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Pioneering antisense drug heads into pivotal trials for Huntington disease

Gene-silencing therapies promise progress in neurodegenerative diseases, with Roche and Ionis Pharmaceuticals testing whether such a drug can delay the progression of Huntington disease.

Asher Mullard

A phase III trial of Roche and Ionis's RG6042 is recruiting patients with Huntington disease (HD) to test whether a gene-silencing drug can slow the progression of a neurodegenerative disease. A positive outcome would be a much-needed boon for patients, while boosting enthusiasm for related strategies in other neurodegenerative diseases in which the accumulation of aberrant proteins damages the brain.

"Deep down we all feel like this is doable," says George Yohrling, senior director at the Huntington's Disease Society of America. "We've got this."

HD is a monogenic disease, and there is a direct link between pathogenic expansions in the huntingtin gene (*HTT*), the resulting mutant huntingtin protein (mHTT) and the onset of the fatal neurodegenerative disease. The higher the number of trinucleotide repeats in the CAG sequence in *HTT*, the earlier and more severely the disease strikes with its slew of motor, cognitive and psychiatric effects.

Although it remains unclear exactly how CAG repeats drive neurodegeneration, the mHTT fragments are thought to have toxic properties that disrupt multiple cellular pathways (see *Nat. Rev. Drug Discov.* **17**, 729–750; 2018). Roche and Ionis, as well as a few competitors, believe that HTT-lowering drugs can now prevent the build-up of these toxic fragments. Wave Life Sciences and its partner Takeda are also in the clinic with antisense HTT-lowering candidates, and other sponsors are set to initiate trials of miRNA-based gene-silencing candidates in 2019 (TABLE 1).

There are currently only two approved drugs for patients with HD: tetrabenazine and deutetrabenazine, both to control chorea associated with the disease. Experimental gene-silencing agents promise instead to modify the course of the disease entirely. "It's very exciting that we are not just addressing the symptoms of the disease, but that we may be getting at the underlying disease process itself," says Samuel Frank, neurologist at Harvard Medical School and investigator on the upcoming trial.

There are still a lot of open questions about this strategy, however, with potential implications beyond HD. Will treatment work at all? Is it better to target all forms of HTT, or only the mHTT form of the protein that is thought to do the damage? Which modalities and delivery strategies will get the gene-silencing drugs to the tissues where they are most needed? How early in the course of the neurodegenerative disease does treatment need to be started? And are the existing clinical trial end points suited to detecting treatment effects?

Yohrling is optimistic that Roche and Ionis's landmark trial will start to provide answers. "I don't want to get too excited, but it's hard not to," he says. "I'm very hopeful that this will move us in the right direction."

Table 1 | **Select list of potentially disease-modifying Huntington drugs in development**

Drug	Sponsor	Properties	Status
RG6042	Roche/Ionis Pharmaceuticals	HTT-lowering antisense	Phase III
WVE-120101	WAVE Life Sciences/Takeda	mHTT-lowering antisense	Phase I/II
WVE-120102	WAVE Life Sciences/Takeda	mHTT-lowering antisense	Phase I/II
AMT-130	uniQure	HTT-lowering miRNA	IND
VY-HTT01	Voyager Therapeutics/ Sanofi/CHDI Foundation	HTT-lowering miRNA	IND in 2019
HTT Program	Exicure	HTT-targeted spherical nucleic acids	Preclinical
VX15	Vaccinex	Anti-semaphorin 4D mAb	Phase II

IND, investigational new drug application; mAb, monoclonal antibody; mHTT, mutant huntingtin; miRNA, microRNA.

From gene to drugs

The case for HTT-lowering drugs has been gaining momentum for decades. HD was the first disease to be mapped to a human chromosome, in 1983, and researchers identified the variants that cause the deadly disease just 10 years later. In 2000, researchers showed that the abolition of mHTT in mice could reverse the neuropathological and motor symptoms of HD, prompting this team to conclude almost 20 years ago that "therapeutic approaches aimed either to destroy or inactivate the mutant huntingtin protein might be effective."

Gene-silencing technology has at last caught up to this science, as trailblazers in this space have developed oligonucleotide modalities that can act on targets in the brain. "There are many stages in the evolution of the chemistry and biology to have brought us to this point," says Scott Schobel, clinical science leader for the RG6042 programme at Roche. But the remarkable aspect of that evolution is that even a mere 6 years ago it would have seemed like science fiction that we could go into a human with a mutated gene and lower the production of a toxic protein safely and sustainably."

The leading HTT-lowering technologies come in a few flavours. Roche and Ionis's drug, also known as IONIS-HTTRx, is an antisense product that silences the expression of all forms of HTT, taking mHTT out in the process. HD patients have CAG repeats in at least one of their *HTT* genes, and the length of these repeats varies from patient to patient. There are also single-nucleotide polymorphisms (SNPs) that are associated with disease, but these are not conserved across all patients. With Roche and Ionis's non-selective approach, a single product — if effective — would cover all of this genetic variation.

