

# HD Insights™

A Huntington disease research periodical

Issue N° 11-- Spring 2015



## Meet the Attorney

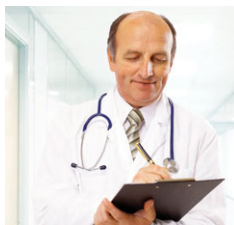
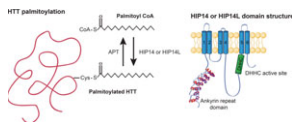
We interview Frank Sasinowski, JD, about his work with orphan drug development.

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## HD Research at UBC

Dagmar Ehrnhoefer, PhD, and Shaun Sanders, PhD, describe their research on post-translational modification of HTT.

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## Future of HD therapy

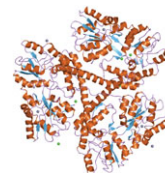
Daniel Zielonka, MD, PhD, summarizes disease-modifying therapies in development.

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## Clinical Trials Update

We bring you the latest in HD clinical trials.

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## Highlights of CHDI 2015

Francesca Cicchetti, PhD, shares the highlights of the February 2015 meeting in Palm Springs, CA.

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# Teva acquires Auspex for \$3.5 billion

By: Ryan E. Korn, BA

On March 30, 2015, Auspex Pharmaceuticals, Inc. (La Jolla, CA, USA) and Teva Pharmaceutical Industries, Ltd. (Tel Aviv, Israel) announced that Teva will buy Auspex in a cash deal valued at \$3.5 billion. The deal will enhance Teva's central nervous system portfolio with the addition of Auspex's deuterated compounds for movement disorders, including SD-809 (dutetrabenazine), which recently demonstrated efficacy and safety in Phase 3 trials conducted by the Huntington Study Group (see [HD Insights, Vol. 10](#)). The transaction is expected to be completed by mid-2015. Auspex plans to submit a New Drug Application (NDA) to the US Food and Drug Administration for SD-809 in HD during 2015. The company expects to receive regulatory approval and begin marketing the drug commercially in the US in 2016.<sup>1</sup>

Auspex has used its deuteration technology to develop therapeutic candidates for other orphan, hyperkinetic movement disorders, including Tourette syndrome and tardive dyskinesia (TD). The company is currently conducting two studies using SD-809 to reduce involuntary movement in individuals with TD. The [ARM-TD](#) (Aim to Reduce Movements in Tardive Dyskinesia) study is a Phase 2/3 randomized, double-blind, placebo-controlled, dose-titration trial of SD-809 in 90 people with TD. Topline results are expected in mid-2015. The [AIM-TD](#) (Addressing Involuntary Movements in Tardive Dyskinesia) study is a double-blind, placebo-controlled, parallel group trial in approximately 200 people with TD.<sup>2</sup>

**“The acquisition of Auspex... adds to the broadest and most ambitious development portfolio in the industry.”**

Dr. Michael Hayden, President of Global R&D and Chief Scientific Officer at Teva, told *HD Insights*, “Teva has a longstanding commitment to patients and clinicians in the HD community. The acquisition of Auspex represents an exciting new dimension to Teva's deep focus in this field, and adds to the broadest and most ambitious development portfolio in the industry.” Teva has two ongoing phase II HD clinical trials: the [LEGATO-HD](#) study of

laquinimod (see [HD Insights, Vol. 10](#)), and the [PRIDE-HD](#) trial of pridopidine. Teva's large, international development infrastructure is expected to allow faster development and distribution of Auspex's deuterated compounds.

Teva's acquisition of Auspex is part of an ongoing trend toward consolidation within the pharmaceutical industry, including companies that develop central nervous system therapies ([Table](#)).<sup>3</sup>

(continued on Page 2...)

## Teva/Auspex merger, cont...

Table. Selected acquisitions of pharmaceutical firms developing novel central nervous system therapies, 2011-2015

| Year | Acquirer                   | Target              | Amount        | Lead Compound   | Indication   | Phase of Development    |
|------|----------------------------|---------------------|---------------|---|--|-------------------------|
| 2015 | Actavis[4]                 | Allergan            | \$66 billion  | OnabotulinumtoxinA (BOTOX®)                                     | Variety of neurological and cosmetic indications           | FDA-approved            |
| 2015 | Teva[1]                    | Auspex              | \$3.5 billion | Dutetrabenazine (SD-809)  | Huntington disease   | Pre-NDA                 |
| 2014 | Actavis[5]                 | Forest Laboratories | \$28 billion  | Memantine HCl (Namenda™)  | Moderate to severe dementia from Alzheimer disease         | FDA-approved            |
| 2014 | Otsuka[6]                  | Avanir              | \$3.5 billion | Dextromethorphan hydrobromide and quinidine sulfate (NUEDEXTA®) | Pseudobulbar affect  | FDA-approved            |
| 2014 | Acorda[7]                  | Civitas             | \$525 million | Inhaled L-dopa (CVT-301)  | Parkinson disease  | Pre-NDA                 |
| 2013 | Allergan[8]                | MAP                 | \$958 million | Inhaled dihydroergotamine (Levadex®)                            | Migraines  | Rejected by FDA in 2014 |
| 2012 | Mallinckrodt (Covidien)[9] | CNS Therapeutics    | \$100 million | Baclofen (Gablofen®)  | Muscle spasms caused by damage to the brain or spinal cord | FDA-approved            |
| 2011 | Teva[10]                   | Cephalon            | \$6.8 billion | Modafinil (Provigil®)   | Narcolepsy   | FDA-approved            |
| 2011 | Biotie[11]                 | Synosia             | \$126 million | SYN-115 (Tozadenant)  | Parkinson disease  | Pre-NDA                 |

<sup>1</sup>Teva Reinforces Leadership Position in CNS with Acquisition of Auspex [Internet]. March 30, 2015. Available from: [tevapharm.com/news/?itemid=%7BF45C98FD-CEA7-48C4-B9CB-A6BD00D0BEDB%7D](http://tevapharm.com/news/?itemid=%7BF45C98FD-CEA7-48C4-B9CB-A6BD00D0BEDB%7D).

<sup>2</sup>Auspex Pharmaceuticals. Pipeline - Auspex Pharmaceuticals 2015 [May 8, 2015]. Available from: [auspexpharma.com/pipeline/](http://auspexpharma.com/pipeline/).

<sup>3</sup>The Economist. Invent it, swap it or buy it. The Economist. November 15, 2014. Available from: [economist.com/news/business/21632676-why-constant-dealmaking-among-drugmakers-inevitable-invent-it-swap-it-or-buy-it?src=rss](http://economist.com/news/business/21632676-why-constant-dealmaking-among-drugmakers-inevitable-invent-it-swap-it-or-buy-it?src=rss)

<sup>4</sup>Actavis Completes Allergan Acquisition [Internet]. Online; 2015; March 17, 2015. Available from: [prnewswire.com/news-releases/actavis-completes-allergan-acquisition-300051633.html](http://prnewswire.com/news-releases/actavis-completes-allergan-acquisition-300051633.html)

<sup>5</sup>Actavis Completes Forest Laboratories Acquisition [Internet]. July 1, 2014. Available from: [actavis.com/news/news/thomson-reuters/actavis-completes-forest-laboratories-acquisition](http://actavis.com/news/news/thomson-reuters/actavis-completes-forest-laboratories-acquisition)

<sup>6</sup>Avanir Pharmaceuticals To Be Acquired By Otsuka Pharmaceutical For \$3.5 Billion [Internet]. Online; December 2, 2014. Available from: [prnewswire.com/news-releases/avanir-pharmaceuticals-to-be-acquired-by-otsuka-pharmaceutical-for-35-billion-300003185.html](http://prnewswire.com/news-releases/avanir-pharmaceuticals-to-be-acquired-by-otsuka-pharmaceutical-for-35-billion-300003185.html)

<sup>7</sup>Acorda Therapeutics Completes Acquisition of Civitas Therapeutics [Internet]. Online; 2014; October 22, 2014.

