evotec

DRUG DISCOVERY
EXPERTISE #01

DDxp

Rare *Diseases*

Introduction: Rare Diseases

Rare Diseases are individually rare but collectively common.

1 in 17 people[1] will be affected by a Rare Disease at some point in their lives. Half of those affected are children, with 30% not living to see their 5th birthday. Estimated to impact 263 to 446 million people globally at any one time with often severe and life-threatening consequences, development of Rare Disease treatments are increasingly becoming a global health priority.

A Rare Disease is any disease that affects a small percentage of the population. In general, a disease is defined as rare if it affects fewer than 200,000 people (US drug agency)[2]. Another word commonly used is an orphan (drug) indication. This is a subclass of Rare Diseases that have received little to no attention from researchers and the pharmaceutical industry to find a treatment. Many Rare Diseases are genetic and are thus present throughout the person's entire

life, even if symptoms do not immediately appear.

There are many different causes of Rare Diseases. The majority are thought to be genetic, directly caused by changes in genes or chromosomes. In some cases, genetic changes that cause disease are passed from one generation to the next. In other cases, they occur randomly in a person who is the first in a family to be diagnosed.

Rare Diseases are responsible for 35% of deaths in the first year of life. Many Rare Diseases, including infections, some rare cancers, and some autoimmune diseases, are not inherited. While researchers are learning more each year, the exact cause of many Rare Diseases is still unknown.

According to current orphan drug criteria, roughly 5,000–7,000 conditions qualify as Rare Diseases. However, treatment options remain limited, most of these diseases have no known cures or treatments, with therapies available for only 5% of them.

Within this publication we look at different areas of Rare Diseases, with a focus on Huntington's Disease, Gene Therapy and developing solutions for Rare Diseases.

Sources:

1. *European Commission – European Commission. (2020). Rare iseases. [online] Available at: https://ec.europa.eu/info/research-and-innovation/research-area/health/rare-diseases_en [Accessed 27 Jan. 2020].*
2. *U.S. Food and Drug Administration (FDA) – https://www.fda.gov/patients/rare-diseases-fda*

- *https://www.raregenomics.org/rare-disease-facts*
- *https://globalgenes.org/rare-disease-facts/#*
- *https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases*

Developing Solutions for *Rare Diseases*

Petra Dieterich

CMC & Commercial Manufacture

Scientists in Evotec's Chemical Development Division have been working on developing scalable processes for small molecule manufacture for over 25 years. During this time, the teams have supported partners by supplying more than 250 different API's for use in clinical trials. Some of our partners have been successful in taking their products all the way to market to which Evotec continues to supply these small molecule API's. Others have had block-busting success and, under the appropriate technocommercial factors, Evotec has assisted in the technical transfer to large scale, dedicated commercial manufacturing plants.

Developing small molecule treatments for Rare Diseases presents some unique challenges. Fast track designations means that CMC timelines are short, analytical methods must be quickly made fit-for-purpose and raw materials must be made accessible through qualified supply chains, with optimised cost of goods and timelines. Evotec's drug development strategies are focussed on integrated services that combine to rapidly create safe and robust processes that can be scaled-up in optimum timeframes to supply critical materials into drug development from pre-clinical studies and small volume market supplies. At Evotec's Europe-based development facilities,

scientific functions in synthetic chemistry, analytical chemistry and manufacturing operations are co-located, creating an ideal environment for integrated problem-solving that is required to quickly transition an asset from the discovery phase into clinical development and beyond. Evotec's integrated drug discovery centres are located at Manfred Eigen Campus in Hamburg, Germany, Campus Curie in Toulouse, France, and Dorothy Crowfoot Hodgkin Campus in Abingdon, UK. Evotec's site in Verona, Italy, is a premier site for small molecule integrated drug development with over 40 years' experience of drug development. The Verona site covers the whole drug development continuum and has capability to produce commercial drug product at volumes compatible with Rare Disease demand.

