In this edition of HD Insights, we continue our focus on gene-targeting therapies for HD and hear from influential scientists about their work to treat HD at the genetic source.

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Welcome to the 17th edition of HD Insights, timed for release at the 21st International Congress of Parkinson Disease and Movement Disorders in Vancouver, BC. We continue our mission to promote, disseminate, and facilitate HD research with content that is valuable and informative to the global community of HD researchers.

In this edition, we continue our focus on gene-targeting therapies for HD, and explore other developments in HD therapeutics. We begin with an article about the recent FDA approval of Teva’s deutetrabenazine (AUSTEDO™). Dr. Lise Munsie investigates recent publications on gene-targeted therapies in her “Research Round-up” series. We talk with Dr. Beverly Davidson about her many contributions to gene-silencing therapies for HD and other neurological diseases, and explore the latest in game-changing gene-silencing therapies with Dr. Amber Southwell. Dr. Nicholas Caron reports on the highlights of the CHDI meeting in Malta in April. Dr. Irina Kerkis describes the latest in HD research in Brazil, especially research on stem-cell-based therapies developed with Dr. Monica Haddad. Ms. Jennifer Simpson and Dr. George Yohrling from the HDSA describe the findings of their survey exploring the preferences and priorities of the HD community for HD research, a highlight from the Journal of Huntington’s Disease. Finally, we continue to update the HD community on upcoming, ongoing, and recently completed clinical trials.

This edition marks the last edition of Meredith Achey’s tenure as Deputy Editor. Through boundless energy and dedication, Meredith has helped shape every aspect of HD Insights for the last four years. Only the increasing demands of medical school took her away from her work at HD Insights, and we wish her all the best. We welcome incoming Deputy Editor Sara LaJeunesse to the HD Insights team. Sara comes to us with a wealth of writing, editing, and publishing experience, and we are excited to continue to grow with her leadership.

If you or your colleagues would like a free electronic subscription to HD Insights, please visit www.HDInsights.org and complete the subscription form. We welcome your job postings, scholarship announcements, and other opportunities you would like to share with the HD community. If you have an opportunity you would like to share with nearly 3,000 HD researchers and clinicians, or would like to give us feedback, comments, or contributions, please email us at editor@hdinsights.org. Thank you.

-- Ray Dorsey
Editor, HD Insights

Ray Dorsey’s Disclosures: Dr. Dorsey receives grant support from Prana Biotechnology, Teva, Roche, Biomarin, Raptor Pharmaceuticals, and the Huntington Study Group.
FDA approves deutetrabenazine (AUSTEDO™) to treat chorea

On April 3, 2017, the FDA approved a new drug, deutetrabenazine, to treat HD-associated chorea.

By: Sara LaJeunesse, MSc

Deutetrabenazine (AUSTEDO™, see HD Insights, Vol. 7) is the first deuterated product approved by the FDA, and only the second product specifically approved for symptomatic treatment of HD. The pivotal clinical trial, designed and conducted by the Huntington Study Group (HSG) in partnership with Teva Pharmaceuticals, comprised a Phase III randomized, double-blind, placebo-controlled study of 90 ambulatory HD patients to assess the safety and efficacy of deutetrabenazine in reducing chorea.

Chorea affects approximately 90 percent of patients with HD. “We think that chorea may be related to too much effect of dopamine in the brain,” said Samuel Frank, MD, PhD, associate professor of neurology at Boston University, and principal investigator of the clinical trial. “Deutetrabenazine may reduce chorea by decreasing the amount of dopamine in the brain and reducing communication between certain brain cells.”

In the clinical study, the researchers found that people who were on active drug had a significantly higher rate of saying they were “much improved” or “very much improved” on their global impression of change compared to those on placebo. “The goal in symptom management is to give people the best possible day,” said Claudia Testa, MD, PhD, associate professor at Virginia Commonwealth University, and a co-principal investigator in the clinical trial. “We now have proof that reducing chorea with deutetrabenazine can improve quality of life.”

Deutetrabenazine can increase the risk of depression and suicidal thoughts in patients and is contraindicated in people who already suffer from these conditions. The most common adverse side effects observed in the clinical trial were somnolence, diarrhea, dry mouth, and fatigue.

According to Dr. Testa, the molecular backbone of deutetrabenazine is the same as that of tetrabenazine, a drug already in use for HD-associated chorea; however, in deutetrabenazine, deuterium replaces a few key hydrogen atoms, which strengthens the bonds so the enzyme CYP2D6 breaks down the molecule more slowly.

“Using deuterium reduces medication peaks in the bloodstream and in the brain,” said Dr. Testa, “therefore, the drug is easier to tolerate. Patients can also take it fewer times per day, but with the same potential impact on symptoms.” Dr. Testa explained that taking a drug fewer times per day can be important for HD patients. For example, some nursing homes and adult daycare centers will not administer doses in the middle of the day, and for home-based patients, it can be difficult to remember a midday dose.

In addition to the direct benefits deutetrabenazine will provide to patients, some intangible benefits have been demonstrated by the drug’s success. “This study proved that a raw startup company could choose to work in HD and have a massive success,” said Dr. Testa. “That is very attractive to other startups (the work on deutetrabenazine began with startup Auspex Pharmaceuticals, which was later purchased by Teva Pharmaceutical Industries Ltd.), and pharmaceutical companies that might be thinking about where to invest their resources. Ultimately, the more companies that focus on HD, the better.”

Furthermore, the novel use of deuterium in a therapeutic agent will likely draw interest from researchers who are not involved with HD. “It puts the HD community and the HSG on a much bigger map,” said Dr. Testa. “People who may have never heard of HD may be reading about this compound.”

Ultimately, however, it is the patients and their quality of life that matter most.

“People don’t like sitting in the front row in church and wiggling all over the place. They also don’t like not being able to feed themselves because they throw food around,” said Dr. Testa. “Not everybody with HD has chorea as a major symptom concern, but for those who do, a compound such as deutetrabenazine can improve their quality of life.”
Research Round-Up

By: Lise Munsie, PhD

In neurons...