But, the HTT protein is highly conserved and has essential roles in neuronal survival, transcriptional regulation, mitochondrial function and more. By knocking down wild-type HTT expression, Roche and Ionis's strategy might have safety limitations that they need to watch for in clinical trials.

Wave and Takeda, by contrast, are advancing antisense drugs that only silence mHTT transcripts. WVE-120101 and WVE-120102 each target SNP variants that are linked to CAG expansions. These two candidates could cover around 60% of individuals with HD. Although this strategy would require multiple drug candidates, tested in multiple clinical trials, to help all patients, these drugs might have improved safety profiles versus non-selective HTT drugs.

All three of these candidates need to be delivered regularly via lumbar puncture to reach the central nervous system (CNS). Roche and Ionis will administer RG6042 every month and every other month in their pivotal trial.

Voyager Therapeutics and uniQure are meanwhile independently developing microRNA-based strategies to harness the RNA interference (RNAi) pathway to silence HTT and mHTT expression. Both companies are using viral vectors to deliver their gene therapies, counting on direct injection of the therapy into the brain via one-time brain surgery to provide lifelong silencing.

Only clinical data will determine how well these different HTT-lowering approaches work in humans, says Schobel. "But we certainly feel good about our total lowering approach. So far it's been safe in animals and our early clinical experience was positive in terms of the drug being safe and well tolerated," he says. Roche and Ionis spent a lot of time studying various HTT-lowering strategies, including mutant-selective drugs, he adds, and found that the total-lowering approach offered potency and safety benefits without any apparent adverse event red flags. "We've picked our total lowering approach with careful consideration of safety, tolerability and potency," he says.

In the proof-of-concept phase I/II trial of RG6042, the drug lowered cerebrospinal fluid levels of mHTT by 40–60%. Because of how the drug traffics through the brain, this should correspond to a 55–85% reduction of mHTT in the cortex and a 20–50% reduction in the deeper, caudate regions of the brain. Mouse model data suggest that mHTT knockdown in the cortex is most important for drug efficacy, says Frank Bennett, senior vice president of research at Ionis. But ideally the drug will lower mHTT expression in both regions.

The companies did not report any serious adverse events in their 46-patient, 13-week study.

Trial tribulations

The big question for the pivotal trial will be to see whether reductions in mHTT, if achieved in this trial, will translate into functional, motor or cognitive benefits for patients.

Roche and Ionis's phase I/II trial of RG6042 was not designed to assess function, and on a groupwise basis the companies didn't see any differences between treated and placebo recipients in the small, short-term trial. But in a post-hoc analysis, presented at the American Academy of Neurology meeting in 2018, they showed that mHTT lowering seemed to correlate with directional improvements in motor, cognitive and functional scores. "That was encouraging to us," says Schobel.

Frank is also optimistic that the mHTT surrogate signal will translate into a functional benefit in a pivotal trial. "If there had only been a 20% reduction in mHTT, I think that there would have had to be a bigger phase II trial. But a 40–60% reduction in mHTT is not subtle. If there's that same signal in the larger trial, that's going to be impressive," he says. "I think they're doing it right."

The pivotal trial will use two functional primary end points — Total Functional Capacity (TFC) in the US and the composite Unified Huntington's Disease Rating Scale (cUHDRS) in Europe — to monitor for clinical benefit. TFC assesses daily functional ability, such as the capacity of a patient to work, handle finances, perform domestic and self-care tasks and live independently. The cUHDRS scale is a more sensitive, broader composite measure that tests movement scores and cognitive ability as well as daily functional ability.

Regulators might also be flexible if there isn't a clearcut success on these multicomponent end points, says Frank. "If there can be a change in a potential biomarker like mHTT and the preponderance of evidence shows that there is some other type of functional or symptomatic improvement as well, there's a much stronger case from a regulatory perspective," he says.

With industry shifting away from treating only the symptoms of HD and towards disease-modifying candidates, the research community has also been working hard to identify surrogate end points that can better track neurodegenerative disease progression. "We are changing how we're thinking about the disease and we're changing how we're thinking about treating the disease, and I think that in the future the end points that are being used in clinical programs will probably reflect that shift," says Ariana Mullin, executive director of the Huntington's Disease Regulatory Science Consortium (HD-RSC) at the Critical Path Institute.

Fourteen biotech and pharma groups, including Roche and Ionis, are collaborating through the HD-RSC to identify and validate new regulatory tools.

"It's going to be a really exciting few years as all of these different programs advance and we start changing the way that we address these challenges," says Mullin.

End points that are under academic and industry consideration include magnetic resonance imaging as a means of measuring for brain atrophy, positron emission tomography imaging to measure metabolic activity in the brain, translocator protein levels to assess microglial activation, smartphone-collected digital biomarkers to assess function, and more.