Figure 1: *Evotec's Integrated Drug Development Platform for Small Molecules*

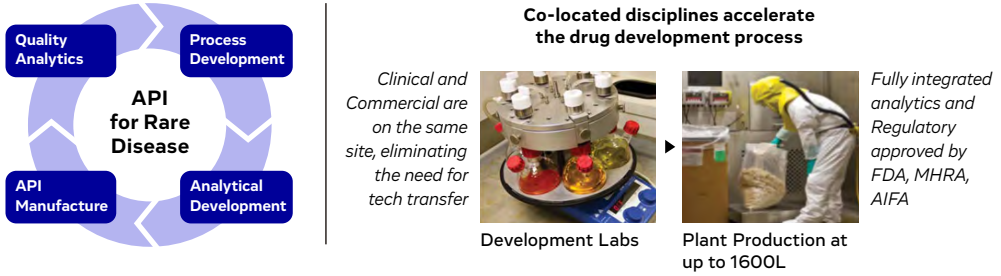
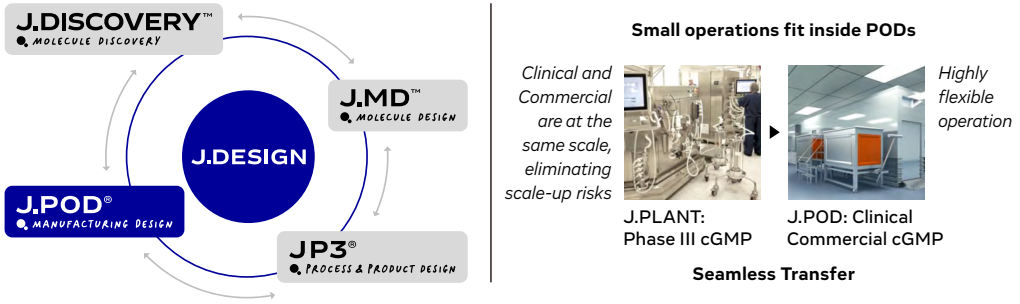


Figure 2: *Just – Evotec's Integrated Drug Development Platform for Biologics*



With the launch of the J.HAL℠, our AI-based antibody and nanobody discovery platform, Just – Evotec Biologics offers fully human antibodies and humanized nanobodies biased toward improved developability, thereby reducing the discovery and development timeline by several months. With regard to cell-line development, clinical and commercial manufacturing of biologics, Just – Evotec Biologics' platform is specifically well suited for the Rare Disease space as it was designed from its inception to provide the highest manufacturing yields while reducing COGS using its perfusion-based continuous-manufacturing platform. For a rare-disease indication this approach is especially attractive: high yields reduce the need for multiple expensive manufacturing campaigns thereby keeping overall development cost lower. Combining this benefit with Evotec's newly acquired pre-clinical development capabilities (IND-enabling studies) and first-in-human (FIH) clinical study support streamlines the timeline to the clinic, also saving precious time and development costs. Importantly, the Just – Evotec Biologics team have over 250+ combined years' of experience in the development and manufacturing novel biologics, biosimilars, and next-generation processes.

Table 1: *Summary of Incentives offered for Rare Disease Development in Major Global Markets*

	USA	EU	Japan	Australia
Prevalence	<6.25 in 10,000	<5 in 10,000	<4 in 10,000	<1.1 in 10,000
Market Exclusivity	7 years	10 years	4 to 10 years	none
Fee Waiver?	Yes	part	no	yes

Source: Nature Reviews: Volume 18, Jan 2019

Pharmaceutical Regulators have put measures in place to encourage companies to invest in R&D for Rare Diseases such that return on investment can be achieved. Orphan drug designation gives the drug developer tax savings and fee waivers, whilst priority review, accelerated approval, fast track designation and breakthrough therapy status offer a range of additional support, accelerated timelines to approval and marketing exclusivity.

Evotec's processes are compliant and undergo strong regulatory inspections by the FDA, MHRA and AIFA.

Regulators have incentivized repurposing drugs for Rare Diseases through a market exclusivity which can last up to ten years (see Table 1), and avoid generic versions from being sold during that period. However, to that end, the patentee needs to demonstrate that the new medical use is novel to obtain a 'method of use' (MOU) patent. Drug repurposing is a strategy for identifying novel applications for approved or investigational drugs that do not overlap with the originally intended medical treatment.

One of the oldest and most notorious examples of drug repurposing is Thalidomide, first marketed in Germany in 1957 for anxiety, its then unknown teratogenic properties caused devastating birth defects when given to pregnant women in the first trimester. It was banned worldwide in the 1960s. In 1964, however, Thalidomide was found to eradicate the symptoms of Erythema nodosum leprosum (ENL) when given to a leprosy patient as a tranquiliser. Research with off-patent Thalidomide continued in the 1990s and leading to FDA approval as treatment for multiple myeloma, a rare bone marrow cancer. Later, Celgene's Lenalidomide (RevliLater, Celgene's Lenalidomide (Revlimid), a derivative of Thalidomide, was subsequently found to be more efficacious for the treatment and maintenance of multiple myeloma and granted Orphan Drug Status for Multiple Myeloma treatment in 2001.

From 2001 until 2021 Bristol Myers Squibb (who acquired Celgene in November 2019) earnt $12.8 billion in global sales revenue for this drug. Another example of a successful partnership leading to regulatory approval of Evotec's manufacturing processes is the development of the API Fenfluramine (FINTEPLA, ZX008) in 2015.