The HD Induced Pluripotent Stem Cell (iPSC) consortium differentiated HD patient iPSCs into neuronal cultures.1 RNA-seq and ChiP-seq analysis from these cultures indicated subtle alterations in expression and epigenetic signature of genes involved in neural development, function, and striatal maturation in the presence of mHTT. The small molecule isoaxazole-9 is known to target some of the disrupted gene networks, and when tested in this system, was able to normalize some of the genetic phenotypes. This compound also showed beneficial effects in HD-related pathologies in the R6/2 mouse model, indicating that some of these pathways are linked to pathology.

Yu and Tanese used mouse embryonic stem cells provided by the Zeitland group to investigate HTT involvement in differentiation.2 The lines they used came from the same background, but were either huntingtin-null (Htt-null) or had tagged wild-type Htt (Q7) or mHtt (Q140). The group found that the presence of HTT, either wild-type or mutant, allowed all three germ layers to form, but Htt knockout blocked the ability of the cells to differentiate down the ectoderm pathway to form neural stem cells (NSC). Although mHTT still allowed NSC formation, it inhibited further differentiation into neurons. RNA-seq data from these lines revealed that MaoA and Oligo1/2 downregulation and upregulation of the PRC2 repressor complex may be involved in these developmental changes. One well-described effect of mHTT is the dysregulation of Ca2+ signaling. A new drug lead that corrects deficiencies in store-operated calcium entry (SOCE) in YAC128 medium spiny neurons (MSNs) has been described in a recent publication.3 SOCE was found to be increased specifically in MSNs but not in other neuronal subtypes in this model. The group identified a tetrahydrocarbazole that attenuated this phenotype in addition to normalizing mitochondrial function. The group postulates that the dual benefit might come from preventing abnormal Ca2+ accumulation in the mitochondria and endoplasmic reticulum.

In gene editing...

Allele-specific silencing of mHtt with methods that degrade mHtt mRNA is a promising treatment for HD, but that silencing is neither complete nor permanent. The discovery of the CRISPR/Cas9 nuclease system has created the possibility of altering genomic DNA in affected cells, and permanently silencing mHtt. Two groups have recently published studies that attempt this in mice.1,2 Both groups utilized the existence of allele-specific single-nucleotide polymorphisms (SNPs) that create or destroy protoscaler adjacent motif (PAM) elements in an allele-specific manner in the mHtt promoter. The groups then used a two-guide RNA (gRNA) system, with one gRNA targeted against the SNP in the promoter, and one in a downstream intron, leading to excision of the mHtt promoter and first few exons. The Davidson group used this technique, excising exon1 of mHtt in an allele-specific manner, in immortalized cells, in human HD fibroblasts, and in vivo in a BACHD mouse model.1 Shin and colleagues excised a 44 kb segment of mHtt, including exons 1–3, and successfully used their platform in induced pluripotent stem cells and neural precursor cells.2 Together, these data demonstrate the reproducibility and utility of using the CRISPR nuclease system to potentially permanently alter DNA to silence mHtt for therapeutic effect. CRISPR/Cas9 also can be used to create tools for drug screening. The Pouladi group coupled CRISPR/Cas9 technology with piggyback transposon technology to create corrected isogenic HD lines.3 The corrected lines maintained their pluripotency, differentiation potential, and karyotype, with no off-target effects. The correction restored HD-induced phenotypes, including neural rosette formation deficiencies, apoptotic susceptibility, and energetic defects in the isogenic iPSC line. Performing global differential gene expression analysis on the parental line, the corrected line, and a non-related control line allowed the scientists to determine which genes were differentially expressed because of the HD mutation, and which genes were differentially expressed because of genetic background.

In imaging...

Dr. Sarah Tabrizi’s group continues to data-mine the extensive human imaging and disease phenotype data available from the two large multi-center cohort studies, Track-HD and Track-On HD. In the largest imaging study ever done to assess depressive symptoms in HD, the group examined variation in structural and functional brain networks in relation to symptoms of depression in premanifest HD (preHD) and healthy controls.1 Onset of depression precedes onset of motor symptoms, and neuroimaging studies may reveal the early-affected brain networks. The group found that depressive symptoms in preHD are correlated with specific connectivity changes in the default mode network and the basal ganglia.

Another group published its imaging and electrophysiological study in Nature’s Scientific Reports, looking for functional and structural changes that are present prior to clinical diagnosis.2 This study looked at preHD patients who had a very low disease burden score, far from disease onset. All methods used in this study agree that brain function and structure is normal in this cohort, meaning that symptoms are reflective of an ongoing neurodegenerative process. This may have implications for timing of treatment.

Finally, another large-scale patient-based collaborative effort aimed to identify patients with extreme HD motor phenotypes with respect to their CAG repeat length and age, in order to search for disease modifiers.3 By looking at more than 10,000 HD patients, the group found that the total motor score (TMS) could vary by up to 30 years in individuals with the same CAG repeat length. They found that a TMS score of more than 13 would predict motor onset regardless of age and CAG length. The identified patients in the upper and lower quantiles can be further examined for biological, medical, or environmental factors that may lead to their extreme motor phenotype, which will inform patient care and prognosis.

Meet the Scientist

VITAL SIGNS

NAME: Beverly Davidson, PhD
TITLE: Chief Scientific Strategy Officer at the Children's Hospital of Philadelphia (CHOP); Director of the Raymond G. Perelman Center for Cellular and Molecular Therapeutics; Arthur V. Meigs Chair in Pediatrics, CHOP; Professor of Pathology and Laboratory Medicine, University of Pennsylvania
EDUCATION: PhD and post-doctoral research fellowship, University of Michigan
HOBBIES: Cycling, running, water- and snow- skiing; visiting museums; spending time with her children

Dr. Beverly Davidson is a geneticist of the first rank, who has made groundbreaking advances in our genetic understanding of HD, and is working hard to develop new gene-based therapies for HD and other conditions. HD Insights recently spoke with Dr. Davidson about her ongoing research. The following is an edited transcript of the conversation.

HD INSIGHTS: You have been studying HD and its genetics for nearly 20 years. Can you tell us how you got into the field?