Available from: [ir.acorda.com/investors/investor-news/investor-news-details/2014/Acorda-Therapeutics-Completes-Acquisition-of-Civitas-Therapeutics/default.aspx](http://ir.acorda.com/investors/investor-news/investor-news-details/2014/Acorda-Therapeutics-Completes-Acquisition-of-Civitas-Therapeutics/default.aspx)

<sup>8</sup>Allergan, Inc. to Acquire MAP Pharmaceuticals, Inc. [Internet]. Online; January 22, 2013. Available from: [reuters.com/article/2013/01/23/ca-allergan-inc-idUSnBw4rFID9a+114+BSW20130123](http://reuters.com/article/2013/01/23/ca-allergan-inc-idUSnBw4rFID9a+114+BSW20130123)

<sup>9</sup>Mallinckrodt Announces Definitive Agreement to Acquire CNS Therapeutics, Inc. [Internet]. Online; September 24, 2012. Available from: [newsroom.medtronic.com/phenix.zhtml?c=251324&p=iro1-newsArticle&ID=2004166](http://newsroom.medtronic.com/phenix.zhtml?c=251324&p=iro1-newsArticle&ID=2004166)

<sup>10</sup>Teva to buy Cephalon for \$6.8 billion, tops Valeant [Internet]. Online; May 2, 2011. Available from: [reuters.com/article/2011/05/02/us-teva-cephalon-idUSTRE74133720110502](http://reuters.com/article/2011/05/02/us-teva-cephalon-idUSTRE74133720110502)

<sup>11</sup>Biotie to Acquire CNS Therapeutics Firm Synosia in €93.6M All-Shares Deal [Internet]. Online; January 11, 2011. Available from: [genengnews.com/gen-news-highlights/biotie-to-acquire-cns-therapeutics-firm-synosia-in-93-6m-all-b-b/81244507/](http://genengnews.com/gen-news-highlights/biotie-to-acquire-cns-therapeutics-firm-synosia-in-93-6m-all-b-b/81244507/)

## Meet the Attorney

### VITAL SIGNS

NAME: Frank J. Sasinowski, MS, MPH, JD

POSITION: Director, Hyman, Phelps & McNamara, PC; Member, Board of Directors, [National Organization for Rare Disorders](http://www.nord.org) (NORD)

EDUCATION: JD, Georgetown University Law Center; MS, Nutritional Sciences, University of California at Berkeley; MPH, University of California at Berkeley; BS, Biological Sciences and Genetics, Cornell University

HOBBIES: Contemplation and meditation (see [www.onewednesday.org](http://www.onewednesday.org))



*Mr. Frank Sasinowski has dedicated his career to helping patients and companies bring new therapies for rare diseases to market. He recently shared his work, his hopes for orphan drug development, and his advice for researchers and companies with HD Insights. The following is an edited transcript of the conversation.*

**HD INSIGHTS:** How did you become interested in orphan drug development?

**SASINOWSKI:** I worked at the Food and Drug Administration (FDA) when Congress enacted the orphan drug law. I was asked to investigate how to make it work, because initially it wasn't working. My research led to the 1984 and 1985 amendments to the original 1983 law that made it as positive, constructive, and beneficial as it has proven to be. I drafted the original implementing regulations before I left the FDA in 1987. After that, I helped companies through the FDA pre-approval gauntlet for getting new orphan drugs to the market and patients in need. Due to my experience with the orphan drug law, I had a particular passion for helping with therapies for patients who are afflicted with rare conditions. I had also worked on developing the accelerated approval track for therapies for AIDS, because in the mid-1980s, the AIDS crisis was upon us. Fast Track is essentially a way to get drugs approved on the basis of a surrogate endpoint, where the ultimate clinical endpoint can be proven in a confirmatory post-approval trial. I helped Berlex Pharmaceuticals (now Bayer Healthcare Pharmaceuticals) with Betaseron (interferon beta-1b), the first therapy approved for multiple sclerosis. Betaseron was the first therapy ever approved by the FDA for a condition other than AIDS or cancer that relied upon this new system for accelerated approval. It was really ground-breaking, not only for patients with multiple sclerosis, but also as a trail blazer for other FDA regulatory precedents.

**HD INSIGHTS:** How did you become interested in HD?

**SASINOWSKI:** I have a long history of working with HD therapies. I was involved in the Care-HD study, the largest HD study that had yet been conducted. I was actually there 15 years ago when Drs. Karl Kieburtz and Ira Shoulson, professors at the University of Rochester and principle investigators for the study, broke the blind and announced the results. I represented VitaLine, one of the two companies that had therapies being investigated. VitaLine's Coenzyme Q10 (see [HD Insights, Vol. 6](#)) showed a 13% slower decline in the Total Function Capacity subscore of the Unified Huntington's Disease Rating Scale (UHDRS) compared to placebo. This was startling to the investigators, because a 13% between-group difference was by far the largest they had ever witnessed.

More recently, I helped Prestwick Pharmaceuticals with getting FDA approval for tetrabenazine for treatment of chorea associated with HD (see [HD Insights, Vol. 7](#)). The company showed positive results in a single trial on its primary endpoint, and an effect on global impression, a secondary endpoint, but the FDA was also impressed with patients' stories. You will not find this talked about in the labeling for the product, nor if you scour the FDA medical reviews or statistical reviews. However, we found in our interactions with the FDA that they were impressed by anecdotal reports that some patients whose chorea was so severe that they needed help in feeding themselves were able to self-feed after treatment with tetrabenazine. This demonstrates that the FDA wants to see that a therapy is going to improve how a patient feels or functions on a daily basis, or survives. Also related to HD, I aided Avanir Pharmaceuticals with its dextromethorphan and quinidine (NUEDEXTA®) therapy for pseudobulbar affect, which was approved in 2010.

Significantly, this was before the *FDA Safety and Innovation Act* (FDASIA) of July 8<sup>th</sup>, 2012, which represents the first time in the history of our drug laws that the word "patient" appears. Our drug law started with the 1906 *Pure Food and Drug Act*, and one would think that in over a century of law-making, it would be impossible that the law would never mention patients, but it is true. Congress relied on the medical community and the regulators to decide what was best for patients. There was a shift in 2012, and Congress told the FDA—and in effect the medical and patient communities—that patients need to have a role in approval of new drugs. I have had about 10 meetings this year with the FDA division of neurology, and they want companies not just to rely upon measurements of physiological outcomes that have an unclear connection with a patient's daily life, but to discover how a new therapy affects how that patient is feeling on a daily basis, and how they are engaging in their activities of daily living.

**HD INSIGHTS:** The *Orphan Drug Act* has been a great policy success. What are some of the remaining policy and regulatory challenges, especially as they might apply to HD?

**SASINOWSKI:** A major initiative in the evolution of drug development is just now emerging: the engagement of the patient voice in all drug development issues. FDASIA mandated that FDA hold hearings to bring patients' voices into the regulatory process, and I think getting patients' voices into the conversation remains a challenge. The HD community has the [Huntington's Disease Society of America](#), which was invited to be at that unveiling of the Care-HD study results 15 years ago. This is an example of how visionary people such as Drs. Kieburtz and Shoulson were already looking out for patient interests, but I think that kind of engagement has been slow in coming from the broader research community. We are on this cutting edge, and I predict that we will see more and more collaboration: for example, researchers and sponsors going out to patient groups as they plan trials to ask, "What do you think? What is important to you in your daily life?"

