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Kevin Gregory (Host): Hello, and thank you for listening to the HD Insights Podcast. I'm Kevin Gregory, Senior Director of Education and Communications at the Huntington Study Group, and your host for this episode. [00:01:00] Today, you'll meet and hear from Dr. Michael Hayden, Chief Executive Officer for Prilenia Therapeutics, and a Killam Professor at the University of British Columbia.

Prilenia is sponsor for the currently active PROOF-HD trial, a global study evaluating the efficacy and safety of pridopidine and patients with early stage of Huntington disease. Dr. Hayden [00:01:30] will talk about this new study and its unique endpoint around total functional capacity. You'll also want to hear his inspiring personal journey that led him into Huntington disease research while growing up in South Africa. So without any further delay, here's my conversation with Dr. Michael Hayden.

Before we get started, I wanted to first welcome you to the HD Insights Podcast. And thank you for taking the time to join us for this episode today.

Dr. Michael Hayden: [00:02:00] Well, thank you for this privilege and opportunity to be part of this.

Kevin Gregory: Dr. Hayden, there's a lot of buzz and excitement surrounding one of the latest clinical studies for Huntington disease, which is the PROOF-HD study, which your company, Prilenia, is sponsoring. We'll certainly get into more of the study specifics, but if you don't mind, I'd really like to start by having you explain what makes this study so unique and important to the HD community?

Dr. Michael Hayden: [00:02:30] Well, I think that this is an important study with a drug that's easily taken, an oral drug, that has been shown now in about 1300 patients to be safe and tolerable similar to placebo, and a drug that's already shown in prior studies in a subset of patients, so in patients who have early Huntington disease, to have [00:03:00] potential impact on maintaining their functional capacity.

And just to mention about functional capacity, because of course, patients with Huntington disease have numerous signs and symptoms, personality change, involuntary movements, but what upsets and really causes most consternation to patients is the relentless progression of this disease. They lose the ability [00:03:30] to function, they lose the ability to hug their children and grandchildren, they lose the ability to continue employment, and it's the opportunity to assess whether the drug has impact on their functional capacity represents a major opportunity.

And the FDA and all the regulatory agencies have now recognized that total functional capacity is a [00:04:00] acceptable single endpoint in late phase clinical trials. And they've recognized it, and there's been evolution in the regulatory authorities because they've listened to the voice of patients, and they've listened, they had a Voice of Patients Day in 2015. Prior to that, they had wanted either motor as the endpoint or combined endpoints of motor and function, but after hearing that, the voice of patients [00:04:30] about what really concerned them, and that was really to stay functional to be able to continue doing their daily activities, riding their bikes, participating in family life, the FDA made functional capacity and accepted this as a single primary endpoint in clinical trials. This was an evolution. And now for late stage clinical development, late stage being phase three, or even late stage two, [00:05:00] this TFC or total functional capacity, is accepted as an endpoint and a validated endpoint.

TFC has a long history. Discovered essentially initially put forward by Fahn and Shoulson, Ira Shoulson, in the early 80s. Developed further and modified and further described by Karl Kieburtz. And we've learnt a lot about total functional [00:05:30] capacity. We know how it decreases over time, we know that this is particularly useful for patients with early Huntington disease, where it measures the ability to function at home, activities of daily living, it measures who takes care of you, it measures how you're able to continue with your finances, it also measures whether you're still employed or have some decrease of employment. And all of this [00:06:00] gives an assessment, an objective assessment, of function. This is now accepted and is the single endpoint in our own trial at Prilenia, but of course, it's the endpoint also in the United States, in the Roche trial for Antisense Therapy.

Kevin Gregory: I appreciate that explanation. I want to dive a little bit deeper into that, if we can. I know chorea tends to be [00:06:30] one of the most widely associated symptoms that people are familiar with, with Huntington disease, and you've talked about the importance of functional capacity and impact on quality of life. In terms of this trial, and I guess in terms of assessing total functional capacity as a whole, can you explain for those listening that may not be fully aware of it, how do you go about assessing one's functional capacity through the course of the study or applying [00:07:00] those assessments or measurements that you spoke of?

Dr. Michael Hayden: Well, total... Thank you, Kevin. Total functional capacity has five components, and they're measured, at normal function would be a three, and as you go down, you would go down to two or one or zero. And there are specific careful questions that are asked to the patient and often a caregiver together as [00:07:30] to what the level of function is.