DAVIDSON: I recently woke up in the middle of the night thinking, "It has been 12 years since the publication of our knockdown studies." I had no idea that it would take us this long to get to the clinic. How did I originally get into HD? I first started working in inborn errors of metabolism that affect the CNS. As a graduate student, I worked on Lesch-Nyhan syndrome. It always fascinated me how seemingly ambiguous mutations would induce such profound changes in the brain. I became fascinated by learning how mutations induce neuropathology, and developing ways to mitigate that neuropathology. I started early on in gene replacement strategies, always thinking in the back of my mind how we could apply some of the things we learn about getting genes into cells, and use this in some of the dominant neurodegenerative disorders.

We started working on RNA interference (RNAi) shortly after the seminal discovery by Fire and Mello in the late 1990s. We really did not have much success in achieving very selective knockdown until Tom Tuschl's paper came out some time later, showing us that the best way to accomplish selective knockdown was by using very small RNA fragments that were complementary to the gene you were trying to knock down.

We started working on this with two collaborators at the time. We had developed the technology, but we needed an animal model, and in the laboratory next door to mine was Henry Paulson, who worked on spinocerebellar ataxia. Through close interactions with Dr. Paulson we came to know Dr. Harry Orr, Dr. Nancy Bonini, and others working in the polyglutamine repeat field. We collaborated with Drs. Orr and Paulson to test some of our ideas in cell and mouse models. That is how we came to work in polyglutamine repeat diseases. It was really by chance that we began to focus on these sorts of therapeutics for spinocerebellar ataxia, and then also HD, both of which are classical polyglutamine repeat disorders.

Actually, my interest in HD goes back a bit further. My very close friend’s father had HD, and I recall seeing her grandmother cross the street when I was a child. I was with my dad, who was the local physician in our small community in south central Nebraska. I asked dad what was wrong with Shelly’s grandmother – she acted as if she could not walk very well. I was too young to know what a drunk looked like, and dad had told me that she had HD, and of course that meant nothing to me. But now we have come full circle. Many of Shelly’s family have succumbed to HD, so maybe I was destined from a very young age to work on this disease.

HD INSIGHTS: That is a powerful story. You mentioned that when you first published your seminal paper looking at the knockdown of the HD gene 12 years ago, you did not think it would take so long to get new therapies to the clinic. Why has it taken so long?

DAVIDSON: As with any new technology, in 2004-2005 we were using state-of-the-art methods for the time. As we began to learn more and more about the biology of the system that we were co-opting to perform RNAi in cells, we learned that there were better and safer ways to accomplish this.
DAVIDSON: The next six to seven years were to perfect the system and understand the basic ingredients of what it was we were making, and understand the impact of what we were making on the cell. The reason for taking this stepwise, careful, methodical approach is that HD is already terrible, and the last thing I want to do is take something that is very debilitating and make it worse.

HD INSIGHTS: Can you tell us about what is most exciting to you currently in terms of RNAi or antisense oligonucleotides (ASOs)?

DAVIDSON: We focused early on gene-silencing strategies, the idea being that the delivery of the viral vector to the affected cell would provide a one-time treatment to the brain. Sometime after our studies were published, Frank Bennett, at what is now known as Ionis Pharmaceuticals, began a fantastic collaboration with Dr. Don Cleveland’s group. Initially, it was to study ASOs for an inherited form of amyotrophic lateral sclerosis. Then, they transitioned to testing the ASOs in animal models of HD. These were the same models that many of us were using to test therapies at the time. His data showed that just as in our RNAi experiments, he could positively impact the disease course with doses of the ASOs, and I think that really excited the community. Fortunately for Ionis, they have already been into the clinic with many of these molecules.

Ionis is a large company that was well set to do the basic pharm tox that needs to be done to advance these molecules into therapies. Ionis has already started early phase-testing in HD patients, which is exciting. So, while we still remained poised to do our studies, they were already doing some safety studies in HD patients. It is an exciting moment for the gene-silencing community.

HD INSIGHTS: Can you talk about the current status of your gene-silencing therapies and efforts?

DAVIDSON: All the work that was developed while I was at the University of Iowa was licensed to Spark Therapeutics, and remains right now in IND-enabling studies.

HD INSIGHTS: Tell us about the promise of these therapies for HD.

DAVIDSON: Animal data suggest that you need not rid every cell of the mutated huntingtin gene, but to provide benefit, you need to hit a sufficient number of cells. The viral-vector delivered RNAi approach that we are taking, initially, is set to target the striatal region of the brain. This is in contrast to ASO therapies, in which the targeting is best achieved in the cortical structures. You could think of these as two complementary approaches to achieve widespread gene-silencing in the brain, in which the ASO could provide benefit to cortical structures, and the RNAi approach could provide benefit to sub-cortical structures. Our hope is that we can extend the period that HD patients live productively with the disease, significantly delaying its progression.

HD INSIGHTS: In 2011, you published a paper showing the benefits of RNAi in a rhesus macaque model of HD. Can you tell us a little more about that study and what it suggests for humans?

DAVIDSON: That was a study that we felt was really important not only for the RNAi community focusing on HD, but also for the ASO community. The study asked the simple question, can you reduce normal huntingtin in normal monkeys without deleterious effect? These were normal rhesus monkeys, not an HD model, but being a nonhuman primate, their brain closely approximated that of humans.

Our data showed that you could partially reduce huntingtin expression, and it was not deleterious to the animal. That study, published by my group and Dr. Jodi McBride’s group at Oregon Health Sciences University, was the first to show that this approach was safe in a nonhuman primate. That was followed up by a longer-term study published by a group at Medtronic, in which they evaluated a very similar approach for six months, and came to the same conclusion as us.

That suggested to us all that this could work, and really propelled us to move forward with a non – allele-specific silencing strategy as a potential treatment for HD patients.

HD INSIGHTS: You mentioned the promise of RNA silencing treatments. Do you have any concerns about them?

DAVIDSON: I think the first question is, how much gene-silencing do we need? We will not definitively know that until we start human trials, but we think we know what we need to know from a lot of work done in animal models. There is always concern because this is a new and unknown therapy, but we are very hopeful that it is going to be as promising as the animal models predict.
Meet the Scientist, cont...