(continued on Page 14...)

# Research Round-Up

By: Lise Munsie, PhD

## In stem cell research...

Generating GABAergic medium-sized spiny neurons (MSNs) from human pluripotent stem cell (hPSC) sources is a rapidly evolving technique that holds much promise for HD modeling and treatment. Arber and colleagues describe a new method of differentiating hPSCs to MSNs using Activin A (activin).<sup>1</sup> Activin is part of the transforming growth factor beta signaling pathway, involved in neurogenesis and neuronal cell type fate. Arber's paper describes the ability of activin to produce a much higher proportion of MSNs than current techniques, and the ability of these neurons to survive in grafts in rodent models of HD.

Dr. Ihn Sik Seong's group makes an elegant cell model of HD using embryonic stem cells, producing six isogenic lines from one lineage. One line expresses two copies of wild-type mouse huntingtin (Htt) (Q7), an Htt null line, while four heterozygous lines express one Q7 allele and one CAG expanded allele of 20, 50, 91, or 111 CAG repeats.<sup>2</sup> This paper explores histone modifications in the presence of mHtt and Htt, based on research indicating that Htt acts as a polycomb recessive complex-2 facilitator. The authors show subtle alterations to the chromatin landscape and histone methylation states depending on whether Htt or mHtt is present, and whether cells are in a pluripotent or differentiated state.



Mattis and his group used HD-patient-derived induced pluripotent stem cells produced from non-integrating technology to assess how HD and juvenile-onset HD CAG repeat lengths affect neuronal differentiation.<sup>3</sup> The group found a significantly higher proportion of nestin-positive cells in cultures derived from JHD patients after 42 days of differentiation. Cells with juvenile-onset HD CAG repeat length suffer an increase in cell death with brain-derived neurotrophic factor withdrawal, due to glutamate toxicity. The authors posit that this increase may be mediated through the TrkB receptor.

<sup>1</sup>Arber C, Precious SV, Cambray S, et al. Activin A directs striatal projection neuron differentiation of human pluripotent stem cells. *Development*. 2015 Apr 1;142(7):1375-86.

<sup>2</sup>Biagioli M, Ferrari F, Mendenhall EM, et al. Htt CAG repeat expansion confers pleiotropic gains of mutant huntingtin function in chromatin regulation. *Hum Mol Genet*. 2015 May 1;24(9):2442-57.

<sup>3</sup>Mattis VB, Tom C, Akimov S, et al. HD iPSC-derived neural progenitors accumulate in culture and are susceptible to BDNF withdrawal due to glutamate toxicity. *Hum Mol Genet*. 2015 Mar 3. pii: ddv080. [Epub ahead of print]

## In the clinic...

A recent study assesses the clinical manifestation of HD in patients who express intermediate CAG repeat lengths.<sup>1</sup> A group led by Panegyres examined subjects who had repeats in the 27–35 range (at risk for prodromal HD), 36–39 range (mixed penetrance), or 40+ range (HD). No patients with CAG repeat length below 35 developed manifest HD. Smoking and being older than 65 correlated with manifest HD among those with intermediate repeat lengths. Of note, a high level of education was associated with lower odds of manifest HD, and the authors propose several hypotheses about environmental, cognitive or epigenetic factors.

A paper by Hobbs and colleagues in a group led by Prof. Sarah Tabrizi assessed candidate outcomes in HD patients in the imaging, clinical and cognitive streams, at both short (six-month) and longer (15-month) time



periods, in order to further the guidelines for assessing outcomes in HD clinical trials.<sup>2</sup> This is the first study to report significant effect size in short time periods. The strongest longitudinal changes were present in caudate atrophy and ventricular expansion. Small effect sizes were noted in other imaging and clinical measures that will be useful over longer time periods.

To date, there have been few studies assessing changes in the hypothalamus, a brain structure that may be responsible for the sleep, emotional and metabolic changes associated with HD. Hypothalamic changes are noted up to 15 years before predicted onset of manifest HD. In a recent PLoS One article,<sup>3</sup> Gabery and colleagues explored whether alterations to hypothalamic volume may be linked to these symptoms. Using 3T-MRI image data from IMAGE-HD, the group compared hypothalamic volume between patients before and after onset of manifest HD. The group did not find any statistically significant alterations in hypothalamic volume, indicating that the hypothalamic changes noted in previous studies are not likely due to atrophy.

<sup>1</sup>Panegyres PK, Shu CC, Chen HY, Paulsen JS. Factors influencing the clinical expression of intermediate CAG repeat length mutations of the Huntington's disease gene. *J Neurol*. 2015. 262(2): p. 277-84.

<sup>2</sup>Hobbs NZ, Farmer RE, Rees EM, et al. Short-interval observational data to inform clinical trial design in Huntington's disease. *J Neurosurg Neurosurg Psychiatry*. 2015 Feb 10. pii: jnnp-2014-309768. doi: 10.1136/jnnp-2014-309768. [Epub ahead of print]

<sup>3</sup>Gabery S, Georgiou-Karistianis N, Lundh SH, et al. Volumetric analysis of the hypothalamus in Huntington Disease using 3T MRI: the IMAGE-HD Study. *PLoS One*. 2015. 10(2): p. e0117593.

## In the pipeline...

Wild and colleagues report in the *Journal of Clinical Investigation* on an ultra-sensitive method of quantifying mHTT levels in the cerebrospinal fluid (CSF) of HD patients.<sup>1</sup> Using a single-molecule counting immunoassay based on the MW1 antibody specific for the expanded CAG tract, the group demonstrated the ability to detect mHTT in a disease- and onset-dependent manner in the CSF of HD patients in two cohorts. This assay will be useful as a pharmacodynamic biomarker in clinical trials, specifically in trials assessing HTT-lowering strategies.



It has been shown that allele-specific silencing of mHTT can be successful using small interfering RNA (siRNA) targeting the expanded CAG tract, or single nucleotide polymorphisms associated with the mHTT allele. The Davidson group aimed to explore whether specificity for the mHTT allele was maintained when previously tested siRNA sequences were moved into the group's artificial mRNA expression system.<sup>2</sup> This mRNA expression system may be more amenable to sustained delivery of knockdown than previously tested methods of in vivo knockdown. The group tested their system both in vitro and in vivo, and found that only some of the previously tested sequences were efficacious long term.

A report published in *Nature Chemical Biology* by Jimenez-Sanchez and colleagues describes a new therapeutic HD target extracted from an siRNA screen focusing on genes that are amenable to small molecule modulation.<sup>3</sup> The most significant suppressor of mHTT toxicity was glutaminyl-peptide cyclotransferase (QPCT), an enzyme with glutaminyl cyclase activity. The knockdown of this protein inhibits mHTT aggregation, while overexpression exacerbates aggregation. Using pharmacophore models and other known structures, the group designed QPCT inhibitors. These inhibitors have positive effects in several models of HD, and with further development may become clinically relevant.

<sup>1</sup>Wild EJ, Boggio R, Langbehn D, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. *J Clin Invest*. 2015 Apr 6. pii: 80743. doi: 10.1172/JCI80743. [Epub ahead of print]

<sup>2</sup>Monteys AM, Wilson MJ, Boudreau RL, et al. Artificial miRNAs targeting mutant huntingtin show preferential silencing in vitro and in vivo. *Mol Ther Nucleic Acids*. 2015 Apr 7;4:e234. doi: 10.1038/mtna.2015.7.