Generally, in the general population, and when people start off with the earliest signs of Huntington disease, you have a score of around 13, but as you progress, this goes down from 13. And usually, in early Huntington disease, it goes down around one a year. And of course, this is measured annually, and so you go

down [00:08:00] one a year and therefore you have to wait a year to assess that particular endpoint. And the reason you want to wait a year, and that's why studies really won't have the power to detect this in a much shorter time, is that patients on placebo, you have to have a window against which you can detect whether your drug has any effect. So, in one year, for the earliest Huntington disease patients, you go down about one, and then you can see whether your [00:08:30] drug has slowed down or maintained the functional capacity over one year.

It's good to have long-term follow-up because you want to see if there's improvement or maintenance of functional capacity is maintained, and that's why often for these studies, there's an open label extension that allows you to see whether this is durable.

The good news for us is that, in early patients with Huntington disease, we have shown that [00:09:00] the functional capacity may be maintained in patients on this drug called pridopidine. And we've learned a lot. There's been tremendous evolution of thinking around pridopidine, and we've also shown that in an independent measure, placebo independent measure of movement, which is a machine that measures, for example, how quickly you tap and how you do alternating movements of the hands, that there also [00:09:30] appears to be an improvement and less deterioration in patients with early HD.

So this trial termed PROOF is designed to assess and answer the question clearly with all the pre-specified endpoints taking everything we've learnt from prior studies. And these prior studies have helped us to determine the dose, the duration, the most important [00:10:00] endpoints for this particular study. And this is now ongoing. PROOF means pridopidine outcome, assessment of outcome, in Huntington disease. So outcome of function. So, it's PROOF outcome of function, that's P-R-O-O-F, in an effort to see whether this can be replicated, whether the early signs in a phase two study could be replicated in phase [00:10:30] three, so that if replicated, this drug would then be available orally for patients hopefully globally, in an effort to see if there's some way to slow down the progression of this illness.

And this is the excitement around this, the early data, as we've understood all aspects of this and we understand the mechanism of action now in much more detail, we understand issues of the response to different doses, we [00:11:00] understand why we've chosen this particular dose, why we're choosing patients with early HD.

And so the trial is ongoing. The trial will be in 60 sites, 30 in North America, including Canada, and 30 in Europe. And we're delighted to have the endorsement from the European Huntington's Disease Network, EHDN, which has formally endorsed the study of the careful [00:11:30] and diligent review. We're working with the HSG, which is the only CRO in the world that focuses exclusively on Huntington disease. And we're working with 60 sites around the world.

The principal investigators of the study are Andy Feigin in the US, who is also the Chair of the HSG, and Ralf Reilmann in Münster, who has such extensive [00:12:00] experience in Huntington disease and clinical trials. And they are supported as Co-PIs by Anne Rosser, who's the Chair of the European Huntington's Disease Network, and Sandra Kostyk, who is a very well-established investigator and neurologist running the clinic in Ohio, in Ohio State University.

Kevin Gregory: That's a very experienced team that you have put together. And I do want to go back to some of the [00:12:30] points that you touched on in terms of the design and the focus of the endpoints for this trial. I know PROOF-HD is kind of born out of the results from the PRIDE-HD study that you talked about, which I believe was a phase two study. What is the connection between PRIDE-HD and PROOF-HD specifically in terms of what you learned from PRIDE and how you've applied it to PROOF-HD, and not necessarily just from the standpoint [00:13:00] of result, but also you mentioned the timing of the FDA establishing total functional capacity as an endpoint. I'm curious was that... I'm assuming PRIDE began before the FDA made that change, how much did that factor into what you saw from results in terms of where you're taking this PROOF-HD study now?

Dr. Michael Hayden: Yes. I joined Teva at the end of [00:13:30] 2012, and I was already interested to look at pridopidine essentially based on what we knew then. We thought this was a primarily a dopamine modulator. And dopamine similar to L-dopa in Parkinson's is really having impact on movement. And when we brought this into Teva, we were interested in looking at its impact on movement, [00:14:00] but as the study progressed, we learned that its primary mechanism of action appeared to be not dopamine modulation, and we've now proven that in imaging studies, but rather sigma-1 activation.

Now, sigma-1 activation is associated with neuroprotection. And if you wanted to see if there was any impact on that, you would have to have these patients be followed for longer [00:14:30] to look at functional capacity, TFC. So what we did is we extended the study, which was essentially initially mostly focused on movement, but to be extended to 52 weeks where we would know that at 52 weeks TFC if on the placebo group would decline, and we may have a chance to see a window of effect, and that's what we learned.