HD INSIGHTS: Cures for neurological diseases are rare. Is it too soon to think that we could potentially cure HD?

DAVIDSON: This is not a cure. A cure would be where we would ablate the mutant gene product in every cell in the body, and that it would not manifest in any way in any tissue. Our hope is that these approaches will allow HD patients and premanifest individuals to live their lives to the fullest, and lengthen their time with no or minimal symptoms.

HD INSIGHTS: You have also done work in genetic conditions other than HD, and some of that work might even be ahead of where HD is. Could you tell us about some insights you have learned from other conditions?

DAVIDSON: The other condition we work on is spinocerebellar ataxia type 1, which, like HD, is a polyglutamine repeat disorder. We have also done some limited preclinical work in spinocerebellar ataxia type 7. Spinocerebellar ataxia type 1 was the first model in which we tested the RNAi approach, and spinocerebellar ataxia type 7, a second model. We have done more extensive dosing studies in spinocerebellar ataxia type 1 mouse models, and also tested some reversal studies in those models. I would not say that they are ahead of the HD program, I would say they are pretty close together.

We are also looking at the pathogenesis of HD and lysosomal storage diseases. We have some exciting data in HD, and this is really following close on the heels of some exciting work that has come out of Dr. Laura Ranum’s lab, where she has found that there are some funny transcripts that arise from the HD locus as a result of the CAG expansion. She sees transcripts in the nucleus that are not toxic in a normal-length allele, but in the setting of a disease-causing mutation, you can see these transcripts arising from that region, and if they are transported to the cytoplasm, they can be expressed as toxic proteins known as RAN translation products.

I think understanding how those products contribute to disease will be very interesting, as well as understanding other global changes that go on in the HD brain. I wonder whether we can take advantage of that information to develop small molecule therapies.

Will gene-silencing approaches be the be-all and end-all? I think the best approach might be a combination therapy where we tackle some of the downstream cellular impacts of mHTT and the mutant transcript, and in addition try to lower the insult through gene-silencing.

HD INSIGHTS: Thank you very much, Dr. Davidson. We greatly appreciate it.

DAVIDSON: I really thank HD Insights for the opportunity to let people know how we have reached where we are, and how excited we are to be so close to providing benefit to HD patients.

Selected recent publications:


References
Game-changing gene-silencing therapies for HD

What are gene-silencing therapies for HD?
Gene-silencing therapies reduce or prevent the expression of mHTT. They usually interfere with transcription or translation of mutant RNA, or cause the degradation of mHTT RNA.

What are the primary gene-silencing therapies under investigation?
The majority of gene-silencing therapies under current investigation are antisense oligonucleotides (ASOs), RNAi (RNA interference)-based reagents, and CRISPR/Cas9 gene-editing systems.

ASOs are short, synthetic DNA fragments that bind RNA through base pairing, and modulate its function. The majority of ASO drugs in development work through the degradative mechanism in which Ribonuclease H (RNase H) is recruited to recognize and cleave huntingtin transcripts. This process frees the ASO, enabling it to catalyze the degradation of multiple RNA molecules, effectively suppressing the gene product. With their diverse functionality, high target specificity, and suitability for direct CNS delivery through lumbar puncture ASOs are an excellent treatment option for HD. Currently, Ionis Pharmaceuticals has a nonselective ASO in a clinical trial. A nonselective ASO silences both wild-type and mHTT genes.

RNAi-based reagents—especially microRNA-based reagents—are also being developed. These reagents use small RNAs to bind to HTT mRNA molecules in order to silence their activity. RNAi-based reagents are not delivered naked—in other words, without a carrier—as are ASOs. Instead, they are typically delivered by a viral carrier. Two RNAi reagents that have shown a lot of promise are very close to translation to the clinic, one with Sanofi Genzyme and one with uniQure B.V. (see HD Insights, Vol. 16). One of the groups working on RNAi is doing its preclinical studies in the sheep model of HD, because sheep have a very long spinal cord, and a larger brain than nonhuman primates. That group hopes to maximize the therapeutics distribution in a larger brain and spinal cord.

In addition, a number of groups are developing gene-editing approaches to produce gene silencing, using the CRISPR/Cas 9 system. These approaches aim to completely inactivate the mutant copy of the gene. Currently, gene-editing strategies have low efficiency. Basically, you gene-edit some cells in culture, and then select for the cells in which the genes were actually edited. Next, you test the edited genes to make sure they did not receive an unwanted edit. Finally, you find that the cells have been changed in the way you want, and you expand those up to create your population. These studies are in very early preclinical stages, and there is a long way to go before efficiency and specificity will be high enough for use in the human brain.

What does your most recent research focus on?
We have been investigating a selective ASO that suppresses only mHTT and leaves wild type HTT expression intact. We ran a preclinical trial that will be published very soon and had excellent results. Basically, our ASO prevents the onset of HD in presymptomatic mice, and in symptomatic mice we saw recovery of motor and psychiatric phenotypes. Most importantly, we saw a complete rescue of cognitive phenotypes. We have shown that our ASO can not only prevent cognitive decline, but can also restore normal cognition when used post-symptom onset, meaning, after the mice have developed a cognitive deficit. We are very excited about this.

Is your selective ASO better than Ionis’s nonselective ASO?
Our selective ASO was co-developed with Ionis. I think the reason Ionis started with a nonselective ASO for its clinical trial was that it was the fastest way to get a therapy to all HD patients, with the idea that going back and developing selective therapies later would yield drugs that were safer for patients in the long term. I think that nonselective silencing is going to be preferable to not treating HD, but I also think that selective silencing is going to be better for the patient than nonselective silencing. In an effort to preserve wild-type HTT function, the nonselective ASO is being dosed to induce about 50 percent suppression in the cortex, and to have minimal activity in the basal ganglia.
Gene-silencing therapies, cont...

With a selective ASO, it may be possible to use a higher dose, to induce almost total mHTT suppression in the cortex, and have more activity in the basal ganglia.

Is there competition among scientists to be the first to discover the best therapy?