<sup>3</sup>Jimenez-Sanchez M, Lam W, Hannus M, et al. siRNA screen identifies QPCT as a druggable target for Huntington's disease. *Nat Chem Biol*. 2015 May;11(5):347-54.

The Huntington Study Group thanks Lundbeck for its ongoing support for *HD Insights™*, and its support of HSG 2014.

# Moving Together

Lundbeck



The Huntington Study Group thanks the Fox Family Foundation for its support of HSG 2014.

# FOX



# Family Foundation

# Unraveling the Cause of Dysfunctional Autophagy in HD

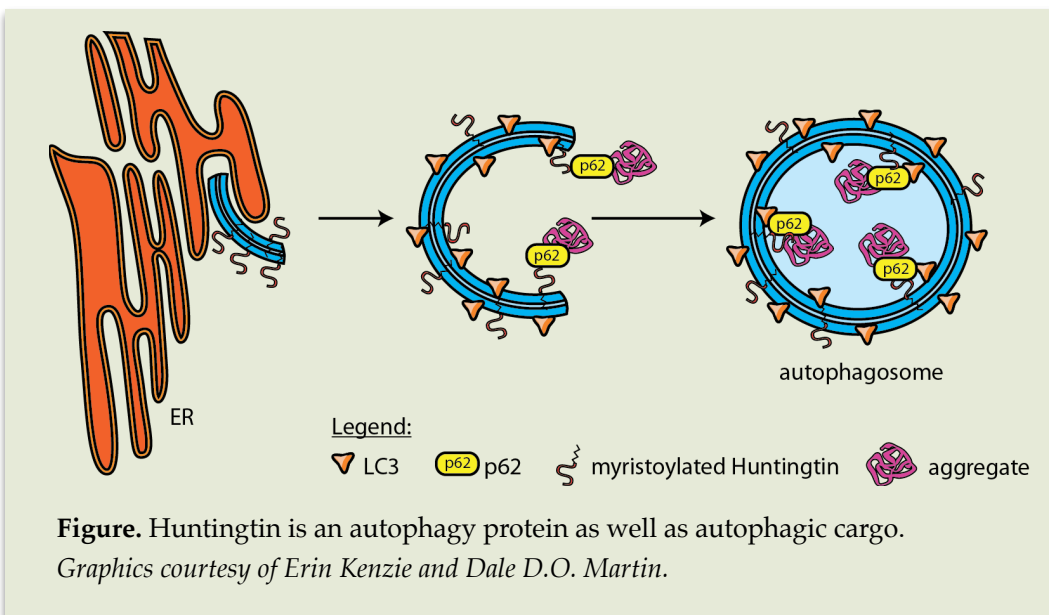
By: **Dagmar Ehrnhoefer, PhD**

Mutant huntingtin (mHTT) is the direct cause of HD, and many exciting new treatment strategies are aimed at lowering its levels. The primary approach is to prevent generation of mHTT. However, there are also intracellular mechanisms to clear mHTT once it has been generated, and even mHTT aggregates can be degraded. The mechanism for this is autophagy, meaning “self-eating.” Autophagy requires cargo proteins to be tagged with an autophagy adaptor protein such as p62, which then links the tagged protein to a membrane structure that slowly closes in around both adaptor and cargo. This autophagic membrane vesicle, called an autophagosome, then undergoes a series of degradation steps to finally clear the cell of unwanted dysfunctional or mutant proteins.

It has been known for some time that autophagy is impaired in HD, and that this impairment contributes to the accumulation of mHTT and its aggregates. In fact, the chemical up-regulation of autophagy has shown beneficial effects in mouse and *Drosophila* models of HD.<sup>1</sup> However, there is substantial evidence to suggest that in HD, cargo proteins are not efficiently loaded into

autophagosomes<sup>2</sup>, a defect that must first be corrected before mHTT degradation can take place efficiently.

More details about this dysfunction have come to light in the past year, as multiple studies have shown that wild-type HTT plays an important role in autophagy (**Figure**). This role is mediated through post-translational modifications: a fragment of HTT released by caspase cleavage at aa552 can undergo myristoylation at aa553, a lipid modification that anchors HTT to the ER membrane<sup>3</sup>, where it facilitates the formation of autophagosomes. Myristoylation is significantly reduced in the presence of mHTT,



suggesting that the normal function of HTT is disrupted. Interestingly, caspase cleavage of HTT is itself a process that is tightly linked to HTT toxicity<sup>4</sup> and, in particular, cleavage at aa586 is important for pathogenesis to occur in a mouse model of HD.<sup>5</sup> We have therefore recently suggested that preventing mHTT cleavage at aa586 may shift proteolysis to favor processing at aa552, which would lead to increased myristoylation and autophagy, and promote the clearance of misfolded mHTT.<sup>6</sup>

In addition, two independent studies have shown that HTT can act as a scaffold in autophagy initiation, bringing together the autophagy adaptor protein p62 and ULK1, a kinase that initiates autophagy.<sup>7,8</sup> The regions of the HTT protein that are required for binding p62 and ULK1 are at the C-terminus, distal from the aa586 caspase cleavage site. All data taken together suggest that cleavage of HTT at aa586 separates the myristoylated ‘membrane-anchor’ (aa553) from other, more C-terminal domains crucial for the interaction of HTT with other autophagy proteins.<sup>6</sup> Since mHTT is both cargo and part of the autophagic machinery, a more detailed investigation of these pathways and how they are disrupted in the presence of mHTT could identify therapeutic targets to increase the autophagic clearance of mHTT, a promising approach to lowering overall levels of mHTT.

<sup>1</sup>Renna M, Jimenez-Sanchez M, Sarkar S, Rubinsztein DC. Chemical inducers of autophagy that enhance the clearance of mutant proteins in neurodegenerative diseases *J Biol Chem*. 2010 Apr 9;285(15):11061-7.

<sup>2</sup>Wong E, Cuervo AM. Autophagy gone awry in neurodegenerative diseases. *Nat Neurosci*. 2010 Jul;13(7):805-11.

<sup>3</sup>Martin DD, Heit RJ, Yap MC, et al. Identification of a post-translationally myristoylated autophagy-inducing domain released by caspase cleavage of huntingtin. *Hum Mol Genet*. 2014 Jun 15;23(12):3166-79.

<sup>4</sup>Graham RK, Deng Y, Carroll J, et al. Cleavage at the 586 amino acid caspase-6 site in mutant huntingtin influences caspase-6 activation in vivo. *J Neurosci*. 2010 Nov 10;30(45):15019-29.

<sup>5</sup>Graham RK, Deng Y, Slow EJ, et al. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. *Cell*. 2006 Jun 16;125(6):1179-91.

<sup>6</sup>Martin DD, Ladha S, Ehrnhoefer DE, Hayden MR. Autophagy in Huntington disease and huntingtin in autophagy. *Trends Neurosci*. 2015 Jan;38(1):26-35.

<sup>7</sup>Ochaba J, Lukacsovich T, Csikos G, et al. Potential function for the Huntingtin protein as a scaffold for selective autophagy. *Proc Natl Acad Sci USA*. 2014 Nov 25;111(47):16889-94.

<sup>8</sup>Rui YN, Xu Z, Patel B, et al. Huntingtin functions as a scaffold for selective macroautophagy. *Nat Cell Biol*. 2015 Mar;17(3):262-75.