The FDA had already suggested to us that we should also look at multiple [00:15:00] doses, and that was very helpful because we were able to determine the right dose for patients for this particular study based on total functional capacity. What we learned from it is that, and just recently published in the Journal of Huntington's Disease, is that pridopidine in this post hoc analysis showed some effect to maintain functional capacity compared to placebo. That was the first time [00:15:30] that this has ever been shown in any analysis for any drug. This was exciting. And it was a result of that, that I really chose to spend my time and focus my time on trying to assess in a formal all very rigorous pre-specified study, whether this drug can be shown to have impact on functional capacity in HD. And this is really what we're doing.

Now, chorea, of course, [00:16:00] I was committed to doing everything I could for patients and families with Huntington disease. And of course, we knew that Tetrabenazine, another drug, had been used for chorea, and I was able to bring in another drug called Austedo into Teva, which then we took through to be approved as the second drug ever to be approved for Huntington disease for treatment of chorea. And that is a different mechanism that is focused [00:16:30] on dopamine and it actually decreases presynaptic dopamine levels and has impact, and is now the second approved drug.

What we're doing from PRIDE and now into PROOF, is really looking at functional capacity. So some of the motor signs, our endpoints, and secondary endpoints, but the primary focus is to see whether we can maintain functional capacity, keep patients working, keep patients at [00:17:00] home, keep patients taking care of themselves, keep them performing the activities of daily living on a daily basis.

My philosophy is that, and it's not just mine, it's many people in this field who have made such amazing contributions, is these patients depend on us. And whilst one does not want to raise undue hopes and undue expectations, this is why we do phase three [00:17:30] clinical trials where we learn as much as we can from prior trials and then design this as efficiently and effectively as we can in an effort to see whether those early science can now be replicated in a formal phase three placebo controlled trial that would then lead to potential approval in the phase of compelling results. And that's what we're committed to do, and I was committed to making [00:18:00] sure that we could raise support to do this, which we did, and this has allowed us to now test this hypothesis in this phase three clinical trial.

Kevin Gregory: Yeah. I'm always amazed to hear about how these trials and treatments develop. Just one quick follow-up, when you observed the improvement in total functional capacity from the phase two trial, you mentioned it was very exciting. [00:18:30] Was it a surprise, or did you have some inkling going in that that could be a potential benefit but more unsure at the time?

Dr. Michael Hayden: I would say, I had heard anecdotally from many patients who'd been on the trial that they had shown some improvement, but this was anecdotally and the placebo response is always great, and you could never differentiate between this. [00:19:00] I would say, I was quite surprised and also surprised that in general, these patients maintained their pretreatment functional level after one year, as a group. There were some who actually showed improvement, there were some who showed mild deterioration, but overall, they maintained their function after one year, which was different to the control.

This was surprising, the extent of this was surprising. Of course, important to know this was also [00:19:30] a post hoc analysis. So, we got hints, but realized this needed to be replicated in a formal phase three study, which is what we're now doing. Just remember, this is an oral drug that has such an excellent safety and tolerability profile that of course allows easy administration. The European

regulatory authorities and the Americans have provided often drug status and we know our key here is [00:20:00] to make sure this drug is readily, if successful, readily available throughout the world. And the administration of an oral drug in this way becomes very feasible to do this.

And so, when I left Teva, I was able to take this with me and it was really great because the people that had worked on this for five, six years actually came to the company initially for three, four months at no salary because [00:20:30] they believed and had seen something and believed this was something worth doing. Also to say, later, just after a few months, Mass General and Harvard Medical School had received a donation at the Healey Center for ALS, and we had some preclinical data showing that this drug may have similar effects in ALS.

And they actually had an international competition. There were greater than 30 applicants. [00:21:00] And again, to my surprise, we were chosen to be funded by them to run an ALS study, which is now being conducted through Mass General Hospital and Harvard, but throughout 30 sites in the US. At the moment we have two trials ongoing, patients have been randomized to both, an ALS study, coordinated through the Healey Center at Mass General and led by Merit Cudkowicz, and in addition, the Huntington study led by the four investigators that we spoke [00:21:30] about before.