I think most people would agree with me that we are all on the same team. HD is the adversary. It is an incredibly complicated disease, and one that we need to come at from every angle we can. There is still so much work to do—after all, the gene was identified in 1993, and today, more than 20 years later, we are only just starting the very first huntingtin-lowering clinical trials. There is enough room for everyone’s work, and there is a lot more collaboration than competition in the field.

Are the patients and families hopeful?

Yes, they are really excited. They often contact me and ask, “When is this going to be available for me?” Sometimes I feel that a single email asks me to be a scientist, a clinician, and a genetic counselor. I have to tell people that it is a really long way between mice and men. A therapy must go through so many steps, so many points of potential failure, and once it gets to human trials, it can take years to prove its safety and efficacy. We are also hindered by our tools; for example, we do not have enough biomarkers to evaluate these therapies. The excitement is pushing the HD community to think that there is going to be something available for them in 5 to 10 years, but we have no idea if that is the case. Yes, we can at last successfully treat a mouse. Yes, we have really great preventative and restorative preclinical data. Yes, we finally have a huntingtin-lowering clinical trial that is targeting the root cause of HD—but unfortunately, none of this means there is an effective treatment just over the horizon. We simply do not know yet.

### Selected gene-silencing therapies in the pipeline

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<tr>
<td>Ionis Pharmaceuticals and Don Cleveland Research group</td>
<td>ASO</td>
<td>Study found ASO infused into cerebrospinal fluid of symptomatic HD mice delays progression of HD and reverses disease phenotypes.</td>
<td>Phase I clinical trial underway</td>
<td>Kordasiewicz HB, et al. 2012. ¹</td>
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<td>Genzyme</td>
<td>miRNA</td>
<td>Research suggests two recombinant adeno-associated viral vectors (AAV), AAV1 and AAV2, successfully target neurons that degenerate in HD.</td>
<td>Clinical trial planned (IND estimated 2018)</td>
<td>Hadaczek P, et al. 2016.²</td>
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<td>uniQure</td>
<td>miRNA</td>
<td>Research demonstrates strong <em>in vitro</em> and <em>in vivo</em> allele-selective silencing of mHTT by miSNP50 and total HTT silencing by miH12.</td>
<td>Preclinical research (IND estimated 2017)</td>
<td>Miniariikova J, et al. 2016.³</td>
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<td>Sangamo Biosciences</td>
<td>Zinc finger</td>
<td>Research revealed that allele-specific zinc fingers lowered production of mutant protein by more than 90 percent, while reducing normal protein by 10 percent or less.</td>
<td>Preclinical research (IND estimated 2017)</td>
<td>Zhang HS, et al. 2014.⁴</td>
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<td>Neil Aronin Research Group</td>
<td>siRNA</td>
<td>siRNA infusion is shown to lower mHTT levels in the striatum of mice without producing a robust immune response.</td>
<td>Preclinical research</td>
<td>Johnson E, et al. 2015.⁵</td>
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<tr>
<td>Ionis Pharmaceuticals Michael Hayden Research Group</td>
<td>ASO</td>
<td>At a wide range of doses, four ASOs potently and selectively silence mHTT throughout the central nervous system for 36 weeks or more after a single intracerebroventricular injection.</td>
<td>Preclinical research</td>
<td>Southwell AL, et al. 2014.⁶</td>
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<tr>
<td>WAVE Life Sciences</td>
<td>ASO</td>
<td>WAVE’s lead compounds are stereopure, allele-specific ASOs that target two difference single nucleotide polymorphisms (SNPs) associated with mutated Huntingtin to enable maximal target engagement with minimal off-target effects.</td>
<td>Preclinical research (INDs expected 2017)</td>
<td>WAVE Life Sciences 2017 Pipeline Update [press release], 2017.⁷</td>
</tr>
<tr>
<td>David Corey Research Group</td>
<td>ASO</td>
<td>Several ASOs targeted to the CAG repeat of HTT and containing a variety of modifications, such as bridged nucleic acids and phosphorothioate internucleotide linkages, demonstrated allele-selective silencing in patient-derived fibroblasts.</td>
<td>Preclinical research</td>
<td>Gagnon KT, et al. 2010.⁸</td>
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Gene-silencing therapies, cont...

Selected gene-silencing therapies in the pipeline, cont’d...

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Highlights of CHDI

The 12th Annual CHDI HD Therapeutics Conference was held in St. Julian’s, Malta, April 24–27, 2017.

By: Nicholas Caron, PhD

The 12th Annual CHDI HD Therapeutics Conference in the town of St. Julian’s, Malta, welcomed scientists from academia and industry to present data and discuss current research aimed at treating HD. The conference opened with a powerful and inspirational keynote speech from the "Miner/Mulligan/Colerdark/Johnson" family, who discussed the impact that HD has had on their lives over the past two years since the mother and two of three daughters were diagnosed with HD.

The first scientific session, chaired by Dr. Jim Rosinski (CHDI) and Dr. Lesley Jones (Cardiff University), focused on the utility of unbiased systems approaches to studying HD. Dr. Jones and Dr. Davina Hensman Moss (UCL) presented work implicating DNA damage repair response genes as key genetic modifiers of HD onset and progression. Dr. Chris Kay (UBC) discussed haplotypes associated with the CAG expansion mutation and how these can be used for allele-specific silencing of the mHTT gene in different HD populations.

The next session, chaired by Dr. Matt Lee (CHDI) and Dr. Marcy MacDonald (MGH), shifted focus to HTT structure and function. Dr. Kevin Weeks (UNC) presented work on novel technology to determine the structure of HTT mRNA and to design small molecule therapeutics against mHTT-specific RNA structures to achieve allele-specific silencing. Dr. Albert Ruzo (The Rockefeller University) presented work showing novel developmental phenotypes present in HD compared to isogenic control human embryonic stem cells (hESCs).