# Clinical Trials Update

| SPONSOR  | STUDY NAME/ IDENTIFIER      | STUDY AGENT  | PHASE  | PRINCIPAL INVESTIGATOR, CONTACT  | DESIGN   | TRIAL LENGTH | SITES  | STATUS   |
|--|-----------------------------|--|--------|--|--|--------------|--|--|
| Charité University   | <a href="#">ETON-Study</a>  | Epigallocatechin gallate                               | II     | Josef Priller, MD<br>+49 (0)30 450 617209  | Randomized double-blind study testing the efficacy and tolerability of (2)-epigallocatechin-3-gallate (EGCG) in changing cognitive function in HD patients   | 1 year       | 4 total - Germany  | <i>Enrollment complete, study ongoing</i>          |
| Charité University   | <a href="#">Action-HD</a>   | Bupropion  | II     | Josef Priller, MD<br>+49 (0)30 450 617209  | Randomized double-blind study testing the efficacy and tolerability of bupropion in changing apathy in patients with HD  | 10 weeks     | 3 total - Germany  | <i>Study complete</i>                              |
| Ipsen  | <a href="#">NCT02231580</a> | BN82451B   | II     | Bruno Padrazzi, MD<br><a href="mailto:clinical.trials@ipsen.com">clinical.trials@ipsen.com</a> | Dose escalation, proof of concept study to investigate the safety and tolerability, the pharmacokinetic and the pharmacodynamic properties of twice daily BN82451B for four weeks in male patients with HD | 28 days      | 1 total - Germany  | <i>Currently enrolling</i>                         |
| Omeros Corporation   | <a href="#">NCT02074410</a> | OMS643762  | II     | Albert Yu, MD<br>206-676-5000  | Randomized, double-blind, placebo-controlled, sequential cohort study to evaluate safety and efficacy of OMS643762 in subjects with HD   | 28 days      | 4 total - United States                                  | <i>Trial suspended</i>                             |
| Prana Biotechnology  | <a href="#">REACH2HD</a>    | PBT2   | II     | Ray Dorsey, MD   | Randomized double-blind safety and tolerability study of PBT2 of individuals with mild to moderate HD  | 6 months     | 20 total - Australia and United States                   | <i>Results published</i>                           |
| Pfizer   | <a href="#">NCT01806896</a> | PF-0254920   | II     | Pfizer CT.gov Call Center,<br>800-718-1021   | Randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and brain cortico-striatal function of 2 doses of PF-0254920 in individuals with early HD                          | 28 days      | Paris, France  | <i>Study complete</i>                              |
| Pfizer   | <a href="#">NCT02197130</a> | PF-0254920   | II     | Pfizer CT.gov Call Center,<br>800-718-1021   | Randomized, double-blind, placebo-controlled proof of concept study of the efficacy and safety of PF-0254920 in HD   | 26 weeks     | 23 total - Europe and United States                      | <i>Currently enrolling</i>                         |
| Teva Pharmaceutical Industries                             | <a href="#">PRIDE-HD</a>    | Pridopidine  | II     | Katie Blatt,<br>Teva<br>610-727-3297   | 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              | 26 weeks     | 57 total - worldwide                                     | <i>Currently enrolling</i>                         |
| Teva Pharmaceutical Industries                             | <a href="#">OPEN-HART</a>   | Pridopidine  | II     | Karl Kiebertz, MD,<br>MPH  | Open-label, single group assignment study to assess the long-term safety of 45 mg of pridopidine in HD participants  | 2 years      | 22 total - United States and Canada                      | <i>Enrollment complete, study ongoing</i>          |
| Teva Pharmaceutical Industries                             | <a href="#">LEGATO-HD</a>   | Laquinimod   | II     | Melissa Grozinski-Wolff,<br>Teva<br>610-727-6581   | Randomized, double-blind, placebo-controlled, parallel-group study evaluating efficacy and safety of Laquinimod (0.5, 1.0 and 1.5 mg/day) in HD  | 12 months    | 46 total - worldwide                                     | <i>Currently enrolling</i>                         |
| Raptor Pharmaceuticals                                     | <a href="#">CYST-HD</a>     | Cysteamine bitartrate delayed-release capsules (RP103) | II/III | Christophe Verny,<br>MD  | Double-blind, placebo-controlled study to be followed by an open-label extension study   | 36 months    | 8 total - France   | <i>Study ongoing, preliminary results released</i> |
| National Institute of Neurological Disorders and Stroke    | <a href="#">2CARE</a>       | Coenzyme Q10   | III    | Merit Cudkowicz,<br>MD, MSc  | Randomized double-blind study to see whether coenzyme Q10 is effective in slowing the worsening of symptoms of HD  | 5 years      | 48 total - United States, Canada, Australia              | <i>Study concluded for futility</i>                |
| National Center for Complementary and Alternative Medicine | <a href="#">CREST-E</a>     | Creatine   | III    | Steven M Hersch,<br>MD, PhD  | Randomized double-blind study to test whether high-dose creatine can slow the progressive functional decline that occurs in adults with early clinical features of HD                                      | 3 years      | 52 total - United States, Canada, Australia, New Zealand | <i>Study concluded for futility</i>                |

To update or add a clinical trial, please e-mail [editor@hdinsights.org](mailto:editor@hdinsights.org).

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



## Clinical Trials, cont...

| SPONSOR                                 | STUDY NAME/ IDENTIFIER   | STUDY AGENT                             | PHASE | PRINCIPAL INVESTIGATOR, CONTACT                          | DESIGN  | TRIAL LENGTH | SITES                   | STATUS   |
|---|--------------------------|---|-------|--|---|--------------|-------------------------|--|
| Auspex Pharmaceuticals                  | <a href="#">FIRST-HD</a> | SD-809 Extended Release                 | III   | Samuel Frank, MD<br>Huntington Study Group: 800-487-7671 | Randomized double-blind study to determine whether SD-809 ER tablets are effective in the treatment of chorea associated with HD. To be followed by an open-label, long-term safety study | 12 weeks     | 7 total - United States | <i>Study complete, top line results released</i> |
| Auspex Pharmaceuticals                  | <a href="#">ARC-HD</a>   | SD-809 Extended Release                 | III   | Samuel Frank, MD<br>Huntington Study Group: 800-487-7671 | Open-label, long-term safety study of SD-809 ER   | 58 weeks     | 7 total - United States | <i>Enrollment complete, study ongoing</i>        |
| Assistance Publique - Hôpitaux de Paris | <a href="#">REVHD</a>    | Resveratrol                             | III   | Tiffany Monier, MS<br>+33 1 57 27 42 22                  | Randomized, placebo-controlled study to evaluate the therapeutic potential of Resveratrol on caudate volume in HD patients, using volumetric MRI  | 1 year       | 1 total - France        | <i>Not yet recruiting</i>                        |
| Assistance Publique - Hôpitaux de Paris | <a href="#">NEUROHD</a>  | Olanzapine, Tetrabenazine, and Tiapride | III   | Anne-Catherine Bachoud Levi, PhD<br>+33 (0)1 49 81 23 01 | Randomized controlled study to compare the beneficial and adverse effects of 3 different neuroleptics in HD   | 1 year       | 1 total - France        | <i>Currently enrolling</i>                       |

To update or add a clinical trial, please e-mail [editor@hdinsights.org](mailto:editor@hdinsights.org).

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

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# Update on HD Disease-Modifying Strategies on the Horizon

By: Daniel Zielonka, MD, PhD

More than 20 years after the identification of the wildtype *HTT* gene and the mutated allele (*mHTT*) that causes HD, we still have no cure, although there are a few therapeutic options for HD symptoms. The most promising disease-modifying strategies on the horizon focus on *HTT* lowering (Figure), and some examples of these strategies are set to enter clinical trials this year.