This is a drug that appears to have beneficial effects around protecting neurons, whatever the insult might be. And so ALS is an example, also Huntington disease. And of course, if you're trying to protect neurons, you want to treat them before they've died. You want to treat them... If you're trying to stop a fire taking care of a house, you don't want the house to be burned down, you want the [00:22:00] house to be early so you can protect it. And that's why treating early becomes effective because there is still injured neurons, but not dead neurons. And perhaps, this drug could further protect against undergoing neurons. We don't know all of this, although the preclinical data and the animal data would suggest this, but we're doing the trial now, looking at the endpoints to see if this could be replicated in [00:22:30] a formal phase three pivotal trial.

Kevin Gregory: Well, that's a good information to build on from there. So taking that to its natural next step, what are the most critical factors for participating in PROOF-HD? What are the key inclusion criteria that a participant would have to meet? And what are some of the critical criteria that might exclude someone from being enrolled in the study?

Dr. Michael Hayden: Thank you for [00:23:00] that great question. The key is to have patients with early Huntington disease. And this is defined, Huntington disease is staged by TFC, which looks at the level of function, and we have patients from seven to 13, 13 being close to normal, normal actually, and seven going down to early, to mild, to moderate Huntington disease. We also are including patients 25 years and above. And [00:23:30] the reason is that patients with juvenile, very early Huntington disease, may have a more progressive course, and that would need to have a separate study to assess that. So, patients are 25 and above, because

if they had onset at 20, or 19, or 18, or 17, these patients would probably be more advanced and wouldn't be eligible based on the TFC inclusion criteria.

We also had no upper age limit. So patients who fulfill [00:24:00] the criteria and have molecularly genetically defined CAG of 36 and above, and also have the appropriate TFC can participate in the study up to any age. And that's also important.

Exclusion would be patients who are more advanced. At this point, we really are excluding patients in stage three and stage four, and these are patients who are more advanced. To assess whether this drug has [00:24:30] impact on more advanced patients, would need a separate clinical trial to really look at these patients.

In terms of TFC, they decline much slower over time with advanced Huntington disease. And so you'd need a longer study with more patients, and that would have to come later where we really want to look primarily at those patients with early HD. So this is a trial that has broad inclusion criteria. [00:25:00] It's not a hassle to take it, we only have a few visits that have to be in person, screening, baseline and week. We're going to week 65, and that just gives a little bit more time for the placebo group to deteriorate so there's a window to detect the effect.

There will be open label extension after that, and we're hoping that people not only in the sites that have been designated, [00:25:30] but in regions around the sites, for example, in Australia, there's only one site, but there are many other sites in Australia where patients could come from in a relatively small geographic country. And so patients from other centers could also be enrolled. And particularly in other parts of Europe as well, the Netherlands and potentially Spain, where there are just a few sites, but people could be enrolled into those sites from other regions as well.

[00:26:00] So the study has broad inclusion criteria, exclusion criteria. You can be, for example, on the Antisense or the Huntington lowering trials, you could have been on that at least six months before, and you can still be part of the study, you can be on Tetrabenazine or Austedo because we don't believe this has any impact.

Our drug is not expected to have impact on chorea, so these drugs work in different [00:26:30] ways and would have different effects, and both may be advantageous. And so the criteria are easy to administer. We recognize that COVID is still present and raging in many parts, and we have a mitigation for COVID where a lot of the assessments like TFC can be done by telephone, but the key endpoint, which is 65 weeks compared to [00:27:00] baseline, this needs to be done in person. And hopefully, by the time patients reach that endpoint, the COVID prevention strategies and vaccinations and other measures will be in place so that all patients could come at least in person for their 65-week visit.

Kevin Gregory: Yeah. I mean, COVID has definitely changed a lot of things. And I wanted to ask you about that, how that may have impacted the study. [00:27:30] I guess my question around that would be, it sounds like this trial has been designed in a way that made it fairly flexible to begin with, or has it become flexible as a result of the pandemic, or a combination of the two, I guess?

Dr. Michael Hayden: Because TFC is a slowly progressive measure, whether patients come on the exact day we schedule them or one or two weeks on either side, [00:28:00] does not really matter. Firstly, there is some flexibility. Secondly, COVID certainly forced us to consider other measures where in clinic visits were not absolutely essential. And we've looked at all the measures and really have included phone visits, we have ways to deliver the drugs to patients, we have blood withdrawn for various assessments, we're looking [00:28:30] at biomarkers in the blood as well to have a biomarker for progression which we're also looking at.

And so I'd say the trial has diminished the burden on patients. We're also not requiring a caretaker or somebody who takes care of these patients to come with them, it's preferable, but it's not required. That's another important measure that gives more flexibility. And that's because we're looking at early patients [00:29:00] and these are patients generally who are still very functional in terms of their community involvement.