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## Clinical Trials Status Report

<table>
<thead>
<tr>
<th>SPONSOR</th>
<th>STUDY IDENTIFIER</th>
<th>STUDY AGENT</th>
<th>PHASE</th>
<th>CONTACT</th>
<th>DESIGN</th>
<th>TRIAL LENGTH</th>
<th>SITES</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beijing Pins Medical Co., Ltd</td>
<td>NCT02263430</td>
<td>PINS Stimulator System</td>
<td>I</td>
<td>Jia Fumin, PhD 010-59361265 <a href="mailto:pins_medical@163.com">pins_medical@163.com</a></td>
<td>Randomized, double-blind, parallel-group, sham-controlled trial of Globus Pallidus Deep Brain Stimulation in HD</td>
<td>1 year</td>
<td>Beijing, China</td>
<td>Not yet enrolling</td>
</tr>
<tr>
<td>Azidus Brasil</td>
<td>SAVE-DH</td>
<td>Cellavita HD</td>
<td>I</td>
<td>Alexandre Frederico, PI +55(19)3829-6160 <a href="mailto:alexandre@azidusbrasil.com.br">alexandre@azidusbrasil.com.br</a></td>
<td>First in human, dose-escalation study to evaluate the safety of the stem-cell based therapy Cellavita HD in HD</td>
<td>5 years</td>
<td>None listed</td>
<td>Not yet enrolling</td>
</tr>
<tr>
<td>Azevan Pharmaceuticals</td>
<td>STAIR</td>
<td>SRX246</td>
<td>I/II</td>
<td>Neal Simon, PhD 610-419-1057 <a href="mailto:ngsimon@azevan.com">ngsimon@azevan.com</a></td>
<td>Randomized, placebo-controlled, double-blind, 12 week, 3-arm dose escalation study of SRX246 in individuals with irritability and early symptomatic HD</td>
<td>12 weeks</td>
<td>22 total - United States</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Ionis Pharmaceuticals</td>
<td>NCT02519036</td>
<td>IONIS-HTTRx</td>
<td>I/II</td>
<td>Ionis Pharmaceuticals 800-679-4747 <a href="mailto:patients@ionisph.com">patients@ionisph.com</a></td>
<td>Randomized, double-blind, placebo-controlled study to to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of intrathecally administered IONIS-HTTRx in patients with early manifest HD</td>
<td>29 weeks</td>
<td>8 total - Canada, Germany, and the UK</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Heinrich-Heine University</td>
<td>HD-DBS</td>
<td>ACTIVA® PC neuro-stimulator</td>
<td>II</td>
<td>Susanne Harnisch +49 6421 286653 <a href="mailto:susanne.harnisch@kks.uni-marburg.de">susanne.harnisch@kks.uni-marburg.de</a></td>
<td>Randomized, double-blind, parallel-group, sham-controlled multi-centre trial of Globus Pallidus Deep Brain Stimulation in individuals with HD</td>
<td>3 months</td>
<td>10 total - Germany, Austria, and Switzerland</td>
<td>Currently enrolling</td>
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<tr>
<td>Institut National de la Santé et de la Recherche Médicale</td>
<td>TRIHEP3</td>
<td>Triheptanoin oil</td>
<td>II</td>
<td>Fanny Mochel, MD, PhD <a href="mailto:fanny.mochel@upmc.fr">fanny.mochel@upmc.fr</a></td>
<td>Randomized, double-blind, controlled study of Triheptanoin oil, an anaplerotic therapy, in early manifest HD</td>
<td>12 months</td>
<td>2 total - France and Netherlands</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Ipsen</td>
<td>NCT02231850</td>
<td>BNI2451B</td>
<td>II</td>
<td>Bruno Padrazzini, MD <a href="mailto:clinical.trials@ipensen.com">clinical.trials@ipensen.com</a></td>
<td>Randomized, double-blind, placebo-controlled proof of concept study of the efficacy and safety of PT-0254920 in HD</td>
<td>26 weeks</td>
<td>56 total</td>
<td>Trial ended</td>
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<tr>
<td>Pfizer</td>
<td>Amaryllis</td>
<td>PF-0254920</td>
<td>II</td>
<td>Pfizer CT.gov Call Center, 800-718-1021</td>
<td>Dose escalation, proof-of-concept study to investigate the safety, tolerability pharmacokinetic and pharmacodynamic properties of twice daily BNI2451B for four weeks in male patients with HD</td>
<td>26 weeks</td>
<td>58 total - worldwide</td>
<td>Top-line results released</td>
</tr>
<tr>
<td>Teva Pharmaceutical Industries</td>
<td>PRIDE-HD</td>
<td>Pridopidine</td>
<td>II</td>
<td>Katie Blatt, Teva 610-727-3297</td>
<td>Randomized, double-blind, placebo-controlled study of safety and efficacy of pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg BID versus placebo for symptomatic treatment in patients with HD</td>
<td>26 weeks</td>
<td>58 total - worldwide</td>
<td>Enrollment complete, study ongoing</td>
</tr>
<tr>
<td>Teva Pharmaceutical Industries</td>
<td>OPEN-HART</td>
<td>Pridopidine</td>
<td>II</td>
<td>Karl Kieburz, MD, MPH</td>
<td>Open-label, single-group assignment study to assess the long-term safety of 45 mg of pridopidine in HD participants</td>
<td>2 years</td>
<td>12 total - United States and Canada</td>
<td>Currently enrolling</td>
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<tr>
<td>Teva Pharmaceutical Industries</td>
<td>LEGATO-HD</td>
<td>Laquinimod</td>
<td>II</td>
<td>Sarah Boe, Teva 610-727-3486</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group study evaluating efficacy and safety of Laquinimod (0.5 or 1.0 mg/day) in HD</td>
<td>12 months</td>
<td>67 total - worldwide</td>
<td>Currently enrolling</td>
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<tr>
<td>Hôpitaux de Paris</td>
<td>REVHD</td>
<td>Resveratrol</td>
<td>II</td>
<td>Fanny Mochel, MD, PhD <a href="mailto:fanny.mochel@upmc.fr">fanny.mochel@upmc.fr</a></td>
<td>Randomized, placebo-controlled study to evaluate the therapeutic potential of Resveratrol on caudate volume in HD patients, using volumetric MRI</td>
<td>1 year</td>
<td>1 total - France</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Vaccinex Inc.</td>
<td>SIGNAL</td>
<td>VX15/2503</td>
<td>II</td>
<td>Andrew Feigin, MD, Huntington Study Group; 800-487-7671</td>
<td>Randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of VX15/2503 in individuals with late prodromal and early manifest HD</td>
<td>12-21 months</td>
<td>19 total - United States</td>
<td>Enrolment by invitation, study ongoing</td>
</tr>
<tr>
<td>University of Auckland</td>
<td>VCAS-HD</td>
<td>Varenicline</td>
<td>II</td>
<td>Ailsa McGregor, PhD +64 3 479 4235 <a href="mailto:ailsa.mcgregor@otago.ac.nz">ailsa.mcgregor@otago.ac.nz</a></td>
<td>Randomized, double-blind, placebo-controlled trial of varenicline using the standard dosing regimen for smoking cessation in patients with HD</td>
<td>16 weeks</td>
<td>1 total - New Zealand</td>
<td>Currently enrolling</td>
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<tr>
<td>Teva Pharmaceutical Industries</td>
<td>ARC-HD</td>
<td>SD-809 Extended Release</td>
<td>III</td>
<td>Samuel Frank, MD Huntington Study Group; 800-487-7671</td>
<td>Open-label, long-term safety study of SD-809 ER</td>
<td>58 weeks</td>
<td>40 total - United States</td>
<td>Study ongoing</td>
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<tr>
<td>Hôpitaux de Paris</td>
<td>NEUROHD</td>
<td>Olanzapine, Tetrabenazine, and Tiapride</td>
<td>III</td>
<td>Anne-Catherine Bachoud Levi, PhD +33 (0)1 49 81 23 01</td>
<td>Randomized, controlled study to compare the beneficial and adverse effects of 3 different neuroleptics in HD</td>
<td>1 year</td>
<td>1 total - France</td>
<td>Currently enrolling</td>
</tr>
</tbody>
</table>