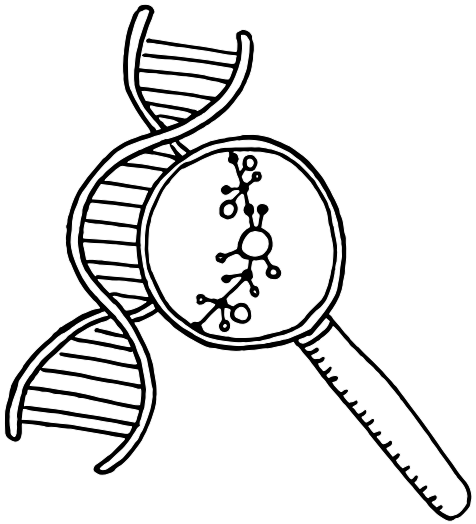
US based biopharmaceutical company, for the treatment of Dravet syndrome, a Rare Disease characterised by severe infant-onset epilepsy causing life-impacting seizures. Fenfluramine is a highly potent molecule scaled-up in Evotec's pilot plant facilities. In June 2020, the FDA granted Zogenix marketing authorisation for FINTEPLA as Orphan Drug for the treatment of Dravet syndrome. Throughout the whole process, Evotec has continuously supported Zogenix through the commercial API manufacturing.

While this article has a strong focus on CMC, it has to be mentioned that Evotec has both capabilities and capacities all along the drug discovery value chain, from idea to IND, manufacturing and early clinical trials, to support Rare Disease projects. This can all be done under one roof, no matter where the project lies on the idea-to-IND (and beyond) continuum.

Figure 3: *Illustrative functional capabilities along the Evotec value chain (***EVO***iR&D)*

Gene therapy *as a possible treatment and potential cure for Rare Diseases*

Hanspeter Rottensteiner
Werner Hoellriegl
Friedrich Scheiflinger



Advanced Therapy Medicinal Products (ATMP)[1] are promising transformational therapies for hitherto intractable genetic diseases. Amongst them, gene therapy has emerged as a disease-modifying and possibly even disease-curing concept that aims to alter or manipulate the expression of a gene for therapeutic use. Monogenic disorders are frequently associated with Rare Diseases, and gene therapy appears as a particularly well-suited treatment option for this class of disorders. Four adeno-associated virus (AAV)-based *in vivo* gene therapies have received marketing authorization (i.e. Glybera, Luxturna, Zolgensma, and EtranaDez) as singular treatments of rare diseases in metabolic, ocular, neuromuscular, and hematologic areas, respectively. In parallel, non-viral genetic medicines (based on lipid-nanoparticles), have been gaining traction as a platform for chronic treatment of rare diseases (e.g. Onpattro, Givlaari).

Gene therapies are highly tailored modalities and involve the introduction, removal, editing or regulation of genetic material, specifically DNA or RNA, within a patient's cells, either administered inside (*in vivo*) or outside (*ex vivo*) the body. For *in vivo* gene therapy applications, AAV-based vectors have emerged as the platform of choice as they are able to infect a broad range of cells, evoke only a mild immune response, have a favorable safety profile and can be produced at high titers. However, alternative viral vector platforms and non-viral approaches are rapidly evolving.

Evotec has adopted genetic medicines into Evotec's modality-agnostic drug discovery platform, the so-called multimodality Autobahn, and has fully integrated gene therapy research and development services at the newly founded Evotec GT, located in the Greater Vienna area at Orth an der Donau, Austria. With over ten years of pharmaceutical legacy insight into various disease areas, our staff offers a wealth of experience in gene therapy and drug development for Rare Diseases. Evotec GT provides gene therapy solutions for every step/phase in the drug discovery and pre-clinical development process, from target identification through to clinical candidates.

Many gene therapy candidates have entered clinical trials and the number of therapies available to patients is to increase significantly in the not too distant future, and some novel therapies may even begin to target diseases that are more common. However, despite the tremendous progress seen in recent years, gene therapy is still in its infancy as a therapeutic modality, with several remaining unknowns such as durability and safety.

Besides deep expertise in models of human disease and associated analytical

tools, Evotec GT leverages a multitude of additional best-in-class technology platforms within Evotec's scientific network. These synergies allow Evotec GT to offer unique and integrated drug discovery packages to their partners that should facilitate a seamless moving from discovery to translational research. This approach is further enabled by direct access to highly translational services in rodent and non-human primate models.

Insights into viral or non-viral genetic vector designs are coupled with unbiased platforms, such as tissue- and single cell-RNAseq or global proteomics. Evotec GT aims to help inform the engineering of novel capsids or vectors, the prediction of clinical response and potential adverse effects (e.g. liver toxicity) in the preclinical phase, while the discovery of biomarkers might allow for patient stratification strategies in the clinic. These customizable multidisciplinary approaches are poised to help overcome hurdles of gene therapy discovery and development and offer new, so far unexplored opportunities for improvement.