Kevin Gregory: With the, Dr. Hayden, with the excitement of new clinical trials, such as PROOF-HD, hitting enrollment totals is certainly critical to the study outcomes. And one of the things you mentioned was that because you're assessing total functional capacity, you need a longer duration. And so someone may hear 65 weeks and think, "Wow, that's a really [00:29:30] long time to be involved in this." Remaining in the study through its conclusion has a huge impact on not just the study results, but the benefits of a treatment to the entire HD community. I guess, in your experience as a researcher, can you talk about what retention means and its importance for clinical trials such as PROOF?

Dr. Michael Hayden: Well, that's such a crucial question. And I would say, remaining in the study is absolutely crucial, even if for whatever [00:30:00] reason, the patient is no longer taking the drug. And so because missing data penalizes the study, necessitates other statistical analysis that diminish the power of the study to see an effect. So, we are really wanting patients to stay in the study, to stay the course, and to contribute to this research that could have impact long-term [00:30:30] in every way.

And so we learn a lot from clinical trials, whether successful or sadly, whether they fail, we learn about clinical progression, we learn about biomarkers, we learn about what works and what endpoints are really measurable. So, we learn a lot that's of great value to the community, whatever the outcome. Of course, here we're hoping for a positive outcome, but the opportunity [00:31:00] to assess it will be enhanced by patients staying in the study.

Retention is critical because from a statistical point of view, you are penalized quite significantly for missing data. And even if the patient is doing better, sometimes through some analysis, you have to give the patient placebo measurements that diminishes the power and strength of the study. So we want to encourage everybody to stay in the study [00:31:30] as a community participation, to really participate, contribute to the overall involvement because that becomes very important in the assessment.

It's not that long, we need a minimum of a year to have an assessment. We've gone just a little longer on the encouragement of investigators to give ourselves the best shot to assess whether this drug is able [00:32:00] to slow or decrease or maintain the TFC over this particular period.

Announcer: We'll return to the interview on the HD Insights Podcast in a moment. We hope that you're enjoying this episode. As a nonprofit organization, the Huntington Study Group relies on the generous support from the community and listeners like you to continue bringing you in-depth [00:32:30] content on HD, like this podcast series. If you like what you're hearing and are interested in supporting HD Insights through a grant or donation, please contact us through our email address, info@hsglimited.org, or by calling toll free at 1-800-487-7671. We greatly appreciate your support. And now, back to our [00:33:00] episode.

Kevin Gregory: We're here with Dr. Hayden on the HD Insights Podcast. And Dr. Hayden, I'd like to switch gears now, if I can, and talk to you a little bit about your experience and your background. I know you have extensive involvement in research and development of products for disorders, specifically, I think you've authored approximately 900 peer-reviewed publications and invited submissions, [00:33:30] and you've led the approval of, I think, some 35 new products to market. How did it all start for a young Michael Hayden? What drove you to get into this specific line of work?

Dr. Michael Hayden: Well, I grew up in South Africa and I was always interested in families and what happens in families. And I started as a medical student intern seeing my first patients with Huntington disease. [00:34:00] And these were patients of color, patients of mixed descent. And in those days, part of the assessment of these patients was visiting them in their home. And I visited patients in the home who were disenfranchised by apartheid, disenfranchised by this disease, lived in absolute poverty, often tin shacks, in different townships around Cape town. And I was moved by firstly, [00:34:30] how little was known about this disease, but I was also moved by despite the poverty, the dignity and the honor and the warmth and the generosity of spirit that these families displayed. They inspired me.

I was reminded of words from Robert Kennedy when he came to South Africa and spoke about being contained in various [00:35:00] forms of oppression. And I saw that this disease was also oppressive for these patients, but they bore it with great courage and dignity. And then I started looking in the literature and I saw that Huntington disease was thought not to exist in Africa. They had been

three or four or five articles on Huntington disease out of 54 countries in Africa. And this was in the late 70s, early 80s. And I said, "This is what I'll do my PhD [00:35:30] thesis on." And I traveled around the country, saw thousands of patients in many hospitals, saw families, and raised awareness of Huntington disease in South Africa.

I also realized these patients needed an organization. So I helped to work to capitalize the first organization for patients, by the way, the first multiracial clinic at the place where the first heart transplant had happened, at Groote Schuur Hospital in Cape Town. [00:36:00] We had the first multiracial clinic taking care of patients as a whole.

