Hunting for help in South America

With potential treatments for Huntington's disease on the horizon, long-moot questions of responsibility towards Latin American communities are being felt acutely. But will the people who contributed to landmark research ever reap its benefits? Dara Mohammadi investigates.

It's dusk in a housing project on the outskirts Barranquilla, an industrial city in the northeast of Colombia. As dogs and children give chase to footballs on the streets outside, Mariela Oviedo, who runs a volunteer patients association for people with Huntington's disease, is sitting with a group of family members in a stuffy front room too small for the 15 or so people assembled.

Oviedo has been on her feet for 14 hours so far today, delivering food and household supplies to the poorest families with the disease in the area. This is her last stop, a family who in the past year lost their mother to the hereditary disease after 20 years of illness and who still care for two of their siblings who also have it. Her arrival is warmly received. She has known this family for more than 3 years and the supplies she brings, along with emotional support and advice, are the only help they receive. Families with Huntington's disease in many parts of Colombia live with no formal social support and scant, if any, medical care .

With Oviedo is Ignacio Muñoz-Sanjuan, vice president of translational biology at the CHDI Foundation, a US not-for-profit research organisation looking for therapeutic strategies. 4 years ago Muñoz-Sanjuan founded Factor-H, a project to help poor families and communities across Latin America affected by the disorder. Huntington's disease, caused by a trinucleotide repeat expansion in one gene, *HTT*, is thought to have arrived on the continent with European settlers. Little movement of people between rural, isolated villages here has led to large, geographically well defined pockets of the disease, especially in Colombia and neighbouring Venezuela. With funds from fundraisers and small donations of about US$1000–5000 from companies that want to remain nameless, Muñoz-Sanjuan assists volunteers, such as Oviedo, to help families in need.

"The conditions that some of these people [with the disease] have to live in are awful", he says. Today, he and Oviedo have met families in which loved ones with the disease are left tied to chairs so that they do not hurt themselves (the disease often causes involuntary jerky body movements). In other families, people in the later stages of the disease, in which patients have a ferocious appetite consuming about 5000 calories per day, lie emaciated and starving in one-roomed shacks.

> **"...people in the later stages of the disease ... lie emaciated and starving in one-roomed shacks"**

A feeling of responsibility towards these people is felt acutely by the Huntington's disease research community. Between the late 1980s and early 1990s, affected families along the shore of Lake Maracaibo, Venezuela, provided blood and tissue samples to US researchers. Thanks to the high number of symptomatic patients and their detailed family histories, these samples led to the identification of autosomal dominant mutations in the huntingtin gene in 1993, a finding from which much of scientists' understanding of the disease has come.

Nancy Wexler, a scientist at Columbia University (New York, NY, USA) who led the gene discovery studies, set up a hospice in Maracaibo, Venezuela, to care for people with Huntington's disease. But with Venezuela's political situation as it is—the country's economy is near broken; little food is available, let alone drugs or medical services, and violent crime is rife—the hospice was forced to close 2 years ago.

For long, whether or not the biomedical community should help people with this disease—not just those in Venezuela, but all families across South America who share their circumstances—was a moot point. With no treatment available, how could the scientific community per se intervene in the many and complex social and economic factors that also keep people in poverty? However, things might change with advances in drug development. Therapeutics under development might be able to target the disease at a genetic level before the ubiquitous and neurotoxic huntingtin gene products are made. These treatments, says Muñoz-Sanjuan, will likely be expensive and need to be delivered in an advanced medical infrastructure currently absent in rural areas. "The conversations about getting help to these people needs to change from 'whether or not to do it' to 'how to get it done'", he says.

At the crest of the wave of potential new treatments, which include zinc finger proteins packaged into viruses, RNA interference compounds, and even gene-editing with new Crispr technology, is IONIS-HTT$_{Rx}$ (Ionis Pharmaceuticals, Carlsbad, CA, USA). This drug is an antisense oligonucleotide aimed at lowering the expression of the mutant huntingtin protein. A phase 1 clinical trial of IONIS-HTT$_{Rx}$ began in September, 2015; it is a multiple ascending dose study in 36 people in the UK, Canada, and Germany. Findings on safety, tolerability, and target engagement are expected to be available by the end of 2017.