Taken together, Evotec GT's ambition is to accelerate and maximize its partners' success in developing gene therapy medicines. We strive for increasing the therapeutic benefits and reducing the risks of gene therapy, thereby aiming to make gene therapy a feasible treatment option for many, otherwise difficult to treat conditions, particularly Rare Diseases.

Huntington's *Disease*

Elizabeth van der Kam

Rare Diseases affect approximately 60 million people across the USA and Europe with often severe and life threatening consequences. Most of these diseases have no known cures or treatments. One such Rare Disease is Huntington's disease (HD).

What Is Huntington's Disease?

Huntington's disease (HD) is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). It was first described in 1872 by an American doctor, George Huntington, who studied an extended family in Long Island affected by the condition. However, it wasn't until 1993 that the gene responsible for the disorder was discovered and confirmed.

Adult-onset Huntington's disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with HD develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of HD usually live about 15 to 20 years after signs and symptoms begin.

A less common form of HD known as the juvenile form begins in childhood or adolescence. It also involves movement

problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30–50% of children with this condition. Juvenile Huntington's disease tends to progress more quickly than the adult-onset form; affected individuals usually live 10 to 15 years after signs and symptoms appear.

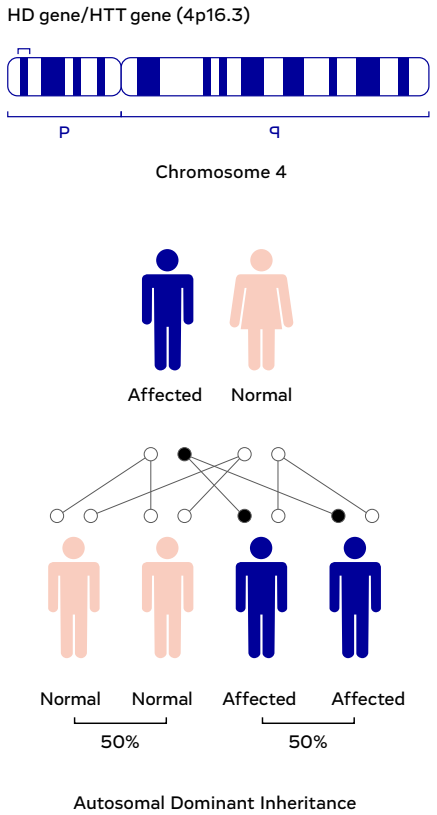
What causes Huntington's disease?

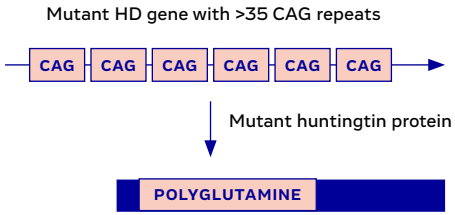
The disease is caused by mutations in a single gene, the huntingtin gene (HTT). The HTT gene provides instructions for making a protein called huntingtin. Although the exact function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain.

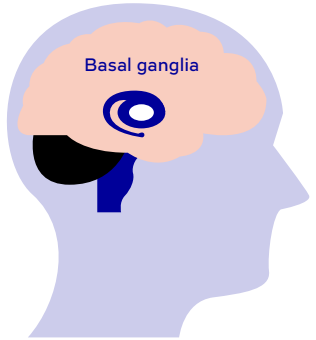
The HTT mutation that causes HD involves a DNA segment known as a CAG trinucleotide repeat (also known as polyQ). This segment is made up of a series of three DNA building blocks (Cytosine, Adenine, and Guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with HD, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms, while people with 40 or more repeats do develop the disorder.

Figure 1: *Huntington's Disease – the HTT gene, CAG trinucleotide repeat and autosomal dominant inheritance*

Source: https://www.onlinebiologynotes.com/huntingtons-disease-causes-symptoms-diagnosis-and-treatment