To update or add a clinical trial, please e-mail editor@hdinsights.org

Sources: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and apps.who.int/trialsearch/
HD Therapeutic Pipeline

As of April 2017

Disease-modifying therapies

- KMO Inhibitor (CHDI Foundation)
- Cellavita HD (Azidus Brasil)
- SRX246 (Azevan)
- Laquiniqmod (Teva)
- OMS643762 (Omeros)
- PBT-2 (Prana)
- PF-0254920 (Pfizer)
- Pridopidine (Teva)
- VX15/2503 (Vaccinex)
- Cysteamine/RP103 (Raptor)

Neuroprotective compounds

- BN82451B (Ipsen)
- Epigallocatechin gallate
- Resveratrol
- Triheptanoin oil

Symptomatic treatments

- Varenicline
- Bupropion
- Deutetrabenazine
- Tetrabenazine

Gene-targeting therapies

- AAV-miRNA (uniQure)
- AAV-RNAi (Voyager/Genzyme)
- AAV-shRNA (Spark Therapeutics)
- Allele-selective ASO (WAVE Life Sciences)
- Zinc-finger binding protein (Sangamo/Shire)
- IONIS-HTTRx (Ionis)

Sources: [www.clinicaltrials.gov](http://www.clinicaltrials.gov), HDSA’s Therapies in Pipeline, and company/developer websites

To add or correct a therapy in development, please email editor@hdinsights.org.
Teva CNS is committed to continued research and development of its product portfolio and to the development of medicines aimed at meeting the specific needs of the patient communities it serves. Teva's legacy in CNS is grounded in its commitment to ongoing collaboration with academia, medical institutions, and patient advocacy groups to find innovative solutions for patients who live with chronic and debilitating diseases.
**Highlights of CHDI, cont...**

The next scientific session, chaired by Dr. Andrew Howard (CHDI) and Dr. Edward Wild (UCL), shifted focus toward HTT-lowering therapeutic approaches for HD. Dr. Wild presented compelling data implicating neurofilament light chain levels in the CSF and plasma as reliable biomarkers of HD progression. Dr. Nicole Déglon (Lausanne University Hospital) spoke of her work using a novel self-inactivating CRISPR/Cas9 system to suppress HTT both in vitro and in vivo.

The next session, chaired by Dr. Roger Cachope (CHDI) and Dr. Andrew Leuchter (UCLA), focused on the role of neuronal dysfunction in HD. Dr. Joseph Cheer (University of Maryland School of Medicine) spoke of the impairment of the endocannabinoid system in HD patients, and the potential benefit of endocannabinoid-based therapies for treating the psychiatric symptoms of HD. Dr. Abdellatif Benraiss (University of Rochester) presented exciting work using virally expressed brain-derived neurotrophic factor (BDNF) and noggin to promote mobilization of endogenous neural stem cells to replace striatal medium spiny neurons (MSNs) as a potential disease-modifying therapy for HD.

The final scientific session was chaired by Dr. Rebecca Fuller (CHDI) and Dr. Francisco Cardoso (University of Minas Gerais), and examined emerging opportunities for HD therapeutics. Dr. Anne Rosse (Cardiff University) presented the current status of cell-replacement therapy for HD via transplantation of hESC-derived MSNs. Dr. Andrew Yoo (Washington University School of Medicine) presented some of his group’s work using micro RNAs along with growth factors, for direct neuronal reprogramming of HD patient somatic cells to model HD.

This year’s CHDI conference saw major advances in our understanding of genetic modifiers on the course of HD; novel therapeutic approaches to target HTT at the DNA, RNA, and protein level; new biomarkers to assess disease onset and progression; and strategies to promote survival of vital neural pathways as well as to replace neurons that have degenerated as part of the disease, among other notable research. Together, the unrelenting efforts of the HD scientific community continue to push us closer to treating this devastating disease.

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**HD Research Around the World: Brazil**

By: Irina Kerkis, PhD

Little is known formally about the exact number of HD patients and individuals at risk in Brazil, but efforts are underway to change this. In 1997, Dr. Monica Santoro Haddad helped to start the Associação Brasil Huntington (ABH), or the Brazil Huntington Association, in São Paulo, Brazil, where she serves as medical advisor. She currently serves on the Board of Directors of the Brazilian Academy of Neurology as a member of the Deliberative Council, and is an active member of the American Academy of Neurology (USA). In her 29-year career as a Movement Disorders specialist, Dr. Haddad has attended to approximately 500 HD-affected families at outpatient Movement Disorders clinics in São Paulo’s largest public hospitals, namely Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, and Hospital Sírio-Libanês. In addition, she has followed more than 70 families in her private practice.