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For more about the **CHDI Foundation** see http://chdifoundation.org/

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For more about the **Leonard Wolfson Experimental Neurology Centre at UCL** see https://www.ucl.ac.uk/lwenc

For more about the **ENROLL-HD platform** see https://www.enroll-hd.org/

Sarah Tabrizi, professor of Neurology and director of the University College London's (UCL) Huntington's Disease Centre at the Institute of Neurology (London, UK), is the lead clinical investigator for the trial, and acknowledges the pivotal role Latin American communities had in improving the understanding of Huntington's disease. "It would be great if we could get a drug that works to them as soon as possible but, for now, testing has to be restricted to places like this", she says, referring to the Leonard Wolfson Experimental Neurology Centre at UCL, where the UK participants are receiving the drug.

At UCL, crash teams are on hand if patients have an adverse reaction to the intrathecally administered experimental drug, and medical specialists have undergone training to ensure the best possible patient care is available. "If after future phase 2/3 efficacy trials IONIS-HTT_{Rx} shows a beneficial effect, then we definitely have to talk with Latin American Governments about how to get the drug to them", says Tabrizi.

If IONIS-HTT_{Rx} proves to be safe, then the Swiss pharmaceutical company Roche has the option to acquire the drug to do the efficacy studies needed for regulatory approval to market the drug. These trials, too, are likely to be done in countries with an advanced research infrastructure, but the testing of other drugs further back in the development pipeline might one day be able to be done in countries such as Colombia.

In 2012, the CHDI Foundation launched Enroll-HD, a global clinical research platform that recruits individuals with Huntington's disease who have yearly follow-ups done, and enters them into a worldwide register that helps researchers learn about the progression of the disease and allows fast patient recruitment to clinical studies. Enroll-HD combines two existing observational studies (REGISTRY in Europe and COHORT in North America and Australia) and is expanding into new sites in Latin America and Asia.

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In April, Cristina Sampaio, chief clinical officer of the CHDI Foundation, travelled to Colombia with colleagues to hold discussions about Enroll-HD's expansion into the country. Initial conversations with centres in Medellín and Bogotá were encouraging, Sampaio says, but she is cautious about over committing. "We don't want to misjudge our capacity and overpromise." Venezuela and parts of northern Colombia are not yet ready for inclusion in Enroll-HD", she adds. By starting slowly in experienced centres in the south and middle of the country, she says, the funds funnelled into the system through Enroll-HD could eventually be used to extend services to rural populations.

Bernhard Landwehrmeyer, a neurologist at the University of Ulm, Ulm, Germany, was co-principle investigator of REGISTRY and now advises the CHDI Foundation. He says that progress in rural areas of countries such as Colombia is necessarily slow but, because of the preparatory work done by Enroll-HD, patients will benefit before trials even begin. "Before we talk about the possibility of any wonder drug, the most important thing for patients and families is to have an experienced and caring neurologist who will spend time with them to help them manage and understand their disease", Landwehrmeyer says. "Be that with available drugs like antidepressants or just by explaining simple things to the family to help them better care for their relatives and live better lives. Things like understanding why relationships might be becoming strained or understanding that thickening up fluids helps to avoid dysphagia."

The problem in Colombia and elsewhere is that specialists for rare disorders are scarce. "As a clinician–scientist, it's risky putting your career into something for which there is not much funding", Landwhrmeyer adds. "By generating a constant stream of income [with Enroll-HD], you generate interest and then expertise. You need that expertise to have good clinical raters to do the best trials, and you need that expertise to improve the lives of patients."

Back in Barranquilla, Oviedo and Muñoz-Sanjuan wave goodbye to the family's matriarch who has walked them back to their car. Oviedo and Muñoz-Sanjuan hope that one day they can return and share the news of an available treatment before some of these people's children start to develop symptoms of the disease. If any of the new drugs prove effective and efforts such as Enroll-HD are successful in boosting care and capacity in the country, perhaps one day they will.

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