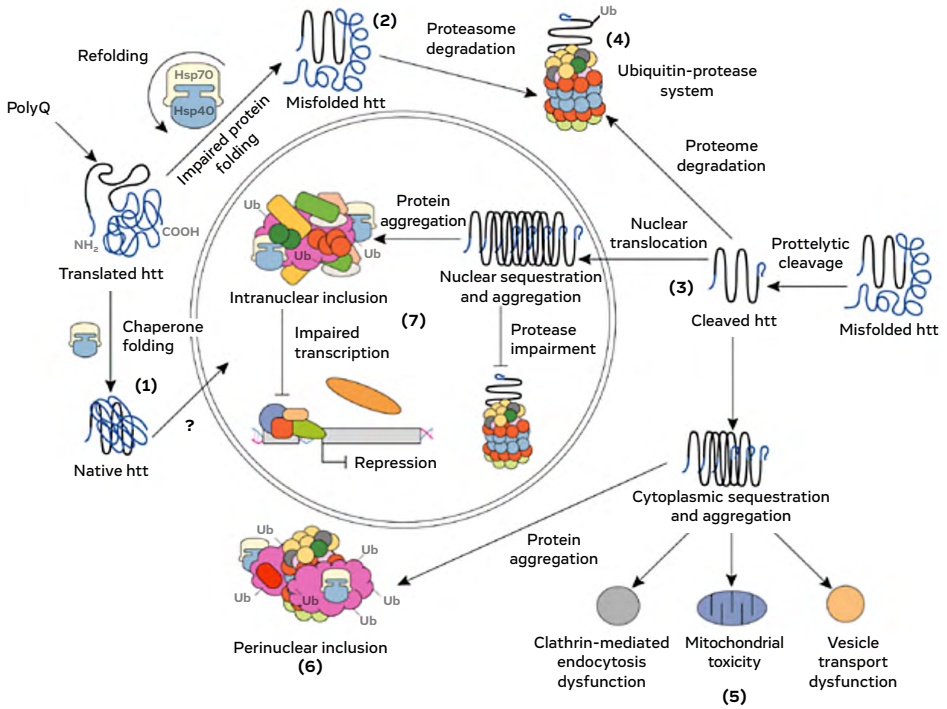
An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. This elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of HD.

The condition is autosomal dominant, which means that one copy of the altered gene is sufficient to cause the disorder. This also means that if one parent has the altered gene, there is a 50-50 chance that a child will inherit the disorder. As the altered HTT gene is passed from generation to generation, the size of the CAG trinucleotide repeat often increases in size and this can result in the more severe early-onset variant of HD. As most patients are not diagnosed until late in life (when the disease presents itself), the disease often affects multiple generations.

What is the impact of this genetic mutation?

The gene HTT produces the protein HTT. The HTT protein interacts with a lot of other proteins and has a key role in many biological functions. The behaviour of the mutated protein is not fully understood and this is a key focus of research, but it is clear that the mutated form is toxic to certain cell types, especially those in the CNS. The earliest damage can be seen in the striatum, but as the disease progresses, more brain regions become affected. Within cells, the mutant HTT protein can be cleaved into shorter toxic fragments, undergo post-translational modifications, misfold and aggregate. These processes then can, to various degrees, impact cell functioning and survival *(see Figure 2)*.

Figure 2: *The HTT protein: its lifecycle in a cell and what can go wrong*
Source: EMBO Rep, Volume: 5, Issue: 10, Pages: 958-963,
First published: 01 October 2004, DOI: (10.1038/sj.embor.7400250)



What is done to understand this disease better?
Although the disease was first diagnosed in 1872, it took more than 100 years (1993) until the responsible gene was discovered and confirmed. That discovery triggered research into the function of the gene, its protein, biomarkers for (early) diagnosis, identification of other (genetic) risk factors, and genetic testing options. The CHDI (Cure of Huntington's Disease Initiative) Foundation has been one of the driving forces in these efforts. Their mission is to collaboratively develop therapeutics that will substantially improve the lives of those affected by HD. To achieve that, CHDI actively support R&D efforts to improve the understanding of the disease. Evotec has been working with CHDI for the last 15 years to aid in this mission.

What role does Evotec play?
Evotec supports the mission to gain further understanding of the disease and to help develop therapeutics. Not only by working with CHDI, but also with other customers (from biotech to pharma). The efforts are supported by a core team of scientists and technicians that are specialized in the disorder or in specific technologies needed to elucidate the mechanisms of the disorder.

Activities range from testing of potential treatments in relevant disease models to the discovery and validation of new biomarkers that allow for earlier identification or more accurate identification of patients and treatment effects. Moreover, activities are ongoing to elucidate the mechanisms of (newly) identified genetic risk factors (genetic risk factors are genes that can contribute to the severity of progression of the disease, but are not the primary cause) and to understand the function of the HTT gene and its protein.

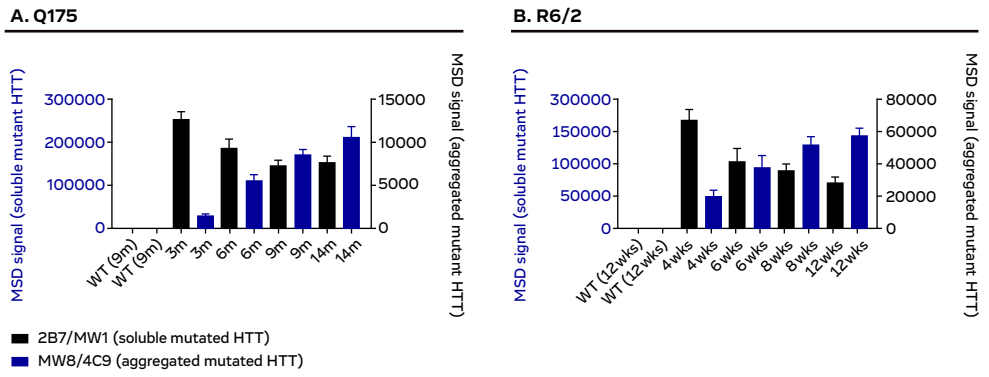
What does Evotec do with regards to biomarkers?
Biomarkers are a key aspect of any disease to either help identify/diagnose patients or to follow their disease progression and any potential treatment effect. Evotec has helped in the discovery and development of specific assays for the detection of forms of HTT in bodily fluids as well as the development of a PET tracer.