The ABH is a voluntary and non-profit national association whose purpose is to provide support and guidance to HD-affected families, to make the disease better known, to stimulate research, and to create specialized service centers in the different regions of Brazil. ABH receives contributions from members and donations. ABH is affiliated with the International Huntington Association, which provides guidance and information on the progress of scientific research in the HD field.

*Continued on Page 16...*
Highlights from the Journal of HD

By: Jennifer A. Simpson, LMSW and George J. Yohrling, PhD


In 2012, the US Food and Drug Administration (FDA) launched a Patient-Focused Drug Development Initiative as required under the fifth authorization of the Prescription Drug User Fee Act. The goal of this initiative was to systematically gather patients’ perspectives on their conditions and the available therapies to treat them. As part of this initiative, the FDA scheduled approximately 20 public meetings, each focused on a specific disease area. HD was chosen as one of the diseases for public input. After announcing that the meeting would be held in 2015, the Huntington’s Disease Society of America (HDSA) distributed two surveys to solicit specific comments from HD patients and their caregivers regarding symptomatology, quality of life, and therapeutic needs. The HD community responded enthusiastically, with 2,591 people providing answers for questions in the symptom-focused survey, and 1,040 people providing answers to questions in the treatment-focused survey. The objectives of these surveys were to identify the specific symptoms that most impact the daily lives of individuals with HD or juvenile HD (JHD) and their caregivers, and to identify the types of treatments desired by HD-affected families.

Although HD has long been classified as a motor disease, analysis of the data revealed that individuals with HD/JHD perceived symptoms related to dysexecutive syndrome to be most impactful (22% of responses). Caregivers responded even more strongly regarding the impact of dysexecutive syndrome, with 54% of caregivers identifying a combination of behavioral and cognitive symptoms such as anger/rage, anxiety, cognitive decline, and depression/apathy as having the greatest impact on daily life.

Although caregivers and HD patients aligned on some responses, there were also major divergences between the two groups. Perceptions of symptom frequency differ vastly between HD patients and their caregivers (See Figure). Nearly 14% of the 248 individuals with HD/JHD reported that they never experience HD symptoms, while just 1% of caregivers reported that they never observe symptoms in their loved ones. Greater than 80% of caregivers said they constantly saw symptoms in their loved ones, while less than 35% of individuals with HD/JHD reported constant HD symptoms.

Caregivers also responded more frequently that their loved ones with HD had completely lost their ability to perform a task, with 60% responding that their loved ones had completely lost the ability to work, drive, manage finances, take care of family, multi-task, or engage in a sex life. More than 85% of caregivers responded that their loved ones had completely lost their employability, while only 47% of individuals with HD/JHD responded similarly. Less than 50% of HD/JHD respondents said that they had completely lost the ability to do any of the 19 daily tasks listed in the survey. Caregivers also reported cognitive symptoms at greater rates compared to individuals with HD/JHD. However, data for both caregivers and individuals with HD/JHD suggest that an inability to maintain employment was among the most frequently experienced effects of HD on their lives.

When discussing treatments, data showed that very few individuals were taking any prescribed or not prescribed medications for some of the most impactful symptoms of the disease, such as dysexecutive syndrome. More than 80% of respondents noted that they or their loved ones with HD were not taking any kind of medication for deterioration in memory and thinking. Similarly, more than 40% of respondents noted that they or their loved ones were not using any form of medication to manage perseverance or anxiety, which can also be associated with dysexecutive syndrome. The only FDA-approved drug to treat a symptom of HD is tetrabenazine (Xenazine), which is used to treat chorea associated with HD. Even with an FDA-approved treatment, nearly 40% of respondents reported being unaware of, or not using, any medication to treat chorea. Just 23% of respondents reported taking tetrabenazine to treat chorea.

The efforts of the FDA in the implementation of the patient-focused drug development meetings are already creating a positive impact on the lives of patients across the spectrum of diseases. Patient and caregiver perspectives on HD symptomatology and treatment efficacy will be critical components in shaping future HD clinical development efforts. With this information, we can tailor clinical development efforts to treat the symptoms that those impacted by HD believe are the most disruptive.
Research from Brazil, cont...

One of the hopes for the treatment of neurodegenerative diseases is advanced stem cell therapy products. Mesenchymal stem cells (MSCs), which can be derived from adult body tissues including bone marrow, fat, and brain, offer great therapeutic promise for a diverse range of medical applications. MSCs are responsible for tissue regeneration throughout life, and this function is mediated by self-renewal and the ability to produce diverse types of differentiated cells. These therapies are used for their dual role. First, they stimulate local cell survival, inhibit inflammation, and stimulate brain tissue regeneration through paracrine action, leading to production of new neurons from both native and likely donor stem cells. Second, they express neurotrophic factors, such as brain-derived neurotrophic factors (BDNF), which plays a key role in the survival and activity of the neurons that die in HD.

Several principal investigators in São Paulo recently created a partnership between public institutions and a private company in order to evaluate the capacity of stem cells to treat HD and to bring stem cell-based therapies into clinical trials. This project aims to use MSCs for the treatment of HD patients. For this purpose, together with my team at the Instituto Butantan, São Paulo, we conducted preclinical studies of MSC-based therapies in a 3-nitropropionic acid – induced HD animal model. The MSCs used in our study secrete neurotrophic and immunomodulatory factors, and showed high migrating capacity and were able to cross the blood-brain barrier in the animal model. After intravenous injection of these cells in 64 HD-induced rats, reduced brain damage, amelioration of striatal degeneration, and enhanced expression of BDNF were observed. The results of the study led to the initiation of a clinical trial, currently approved by the Comissão Nacional de Ética em Pesquisa (National Commission for Research Ethics). The clinical study should start by the end of 2017, as soon as human MSCs can be produced under good manufacturing practice conditions, characterized, and validated. This study is conducted with the support of the international clinical research organization AZIDUS Brazil Ltd.