And I saw that these patients needed help and needed hope, and I ended up being invited to go to a talk in the late 70s in San Diego in International... and I spoke about Huntington disease in Africa, in particular, South Africa. And that's where I met Marjorie Guthrie. And Marjorie Guthrie, the founder of HDSA, [00:36:30] we spoke and Marjorie became a beloved confident friend. And I explained to Marjorie that politically, I was really not in great shape in South Africa, I had already been detained, and Marjorie said to me, "We need you in America." And I explained that if I could come to America, I would need a Green Card.

And Marjorie enrolled and was able to get Ted Kennedy, Senator Kennedy, to [00:37:00] persuade, to write my letter to the INS to get me a Green Card, but he had one condition, and his condition was that I go to Boston. I had to say on where is Boston? Is it on the East or the West coast? Because I knew nothing about it. And I then knew and was able to take up my fellowship at Children's Hospital in Boston in 1980.

Marjorie remained a close source of inspiration, and it's because of Marjorie that I am in North [00:37:30] America and was able to really participate in the early days of genetics then, but my commitment to families was cemented right in the beginning, right when I was a medical student intern. And as a result of that, my commitment was firstly, to define to the best I can what causes this disease, what are the cellular and molecular mechanisms, but that was never enough. I really wanted to be [00:38:00] able to translate that into places and ways that we could help patients.

I was involved in the earliest phases of predictive testing in 1986. We did that in Vancouver. And then also participated in the clinical trials. And when I eventually was recruited to Teva, I was able to continue that commitment by bringing Austedo and getting this approved as the second drug ever approved for Huntington disease in the United States.

That commitment, [00:38:30] because patients need us and need us in the best way possible, is really what also forced me to encourage me to do the PROOF study, only because there were some signs that suggested that this may work, there was no definite guarantee, but it was worth a proper formalized clinical

trial. And I ended up helping to form this company, bringing people with me, in an effort to be involved in this.

Of course, in Vancouver, [00:39:00] we were also setting up the first Huntington disease medical clinic, training people has been important from Jeff Carroll, to Blair Leavitt, to many others, Nando Squitieri, people from in and around Europe and the United States, 150 people have been through the lab. And many of them have continued to be committed to Huntington disease, recognizing the urgent patient need, the terrible suffering, the devastation that families [00:39:30] go through, and our desire to do whatever we can to try and alleviate and contribute in whatever way we can to the suffering.

This is very much been a life's work, and I'm committed to seeing what we can do to see if this drug has any effect. And at the same time, continue to explore basic mechanisms that may open up additional points for therapy for patients in need.

Kevin Gregory: [00:40:00] That is a fascinating journey. I'm so glad to hear that whole story. Dr. Hayden. I mean, I know I've seen your biographies, but to hear that story about coming out of South Africa. If you don't mind, just a quick follow-up on that, have you been back in recent years, I'm just curious to see how things have changed for the Huntington disease community there, how they've evolved since you first got there and saw how [00:40:30] isolating it was and oppressive it was for the community on top of other oppression they were already dealing with socially, economically, and how that looks today.

Dr. Michael Hayden: Well, I would say for patients with Huntington disease, it's not a happy situation. The country is gripped in both political and poverty. Many of these patients suffer [00:41:00] from this. There are many issues around patients with disability that need formal more legal protection similar to what we see in the United States and Canada and parts of Europe.

I would say it's the burden of taking care of patients destined to be ill, but not yet ill is still an issue. When we developed predictive testing, we immediately offered this with the counseling and support to South [00:41:30] Africa, and this was done. We did this through the University of Cape Town, but now University of Witwatersrand, we had a student from there who came to us here in Vancouver, has gone back, who's playing a role in research in molecular genetics there, but the family foundations are still not that strong, they are split in all kinds of ways, also not fully integrated. So, I would say it's got a long way [00:42:00] to go.

We also discovered that Huntington disease is less common in persons of black descent, but it's equally as frequent in patients of mixed and Caucasian descent similar to the rest of the world. So the disease is very prevalent in significant parts of the population, and we're just learning to understand why the disease is less frequent in certain populations. And that's also been seen [00:42:30] in the

United States where there are differential frequencies in populations of different descent. For example, the disease is also less frequent in Japan.

Kevin Gregory: I'm curious in kind of building off some of what you covered there. You've seen an evolution in research and treatments. How do you see Huntington disease care and [00:43:00] treatments evolving in the next five to 10 years? And would you say, is that consistent with how you might have assessed the situation five or 10 years ago? Like did you foresee things being where they are today? Did you see them being further along? Do you think we still have some catching up to do? What are your overall thoughts on where we are and where we'll be going in the near future?