The future use of regulatory tools will also depend in part on which patient populations new drugs are tested in. The average age of onset of HD is 40 years, but with genetic testing it is possible to identify patients much earlier than that. However, it is hardest to measure changes in motor function and cognition in patients in the non-symptomatic or earliest stages of disease.

Roche and Ionis's first trial will test their drug for 2 years in 660 patients with "manifest HD", who have stage I or II disease. "Once they've proved that it does work in people who have onset of symptoms, then it would make sense to start looking at these interventions earlier and earlier in the disease," says Frank.

Even if the trials of HTT-lowering drug fail, it might make sense to test the drugs earlier in the course of disease. "Did we treat patients too late? That would be the next logical question to ask," says Ionis's Bennett.

But the practicalities and economics of such trials would be challenging in the absence of an efficacy signal, caution others. Alzheimer disease (AD) drug developers have been able to embrace this strategy, advancing drugs into asymptomatic and at-risk patients, but only because a huge commercial market and large patient population awaits any approved AD drug.

> "I don't want to get too excited, but it's hard not to"

There are more than 5.7 million AD patients in the US alone. But only around 30,000 patients have HD in the US, meaning there is a far smaller pool of patients for clinical trials and much less of a commercial opportunity.

"If there were limited resources then I think that it would make sense to try treating earlier and to watch people for longer periods of time," says Frank. But in the absence of these resources, the next best bet might be to extend exposure in pivotal trials for longer periods of time — say to 3 or 4 years, instead of 2 years. "That's more likely to happen versus going back and looking at a drug earlier in the course of the disease," he says.

HD drug developers may also ultimately need to combine HTT-lowering drugs with other agents that affect other aspects of HD pathophysiology. Aberrant immune activation is also thought to contribute to disease progression, for example, prompting efforts to develop immunomodulatory drugs as potentially complementary candidates. Vaccinex's VX15, for example, is a monoclonal antibody against semaphorin 4D, a transmembrane protein that modulates microglial activation, oligodendrocyte viability and the permeability of the blood–brain barrier. Top-line data from a phase II trial of the antibody are expected shortly.

"10 years from now we're going to look at Huntington's more like we look at HIV," hopes Frank. "We're going to have multiple drugs that have multiple mechanisms of action, some that work synergistically and some that work in parallel."

"Until we find something that will 'cure' this disease, we have to pursue all avenues," he adds.

Neurodegenerative opportunities

The pivotal trial of RG6042 may also provide encouragement for a small but growing pipeline of gene-silencing candidates aimed at other neurodegenerative indications.

The FDA's approval of Ionis and Biogen's nusinersen for the treatment of spinal muscular atrophy (SMA) in 2016 provided a first proof that oligonucleotide drugs can be used in CNS settings, showing that this modality can modulate gene splicing to boost the production of missing or malfunctioning proteins. RG6042 will now test whether oligonucleotide products can silence protein expression in the brain to stave off toxic byproducts and resulting neurodegeneration.

"I think there will be implications from our programme's results on other neurodegenerative diseases," says Schobel. The success of RG6042 and of the other HTT-lowering candidates may hinge, for example, on how the drugs disperse from the lumbar puncture to and through the brain. By providing insight into the biodistribution characteristics of different gene-silencing modalities in humans, trials of this drug can inform future discovery and development programmes for other neurodegenerative indications.

The pivotal trial of RG6042 could also help to revise how drug developers think broadly about the therapeutic opportunity in these diseases, adds Bennett. Preliminary evidence with nusinersen already shows that the exon-splicing drug might be able to do more than just delay the progression of SMA, and that it might also reverse disease pathology. "This suggests that if you tackle neurodegenerative diseases early enough, you might be able to see reversal of symptoms," says Bennett. A similar finding in HD would push the conceptualization of what's possible in neurodegenerative diseases further still, even if this would have to be explored on a disease-by-disease basis.

Beyond HD, the next place where this work will play out is in familial amyotrophic lateral sclerosis (ALS). Mutations in SOD1 and in C9orf72 account for around 20% and 40% of familial ALS cases, respectively, and so knockdown of these proteins has been proposed as a treatment strategy for these patients. Biogen and partner Ionis recently began planning a phase III trial of the *SOD1*-silencing antisense drug Ionis-SOD1RX (BIIB067). And the partners' *C9orf72*-silencing Ionis-C9Rx (BIIB078) is in phase I trials. Novartis, Voyager and others are independently developing virally-delivered RNAi drugs with similar intent.

Gene-silencing antisense products are also being explored in AD, even if the pathobiology of this neurodegeneration is still a matter of debate. Biogen and Ionis are in phase I/II trials with IONIS-MAPTRx (BIIB080), for example, to see if knockdown of tau in the brain can help these patients and patients with frontotemporal dementia.

And there are several other neurological CAG-type diseases that could also be amenable to gene-silencing strategies, adds Bennett, including Kennedy disease and type 1 spinocerebellar ataxia.

"Researchers of neurodegenerative diseases that involve abnormal proteins can and should learn from each other," concludes Frank.