One example is the use of zinc finger proteins (ZFPs), which silence transcription of *mHTT* by selectively binding to the expanded CAG repeat region of the *mHTT* allele without binding to the wildtype allele. Preclinical testing of this strategy has demonstrated behavioral improvements in an R6/2 mouse model.<sup>1</sup>

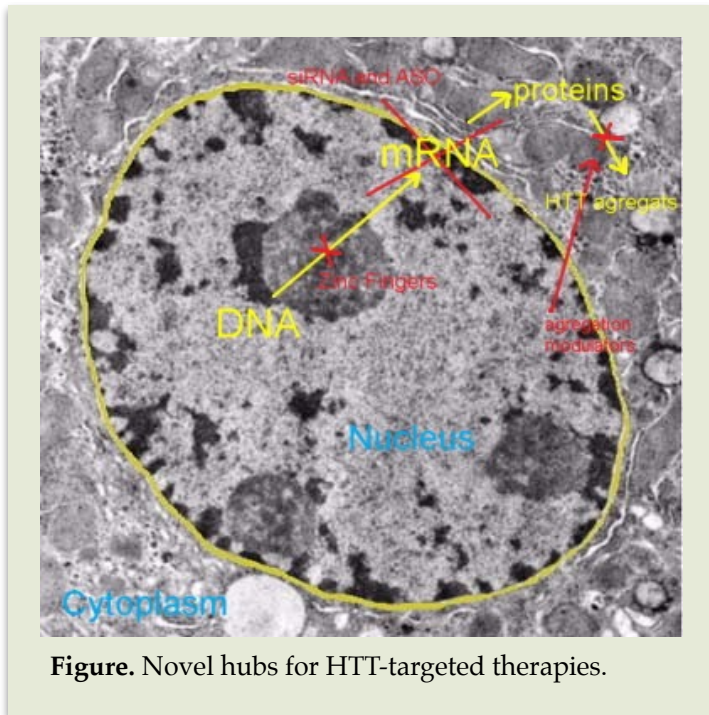


Figure. Novel hubs for HTT-targeted therapies.

Gene silencing approaches that use small interfering RNA (siRNA) or antisense oligonucleotides (ASOs) to selectively suppress mRNA production also demonstrate significant potential for disease modification. siRNAs and ASOs have both been shown to be safe and effective in HD mouse models, and are now entering human trials. Significant challenges remain for the delivery of these compounds to the human central nervous system (CNS), however, because these compounds cannot cross the blood-brain-barrier. Therefore, vector-assisted, intraparenchymal, intra-cerebro-ventricular, and intrathecal delivery methods are all being explored. Intrathecal delivery appears to be easier and less invasive than other methods. In preclinical testing conducted by Isis Pharmaceuticals, *mHTT* expression in mouse models was suppressed by up to 52% in the cortex, 64% in the spinal cord, and 20% in the caudate nucleus with an intrathecal ASO called Isis HTT-Rx<sup>®</sup>. A phase I clinical trial will begin this year to evaluate the compound's safety in humans.

Alnylam Pharmaceuticals and Medtronic have developed an implantable pump infusion system to deliver ALN-HTT<sup>®</sup>, an

siRNA-based therapeutic, into the putamen. The pump infusion system comprises an experimental catheter and the commercially available Medtronic SynchroMed II<sup>®</sup> pump. The companies believe that siRNAs will be evenly distributed between the striatum and other regions of the brain.<sup>2</sup> This approach was validated in Rhesus monkeys with a continuous infusion of siRNA over 7 days, leading to a 45% reduction of *HTT* mRNA in the putamen.

Finally, Roche recently described a new delivery approach using a monovalent molecular shuttle they call a "Brain Shuttle" that modifies the binding mode of an antibody to the transferring receptor and increases blood-brain barrier transcytosis.<sup>3</sup> Their study demonstrated a 55-fold increase in target engagement using the "Brain Shuttle" to deliver antibodies to beta amyloid in a mouse model of Alzheimer disease. This shuttle system may have the potential to deliver *mHTT*-silencing compounds in a less invasive manner than those mentioned above.

Several disease-modifying therapies for HD currently in development focus on selectively lowering *mHTT* in the CNS. As the challenges of CNS delivery and distribution are addressed, the possibility of slowing or reversing the effects of *mHTT* production may become a reality.

For further reading, please see Dr. Zielonka and colleagues' "[Update on Huntington's disease: Advances in care and emerging therapeutic options](#)," published in the March 2015 edition of *Parkinsonism and Related Disorders*.

<sup>1</sup>Garriga-Canut M, Agustín-Pavón C, Herrmann F, Sánchez A, et al. Synthetic zinc finger repressors reduce mutant huntingtin expression in the brain of R6/2 mice. *Proc Natl Acad Sci USA*. 2012 Nov 6;109(45):E3136-45.

<sup>2</sup>Zhang Y, Friedlander RM. Using non-coding small RNAs to develop therapies for Huntington's disease. *Gene Ther*. 2011 Dec; 18(12):1139-49.

<sup>3</sup>Niewoehner J, Bohrmann B, Collin L, et al. Increased brain penetration and potency of a therapeutic antibody using a monovalent molecular shuttle. *Neuron*. 2014 Jan 8;81(1):49-60.

# Highlights from the 10<sup>th</sup> Annual HD Therapeutics Conference

**By: Francesca Cicchetti, PhD**

This year's 10<sup>th</sup> annual CHDI HD Therapeutics Conference, held February 23–26, 2015 in Palm Springs, California, brought together over a hundred researchers from academia and the private sector. The four-day meeting offered an exciting program covering a wide variety of topics related to HD research, from new methodologies to tackle fundamental biological questions, to an entire session dedicated to novel therapies targeting mHTT levels. The presentation of this novel science was accompanied by two significant and memorable events that were highly inspirational to all who attended the meeting. The first was the keynote presentation by **Jeff Carroll**, who shared his personal HD story. Subsequently, attendees were invited to view an extraordinary documentary called, "[The Lion's Mouth Opens](#)," made by independent filmmaker **Lucy Walker**. The film follows **Marianna Palka**, herself a filmmaker, through her journey of being tested for HD and learning that she is a gene carrier.



**Held in Palm Springs, California**

The meeting kicked off with presentations by **Dr. Robert Pacifici**, Chief Scientific Officer, and **Dr. Cheryl Fitzer-Attas**, Vice President of Clinical Research at CHDI. Together, the speakers gave an account of the research that CHDI has sponsored, current and future programs emerging from their various initiatives and collaborations, and the platforms that have been made available through their various endeavors.

In a session titled "Illuminating HD biology and a next generation of therapeutic interventions," **Dr. Hong-Wei Dong** presented his remarkable work decrypting complex brain connections using computational and microscopy approaches. **Dr. Myriam Heiman** described a new technique referred to as "SLIC," with which her laboratory studies the function of individual genes in living animals. They are working to determine why some brain cells are more vulnerable than others in HD. The work of **Dr. Juan Botas** on HD *Drosophila*, which they breed with various fruit fly species characterized by other genetic mutations, is helping isolate changes and responses that are truly HD-specific. **Dr. Jong-Min Lee** outlined his work on genetic modifiers.