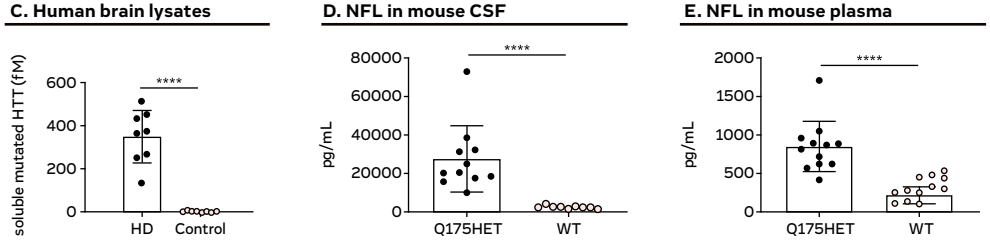
Despite a clear pathogenic role for mutant HTT, understanding its expression during the presymptomatic phase of the disease and during disease progression was long and difficult. Central to clarifying its role in the onset and progression of the disease, is the accurate measurement of mutant HTT in all HD models, from cell to man. This becomes even more critical for clinical trials that wish to examine therapeutic efficacy: assays need to be robust, reliable and completely validated to enable testing in human studies, whether it is in blood or cerebrospinal (CSF) fluid of patients.

Together with others in the HD research community, Evotec has developed several immuno-based assays to quantify huntingtin (HTT) protein in a variety of samples, including tissues and biofluids from preclinical and clinical studies. A platform of assays is now available to detect and measure expanded mutant HTT, HTT in a polyQ-independent manner, soluble, oligomeric, and aggregated HTT states, as well as rodent and non-human primate HTT proteins. Evotec continues to optimize and expands its portfolio of ultrasensitive assays.

Figure 3: *HTT immuno-assays for the accurate and reliable detection of HTT*
Source: commercial flyer Evotec

Case studies





- **Customized robust assays. Ability to run in 384-well format (MSD).**
- **Successfully applied for analysis of total, mutated and aggregated HTT as well as NFL protein levels in HD-relevant cellular and rodent models to support pre-clinical HTT lowering studies.**
- **Quantification of HTT and other biomarkers protein levels in diverse tissues (e.g. brain regions, liver, and muscle).**

HTT and NFL quantification by MSD and SMC-based biomarker assays

A. Detection by MSD of polyQ-expanded and aggregated HTT in wild type and hetQ175 mouse whole brain lysates.

B. Detection by MSD of polyQ-expanded and aggregated HTT in wild type and R6/2 mouse whole brain lysates.

C. Quantification of mutated HTT levels in a set of post-mortem HD patient and control donor brain tissues, by SMCxPRO.

D. Detection of NFL levels in CSF from wild type and Q175 HD mice, by SMC Erenna.

E. Detection of NFL levels in plasma from wild type and Q175 HD mice, by SMC Erenna.

One of the hallmarks of HD is the aggregation of the HTT protein: this process of aggregation is considered toxic and monitoring the formation of, as well as the potential impact of, a therapeutic on such aggregates would be extremely useful. Unfortunately, the assays as mentioned above lack the sensitivity to measure this in CSF. In such cases, a position emission tomography (PET) imaging tracer can help. As such, Evotec helped in the discovery and validation of such a high-affinity PET ligand specific for mHTT aggregates. To identify such compounds with binding affinity for these aggregates, Evotec collaborated with CHDI and embarked on systematic structural activity studies, lead optimization of aggregate-binding affinity, measurement of DMPK and safety properties, and confirmation of target engagement using relevant HD models and post-mortem human HD brain samples. These efforts have led to the discovery of the first suitable mHTT aggregate PET tracer, [11C]-1R (CHDI-180R). This compound has now advanced to human trials as a first-in-class HD PET radiotracer. Evotec continues to work on the development to new PET tracers as well as using such PET tracers to elucidate the different subspecies of mutant HTT aggregates.

