy and similar issues while in animal studies or clinical trials. Then another company identified the issues and narrowed down the populations that are actually treatable.

CEO CFO: *What are the numbers surrounding Huntington's disease. How prevalent is it?*

Dr. Henderson: In the US there are about two hundred thousand people who are genetically positive and roughly thirty thousand who are symptomatic. Therefore, it is not a very large disease. Globally, Asia has a frequency which is a little bit lower than most of the world. Europe is about as equivalent in terms of the per capita incidents as the US is. Therefore, globally there are several hundred thousand patients. It is not a huge disease and it does fall into the orphan category in the US.

CEO CFO: *The six hundred pound gorilla on the wall; what is your funding situation?*

Dr. Henderson: We are talking to multiple partners right now, as well as funding sources. The key for us is to identify a way to complete the critical toxicology work. We think a major milestone is showing, in a formal toxicology setting, that INT41 is safe. That is the stage that we are trying to get funded right now; it is to complete the manufacturing and formal toxicology studies. If we can get that successfully completed then that eliminates an awful lot of risk going forward.

CEO CFO: *Is Huntington's disease in favor with the investment community these days? There does seem to be a kind of an ebb and flow of what people pay attention to. Where is Huntington's on the radar?*

Dr. Henderson: I think Huntington's disease, as well as many of the orphan and rare diseases, were ignored for a long time. Then a number of companies, like BioMarin and Alexion, have focused entirely on these rare diseases. One of the issues has always been reimbursement. That, I think, has been a particularly big issue. If you only have thirty thousand patients and you are treating maybe five or ten thousand of those, your costs are actually quite high per patient as opposed to something like cardiac disease where you may be treating hundreds of thousands of patients and you are able to reduce those costs since they are spread out over so many patients. Therefore, one of the things that have been driving the increased interest in the last decade in rare diseases is the insurance companies being much more willing to bear the cost associated with treating a very small number of patients, which has a much higher price tag per patient.

CEO CFO: *Why does Vybion stand out? There are so many companies in healthcare and drug development. Why pay attention?*

Dr. Henderson: We have a completely new drug class that offers the opportunity to target intercellular drug targets, previously known as hard targets, where many drugs have failed. We think that intrabodies give the best of the world of the antibodies. Intrabodies are derived from antibodies. Antibodies, of course, have been one of the more successful drug classes. A large part of that is because they are safe and specific reducing what is called "off target effects" or side effects. We think intrabodies will reach both of those hallmarks, both in specificity, to eliminate or reduce off target effects, as well as being very safe and therefore enabling one to go after a range of targets that have previously really eluded drug development.