Dr. Michael Hayden: Well, I mean, I'm very encouraged. I'd say for the first time this disease has attracted [00:43:30] investment from the pharmaceutical industry and the biotech industry at a profound level. You know, when you look at Huntington disease and you look at the frequency, this is not such a rare disease, if you look at all people involved. So, if you take about a hundred thousand, 40,000 in the US, 40,000 in Europe, about 20,000 in the rest of the world, that's a hundred thousand. And then you look for every person affected, there's somewhere between three and four people destined [00:44:00] to be ill and not yet ill. So, that's another say 300,000, in total 400,000.

Well, that's the same frequency as multiple sclerosis. If you look at the people affected from this devastating genetic disease, in truth it's not infrequent, and I think that has been recognized as an opportunity. For multiple sclerosis there are 20 drugs approved for those 400,000 [00:44:30] people, and still further improvements in care coming. In Huntington disease, there is nothing approved for this. The exciting thing is that this is attracting investment and attention. Biotech and pharma there are now 10, 12, 15 trials ongoing. Of course, Huntington lowering represents a very important approach to trying to eliminate the course of the disease. And it's likely in the future that there will be [00:45:00] combination therapies, where you treat some of the cellular effects, you may treat also Huntington lowering. And hopefully, there'll be approaches that are both intrathecal, giving it into the spinal cord, but hopefully in the long-term oral therapies that make it easier and more accessible for patients around the world. I'm optimistic.

The disease has attracted the attention like never before, we're making progress, but I do believe [00:45:30] we need to have multiple flowers bloom. We had no guarantee of success with any one measure and any one intervention, and in the end combination therapy may be necessary. So we need to let multiple flowers bloom, we need to support multiple approaches for treating both symptoms as well as treating, hopefully, the cause of the illness, but I do believe within five, seven years, we will have alternate therapies that have [00:46:00] the potential to slow down the deterioration in functional capacity and offer great hope for patients.

Of course, the eventual approach would be not only secondary prevention, not only treating patients who are already affected, but rather treating patient destined to be ill, but not yet ill, people who are close to onset, what we call prodromal HD, so you're treating people at the time where you can [00:46:30] provide most protection, hopefully slow down onset of disease, and give people an improved quality of life for a much longer period. I don't talk of cure. I don't think there are cures here, but there are ways to slow down progression, slow down the deterioration, and there are many different approaches that are being taken, and I think we should celebrate those different approaches and look forward to some of them being successful [00:47:00] in the future and potentially looking at combination therapies that offer the greatest hope for patients.

Kevin Gregory: In keeping with that theme about pharma and biotech and having a number of different flowers bloom to attack and address symptoms, or the causes of Huntington disease, can you talk a little bit about your role at Prilenia? What led you to that and what is the overall goal [00:47:30] and focus of the organization?

Dr. Michael Hayden: Yeah. Prilenia, which comes from pri, which is pridopidine, and lenia, which comes from the Greek, to sooth or to cure, I think it's an aspiration. It's an aspiration that we can have some impact on soothing some aspects of this disease and potentially others as well.

I accepted the role of being CEO for this company [00:48:00] certainly to see to the end of these particular trials, but my goal is not just to support this company. I sit on the board of directors and I own this, and I'm very much supportive of Huntington lowering therapies. I'm supportive of multiple approaches because there's no guarantee which of these will work. And we here we have to be intellectually promiscuous in an effort to really see the right effect.

For Prilenia itself, whilst pridopidine [00:48:30] is the first product, there are other products that act on these pathways that appear to be very intriguing in terms of offering some hope that have impact on some other proteins that certainly Prilenia would be interested in bringing in, even in combination therapies, in an effort to see the effects, not only in Huntington disease, but ALS, also Parkinson's, potentially other forms of neurodegeneration, as [00:49:00] well as also the impact of this particular agonism on other neurodevelopment disorders, such as Rett syndrome and Fragile X syndrome, for which there is already quite a lot of data.

So, I see this as an opportunity to explore this particular area of tremendous unmet need. Huntington disease can serve as a model. If we were able to show some impact here on TFC, there's the potential [00:49:30] to look at other diseases. We already, in preclinical models, we already have shown some beneficial effects, but one step at a time, let's rigorously implement the trial for this disease. We're activating sites, we're on track despite COVID, we've had a

tremendously enthusiastic response from the community, and we're looking forward to implementing this with [inaudible 00:49:55] together with the ALS program, which already has had the first patient [00:50:00] randomized to pridopidine as part of that study.