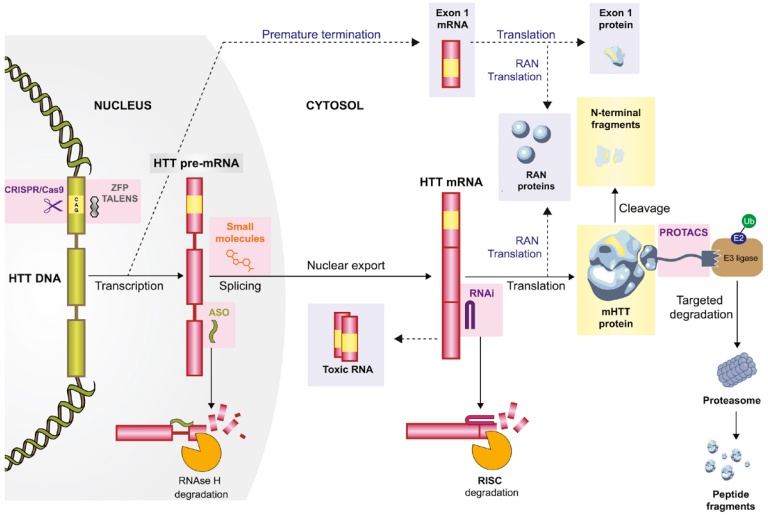
Source:

- *J Huntington Disease 2017 "Validation of Ultrasensitive Mutant Huntingtin Detection in Human Cerebrospinal Fluid by Single Molecule Counting Immunoassay"*
- *Evotec portfolio of HTT assays – please see: https://chdifoundation.org/research-tools-reagents/*
- *J Med Chem, 2020 "Imaging Mutant Huntingtin Aggregates: Development of a Potential PET Ligand"*
- *HDTC 2020 Poster "Ex Vivo Imaging Approaches to Identify the mHTT Target States of mHTT-Directed PET Imaging Agents"*

What techniques does Evotec use to examine treatments or elucidate the function of genes or treatments?

Since Huntington's Disease (HD) is a progressive autosomal dominant neurodegenerative disorder caused by mutant huntingtin (mHTT) protein, lowering mHTT expression is a key therapeutic strategy. Now, over the years, many therapeutics targeting HTT have been developed and/or investigated. A summary is given in Figure 4.

Figure 4: *Production of Potential Toxic Species in HD and Mechanisms for HTT Lowering*



Source: Neuron 2019 "Huntingtin Lowering Strategies for Disease Modification in Huntington's Disease" – https://www.sciencedirect.com/science/article/pii/S0896627319300662#fig1

Yellow sections of DNA, RNA, and protein represent the pathogenic expanded CAG tract and its polyglutamine product.

Pink boxes, therapeutic approaches; yellow boxes, widely accepted toxic species; gray boxes and dotted arrows, proposed mechanisms for the production of alternative toxic species; ZFP, zinc-finger protein; TALEN, transcription activator-like effector nuclease; ASO, antisense oligonucleotide; RISC, RNA-induced silencing complex; RAN, repeat-associated non-ATG; PROTACS, proteolysis-targeting chimera

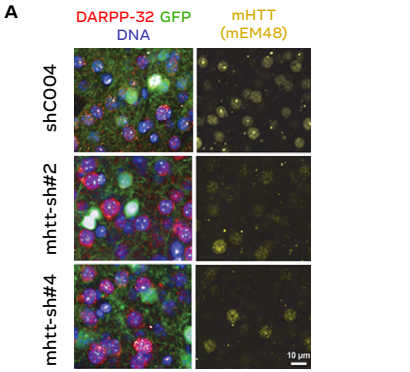
Among the available therapeutic approaches, the use of engineered zinc finger protein (ZFP) transcription repression (mHTT-ZFP) selectively targeting the CAG repeat region of the mutant HTT allele offers one mHTT-lowering strategy. This method allows to target mutant HTT specifically while leaving the normal HTT intact. This is important as normal HTT is thought to be important for normal brain functioning.

In collaboration with CHDI, Evotec helped with running the efficacy studies for such mHTT-ZFP therapies. Using patient-derived fibroblasts and neurons, we demonstrated that ZFP-TFs selectively repress >99% of HD-causing alleles over a wide dose range while preserving expression of >86% of normal alleles. The therapy was well tolerated and one could see an improvement in multiple HD endpoints after treatment. Evotec continues to perform studies with such mHTT-ZFPs to determine efficacy and safety as well as to find new delivery methods by using AAV technology.

Next to these therapeutic interventions, some of these methods can be used to elucidate the mechanism of normal and mutant HTT. For instance, one can selectively knock-out HTT by CRISPR or AAV technology and examine downstream effects by performing proteomics or transcriptomics.