Industry leaders described novel mHTT-lowering therapies. **Dr. George McAllister**, Senior Director, Biology at BioFocus, presented a session on his company's efforts to screen a vast number of chemicals to identify those that show promise in reducing the expression of mHTT. **Dr. Lisa Stanek** from Genzyme presented their small interfering RNA approach to mHTT lowering, while **Dr. Frank Bennett** of Isis Pharmaceuticals presented their antisense oligonucleotide approach. **Dr. Geoff Nichol** of Sangamo Biosciences gave an update on the use of zinc finger proteins and planned clinical trials. The session concluded with CHDI's **Dr. Douglas Macdonald**, who described their efforts to identify biomarkers related to *HTT* silencing.

The last day of the meeting was dedicated to clinical research. **Dr. Gilbert Di Paolo** presented his work on specific lipids identified in the blood of participants in the TRACK-HD study. **Dr. Edward Wild** described his work with cerebrospinal fluid biomarkers, showing a positive correlation between mHTT levels in CSF and HD clinical progression. **Dr. Michal Geva** from Teva gave an update on their ongoing trials, including the PRIDE-HD and the LEGATO-HD trials.

**Dr. Sarah Tabrizi** summarized her group's findings in the TRACKOn-HD study. Using cerebral imaging, the group identified striking compensatory mechanisms that take place in the brains of HD patients years before symptoms develop. They are currently exploring the use of neurofeedback techniques that aim to train patients to modify their brain activity to improve performance. **Dr. Marios Politis** presented on his work on PET imaging, investigating overlapping brain networks involved in HD. Finally, **Drs. Ray Dorsey** and **Bernhard Landwehrmeyer** reviewed recently halted, ongoing, and future clinical trials.

Among the highlights of this 10<sup>th</sup> meeting, attendees had the privilege to hear featured speaker **Dr. Story Landis**, former director of the National Institute of Neurological Disorders and Stroke. The meeting concluded on an entertaining note with a light-hearted award ceremony.

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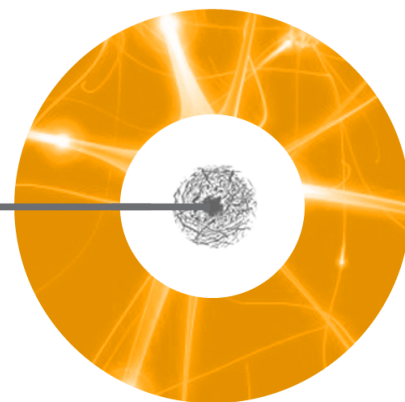
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*Sasinowski, cont...*

**HD INSIGHTS:** Are there current examples of this engagement in development of therapies for orphan neurological conditions?

**SASINOWSKI:** One of my fellow [NORD](#) board members, Pat Furlong, is the founder of a group called [Parent Project Muscular Dystrophy](#). They devised their own [draft guidelines](#) on developing therapies for Duchenne muscular dystrophy and presented them to the FDA, who published the guidelines for public comment. That is an example of a patient-driven, patient-initiated effort to help define what key elements should be considered, what populations should be enrolled in studies, what kind of endpoints should be considered, and what kind of safety risks should be prominently and sensitively monitored.

I'll give you one more example. About a year ago, the FDA published a [guidance document on migraine](#) that said in effect, "We all know that the most prominent feature of migraine is pain, but we need to have other symptoms that will be relieved by any therapy in development, because we do not want to approve drugs such as opioids that might treat only pain. There are three or four other prominent symptoms such as photophobia, phonophobia, nausea, and vomiting. Why don't you, as a sponsor, let each patient decide for themselves what is the most bothersome second symptom?" Why is this different? Let's say you have a therapy and you need to come up with a second endpoint, aside from pain. Normally, you would say, "Well, maybe it's photophobia, so I need only screen those who say that their most prominent second feature is light sensitivity." Thus, you enrich your study population with those who are just light sensitive, and then ask, "How did you do on pain?" and "How did you do on light sensitivity?" and hopefully show a difference. But you have severely limited who can enroll in your trials. The FDA is saying, "Open the floodgates, let them all in, but let them define for themselves what is the most troublesome second symptom after pain," demonstrating a sensitivity to letting patients drive the drug development system.

**HD INSIGHTS:** In 2012, you published [an analysis of FDA approvals for rare and orphan diseases](#), demonstrating variability in the application of evidence standards.<sup>1</sup> What are the implications of your research for companies that are developing drugs for rare and orphan diseases?

**SASINOWSKI:** The exchanges that I routinely heard at public advisory committee hearings for orphan drugs would baffle me. Normally, sponsors need two adequate, well-controlled studies that each hit a P value of less than 0.05 on the primary endpoint in order to even talk to the FDA about approval. For an orphan disease, the sponsor would often come in with something short of that. The chairman of the committee would turn to the FDA and say, "We know that this is not a situation like a new drug for treating hypercholesterolemia or high blood pressure, where you have an unlimited pool of potential subjects to enroll in trials. We know that there are severe constraints on who can be enrolled. So what are we to do with this?" The FDA would answer, "The *Orphan Drug Act* did not change the rules for how much evidence of treatment benefit needs to be presented for drug approval." This left the advisory committee in a quandary, because it seemed that they should be more flexible, but the FDA said that the law did not allow it. This bothered me. When the FDA held its first-ever public hearing on orphan drugs in June 2010, I was invited to speak on behalf of NORD. I said that the FDA ought to articulate a policy that explains how they would deal with this conundrum. The *Orphan Drug Act* did not change the quantum of evidence that is required for drug approval, but every orphan drug is different and every rare disease patient population is different. I suggested that if they could not enunciate a generalized statement of policy, at a minimum they could catalogue everything done with all the orphan drugs so that the world could see what has happened over time and what the evidentiary basis had been for all prior orphan drug approvals by FDA. The FDA approached me after the hearing and said, "We think your idea to catalogue it all is brilliant, but we do not have the time." I knew then that if anybody were to do it, it would have to be me. I printed off all the labeling, medical reviews, and statistical reviews for the 135 new chemical entities for rare diseases, other than cancer, that the FDA had approved from 1983 through June 2010. I took 27 boxes of documents with me to a secluded place in the mountains where I read and catalogued all 27 boxes, to see whether or not they met the usual criteria for approval for a prevalent disease. If they did not, I recorded whether these approvals represented some flexibility in the quantum of evidence, demonstrating that the FDA exercises some discretion while still relying upon good science. I found that two-thirds of all these orphan drug approvals showed some signs of flexibility with regard to the number and scope of trials required. This was eye-opening to everyone, particularly to the FDA, who did not realize they had been acting this way. I've since written an [update](#) that shows the same degree of flexibility. In orphan drugs approved between June 2010 and July 2014, the same ratio of about two-thirds of all approvals show some evidence of FDA flexibility.<sup>2</sup>

**HD INSIGHTS:** Is there any advice that you have for HD researchers or drug developers regarding current regulatory matters in front of the FDA?

*(continued on Page 15...)*

Sasinowski, cont...

**SASINOWSKI:** I think that the FDA is being extraordinarily sensitive to the needs of individuals who suffer from rare, chronic, debilitating, life-threatening diseases such as HD. Sponsors should realize that working with the FDA is extremely beneficial. For researchers and patients, it is important to think about ways to deepen an understanding of the natural history of the disease. We need collaboration between patients and the research community to figure out ways in which everyone will measure the same things under the same conditions. Currently, there is tremendous incentive for people to come up with their own ways of doing things; every major research institution wants to have its fingerprint so that it can publish a paper that says, "This is how we do it." That doesn't help, because that means everybody is evaluating everything differently.