Kevin Gregory: And you're also an educator by nature and practice and your role with the University of British Columbia. What is it about teaching that you found to be the most rewarding? And also I would ask you, for young folks listening, what advice would you offer someone who's thinking about going into Huntington disease research?

Dr. Michael Hayden: Well, for me, the biggest privilege [00:50:30] is having had the opportunity to train people from whom I learn. Essentially, my students and postdocs end up teaching me a lot in many ways, and I've been able to give them a perspective, not to lose faith when they are knocked down by results. We all get knocked down by results, it's about finding ways to stay resilient, be courageous. My advice to them is ask [00:51:00] big questions, give yourselves the opportunity to see what is the best result that you can see from the study? And is it worth you giving up nights and weekends away from family and friends to do this? And if the answer is no, then you have to find a question that's big enough, that warrants the commitment that's needed, find something.

And also just recognize science matters. Science solves problems. [00:51:30] We can solve problems through science. That's how we make advances, more and so beautifully demonstrated through the development of novel vaccines. Well, we can answer fundamental questions and it's a real privilege to be involved. So, I'm really committed to continuing to support graduate students and postdocs and others in an effort to continue to explore, but for me also, it's a wonderful learning experience.

Many of my students [00:52:00] and postdocs have become personal lifelong friends because our journey is on the same travel. We are there trying to do whatever we can in an effort to have some impact on questions that matter. And that's my focus to individuals to ask yourselves, if you had a positive result, would this be important? Does this add value or is this just some replication? And [00:52:30] helping them to be courageous to stand and supported by the data, to represent and be the representative of patients.

And what we see in our own lab, we have a lab where we have patient days like coming in numerous times a year, we built up a tissue and DNA repository with 8,000 DNA samples and over 300 tissues from patients with Huntington disease. We want to continue to use those which have served our own research, [00:53:00] but also make them available to the community that many people can have access to these precious samples. And we're delighted to have people who are willing to fund this as a resource for us, but a resource for the ongoing community.

Canadians have been contributing to this as well as people contributing the most generous gift ever, which are the tissues and organs from patients who are dying or have died, clearly [00:53:30] who have died, but making arrangements before in an effort to contribute to this. So, I see this as an ongoing project that will certainly survive long after me, and have these precious gifts and resources available to the community for further research, so in the end we actually have some way to slow down the course of what is and has been described as one of the most devastating diseases known to people.

Kevin Gregory: [00:54:00] Dr. Hayden, it's just been fantastic speaking with you about all these topics today. I want to end with one last question for you, and that is, what would you hope your lasting legacy to be when all is said and done?

Dr. Michael Hayden: Well, my hope and legacy would be that this commitment, and it's [00:54:30] really my family's commitment to Huntington disease, because I've had the support of my children and my wife in making these commitments they always made in place of some other commitments, and I would hope that somehow the work we've done has contributed to the alleviation of suffering of patients, both patients at risk, patients affected, and hopefully this could have impact beyond Huntington disease in [00:55:00] other forms of neurodegeneration. That to me would be really the most important contribution, and it's ongoing and it never ends.

Kevin Gregory: Dr. Hayden, thank you so much for joining us for this episode. I really appreciate your time and your insight and all the information you shared on the PROOF-HD study, as well as learning more about your background and how you've gotten to where you are today.

Dr. Michael Hayden: [00:55:30] Okay. Great. Well, thank you so much, Kevin. We very much appreciate what you do with HD Insights, giving us an opportunity in the community to talk with the community. And so, thank you for this very special privilege and opportunity. Thank you so much.

Kevin Gregory: And thank you for listening to this episode of the HD Insights Podcast. I truly felt inspired listening to [00:56:00] Dr. Hayden recalling his days trying to help families of HD in South Africa, of all descents, at the height of apartheid before we knew as much about the disease as we do now.

I'd also like to thank him for providing great insights on pridopidine and information about the PROOF-HD study. If you'd like to learn more about the study and active study locations, please visit the current clinical trials page of the Huntington Study Group website at www. [00:56:30] huntingtonstudygroup.org. Until our next episode, stay safe, be well, help one another. And thank you for listening to the HD Insights Podcast.

Announcer: We hope you enjoyed this edition of the HD Insights Podcast. Remember to subscribe to this podcast to make sure you automatically get the latest episodes

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