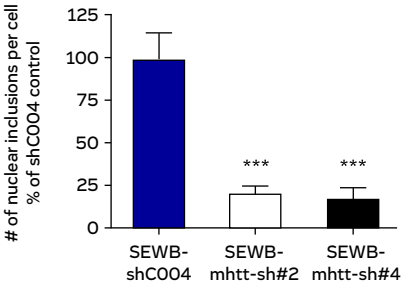
Overall, Evotec has a wide variety of technologies and capabilities that are used in the fight against HD.

Figure 5: *Case study on silencing of HTT by an AAV therapy in a relevant model*



mHtt-sh#2; mHtt-sh#4: directed against HTT shC004: non-target control shRNA

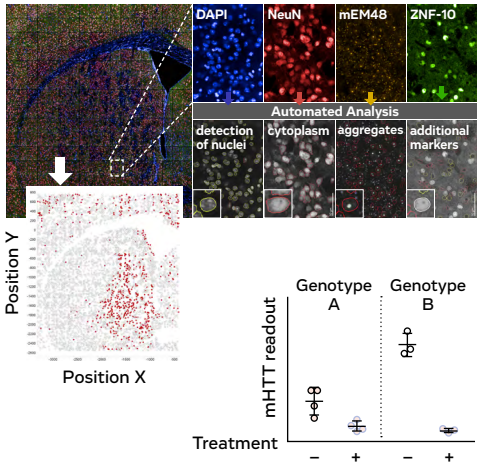
B Nuclear inclusions in GFP+ MSNs



- Modulation of HTT levels using shRNAs delivered by AAVs leads to a significant decrease in the number of nuclear mHTT inclusions in comparison to the control. Data are published: Carty N, et al. PLOS ONE, 2015
- AAV2 1+2 particles encoding GFP and shRNAs directed against HTT were injected in the right ventricle of neonate zQ175 heterozygous mice (analysis at 4m of age):
  - **(A)** DARPP-32 and nHZZ IHC staining in the GFP positive striatal region transducted with AAV2 encoding shRNA
  - **(B)** Quantitive analysis of mHTT nuclear inclusions in GFP positive cells of the striatum demonstrates significant knock-down in target cells

Figure 6: *High Content Image analysis of brain sections treated with a mHTT-ZNF to examine its mHTT lowering capabilities*

Source: commercial flyer Evotec



- Automated recording of mouse/rat brain secions in multiwell plates
- High-Content quantitative analysis of cells & subcellular structures in defined brain regions
- Readouts per section or as single-cell results
- Multiparametric analyses (e.g. LDA)

Source:

- *Nature Medicine 2019 "Allele-selective transcriptional repression of mutant HTT for the treatment of Huntington's disease"*
- *HDTC 2020 conference – poster "Longitudinal in vivo PET imaging of allele-selective mHTT suppression in the Q175DN mouse model as a candidate treatment for Huntington's Disease"*

Sarah Winckless: *Hope*

Sarah Winckless *is an Olympic and World Champion rowing medallist with over 20 years' experience in high performance sport who has successfully made the transition into strategic sports management and corporate development at Executive Board level, working globally with both individualsand teams to drive a sustainable competitive advantage for their organisations. She looks to enable each individual in a team to deliver their potential, whilst contributing to and supporting the overall results of the group. Challenging, warm and perceptive, she has supported many senior executives to unlock their own and their teams' performance often through maximising strengths and removing barriers*

Hope is a four letter word, and as I was growing up four letter words shouldn't be said out loud. In my family living with a Mum who was deteriorating from the ravages of Huntington's Disease (HD), there was no hope, so we didn't need to say it.

This can be the case for many families and sufferers from Rare Diseases, potentially feeling alone to face their challenges. For my family the journey continued, brilliant work from geneticist's relieved the burden of HD for three of my siblings, and gave me, with a positive diagnosis, the knowledge and power to live a life with no regrets and the ability to connect into a wider HD community of families and committed scientists.

I feel fortunate that I've been able to live a varied and exciting life, with passions in Sport, Business and people development. I have loved my time as a professional athlete, winning an Olympic Rowing medal and going on to be Team Leader for Olympic and Commonwealth Teams, working with extraordinary business leaders. As my life as an athlete dropped away, I continued to live in four year cycles; setting goals, learning and developing myself, then setting them for next four years. I thought it was out of habit – an Olympic cycle is four years long, until I realised it was out of fear. Fear that to look any further down to the road could mean I would not stay well enough to be able stay the distance.

As a potential future patient and family member, I want to thank each and every one of you for the precise, intentional work. The hours spent dedicated to increase understanding, and to potentially develop therapeutics that could change our lives. Keep finding the energy and commitment to start again when an experiment or hypothesis doesn't turn out as expected.

It is because of yours and others' everyday actions, that I now no longer live in four year cycles. I feel for my Rare Disease at least, we have extraordinary hope, the most powerful of all human emotions. Thank you.

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