**HD INSIGHTS:** When you are not helping companies develop treatments for orphan diseases, how do you spend your time?

**SASINOWSKI:** I recently set up a program called [One Wednesday](#), which hosts community gatherings for 30 minutes of silence every month. Looking at the suffering of patients tells me that we live in a divided world; we divide ourselves between healthy and unhealthy, between economic classes, political factions, religions and even within religions. One Wednesday is one effort to try to bring people to understand a fundamental truth, and that is that we all are one.

**HD INSIGHTS:** Thank you for all your efforts to help us get better treatments for individuals suffering with rare conditions.

<sup>1</sup>Sasinowski FJ. Quantum of effectiveness evidence in FDA's approval of orphan drugs: cataloging FDA's flexibility in regulating therapies for persons with rare disorders. *Drug Information Journal*. 2012;46(2):238-263.

<sup>2</sup>Sasinowski FJ, Panico EB, Valentine JE. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014. *Therapeutic Innovation & Regulatory Science*. 2015.

**Editor's Desk: The Orphan Drug Act, 1983-2015**

Orphan diseases are rare conditions which affect less than 200,000 individuals in the United States. The NIH Office of Rare Diseases website currently lists over 7,000 orphan conditions that affect a total of 25-30 million individuals in the US. Approximately one-fifth of these conditions are neurological.<sup>1</sup> The 1983 *Orphan Drug Act* encourages pharmaceutical firms to develop new therapies for orphan diseases through several incentive programs, including tax breaks, grant funding, FDA fee waivers, and longer market exclusivity for companies. In the 32 years since the passage of the *Orphan Drug Act*, the FDA has issued approvals for 463 orphan indications (some compounds are approved for multiple indications), 34 of which are for neurological conditions (see **Figure**).<sup>2</sup> Only one, tetrabenazine, is for HD.

**Figure. The total number of FDA-approved drugs for orphan indications has continued to grow since 1983, but drugs for neurological conditions remain only a small fraction of those approved.**

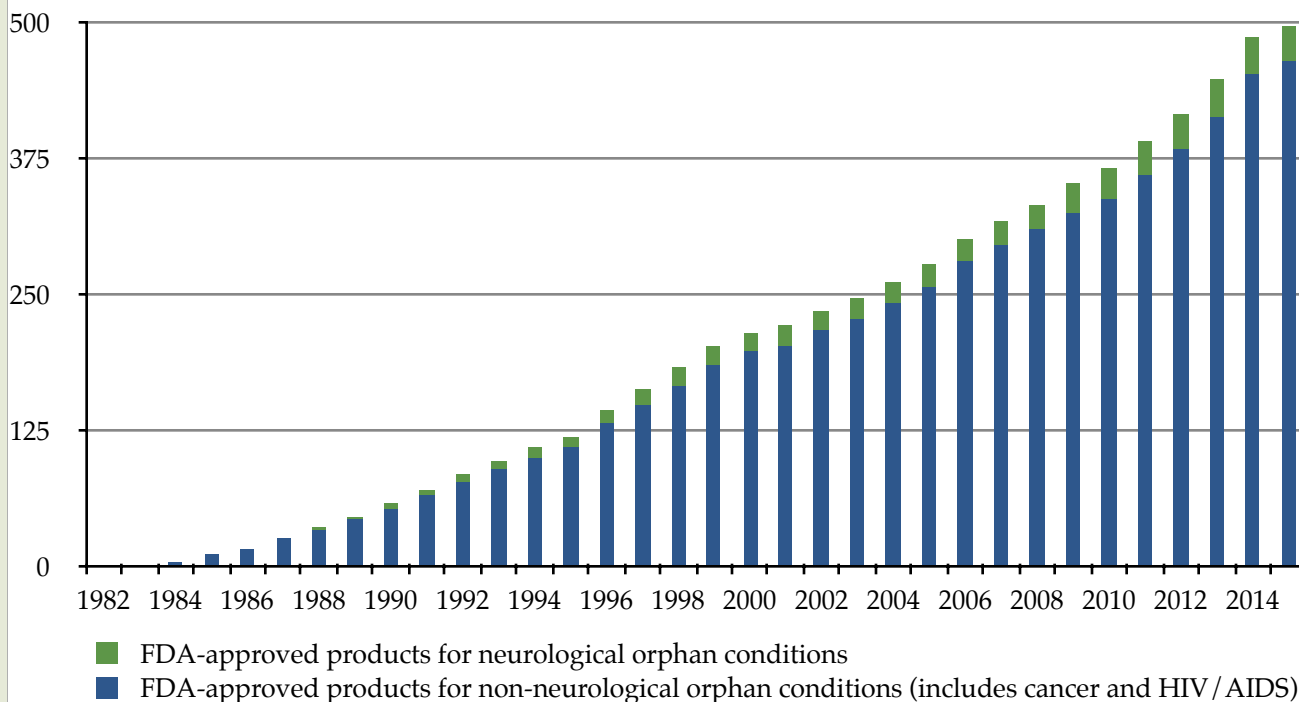


Figure prepared by Ryan E. Korn, BA and Meredith A. Achey, BM. Source: U.S. Food and Drug Administration Orphan Drug Product designation database. 2015. <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/>. Search terms: 01/01/1983-05/04/2015, "Only approved products." Accessed May 4, 2015.

<sup>1</sup>Murphy SM, Puwanant A, Griggs RC. Unintended effects of orphan product designation for rare neurological diseases. *Ann Neurol* 2012;72:481-90.

<sup>2</sup>U.S. Food and Drug Administration (FDA). Orphan Drug Product designation database. Available from [accessdata.fda.gov/scripts/opdlisting/oopd/](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/). Accessed May 4, 2015.

## EDITOR'S LETTER

Welcome to the 11th edition of HD Insights. We are pleased to continue our mission to promote, disseminate, and facilitate research in Huntington disease. We are grateful to the Huntington Study Group (HSG), our sponsors, and our more than 2800 subscribers for their continuing support.

This issue investigates potential therapeutic strategies for HD treatment and provides a detailed update on disease-modifying strategies set to enter clinical trials in the upcoming year. We discuss Teva's recent acquisition of Auspex following the promising results of FIRST-HD released earlier this year. We bring you an interview with former FDA attorney **Mr. Frank Sasinowski**, on his work with the 1983 Orphan Drug Act, his hopes for orphan drug development, and his advice for researchers and companies working to develop new therapies for rare diseases. **Dr. Shaun Sanders** describes the therapeutic potential of increasing palmitoylation of mHTT, thereby decreasing its toxicity and aggregation within HD patients. **Dr. Dagmar Ehrnhoefer** details several studies showing that wild-type HTT plays an important role in myristoylation and autophagy, and promotes the clearance of misfolded mHTT. **Dr. Lise Munsie** summarizes ongoing HD research and **Dr. Daniel Zielonka** discusses promising disease-modifying strategies aimed at lowering HTT. **Dr. Francesca Cicchetti** shares the highlights of February's CHDI meeting. Finally, we continue to provide an up-to-date status report on ongoing and recently concluded HD clinical trials.

The HD Insights team continues to rely on the support of firms dedicated to developing novel treatments to support our efforts to reach and educate the international HD research community. If you are interested in becoming a supporter, please contact me at [editor@hdinsights.org](mailto:editor@hdinsights.org). We welcome new contributors, suggestions for topics, and ideas about how we can better serve you. If you or someone you know would like to share their ideas with over 2800 HD researchers and clinicians around the world, please contact me at [editor@hdinsights.org](mailto:editor@hdinsights.org). Finally, subscription to HD Insights is always free: simply send us an email at [subscribe@hdinsights.org](mailto:subscribe@hdinsights.org).

-- RAY DORSEY, MD  
EDITOR, HD INSIGHTS™

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