CUSTOMER STORY

Tackling Huntington's Disease from All Angles

Photo Courtesy of Vladimir Marcano, "El Mal"

One Scientist's Journey to Change the Status Quo

Even with the strides in research that scientists have made in the last few decades, the inner workings of the brain remain a mystery. Neurological diseases like Huntington's, Parkinson's, and Alzheimer's are just three out of many potentially devastating diagnoses clinicians have the difficult task of communicating to their patients due to the lack of permanent disease management recommendations or treatment options. Dr. Ignacio Muñoz-Sanjuan is looking to change the status quo for Huntington's disease (HD).

As Vice President of Translational Biology at CHDI Foundation, Muñoz-Sanjuan and his team are on a quest to develop new technologies for early diagnosis and better characterization of early stages of this disease and to discover new treatment therapies that could have a major clinical impact on HD.

"A key priority for us is the development of an oral drug that lowers mutant huntingtin (mHTT) protein systemically throughout the body," he says. "And that is a long-term goal for us although there has been some recent research that makes me optimistic."

Muñoz-Sanjuan joined CHDI Foundation, a private, non-profit research organization focused on HD, in 2007 and the organization has only grown since then. In addition to his work at CHDI, Muñoz-Sanjuan also co-founded Factor-h, a non-profit organization focused on helping HD patients in Latin America living in conditions of extreme vulnerability.

Before CHDI, Muñoz-Sanjuan worked at multiple pharmaceutical companies in the neurological disease space after getting his doctoral degree from Johns Hopkins University and doing a postdoc at Rockefeller University.

After establishing his career in academia and industry, Muñoz-Sanjuan was curious to try working for an organization that set itself apart from the traditional corporate route with a completely different business model. CHDI only focuses on HD, which is quite uncommon, and acts as a hub for industry, academia, and contract research organizations who are all working on HD research. CHDI funds and conducts research that larger companies may be hesitant to invest in because of the high business risk associated with an unknown outcome and in a disease that is considered rare.

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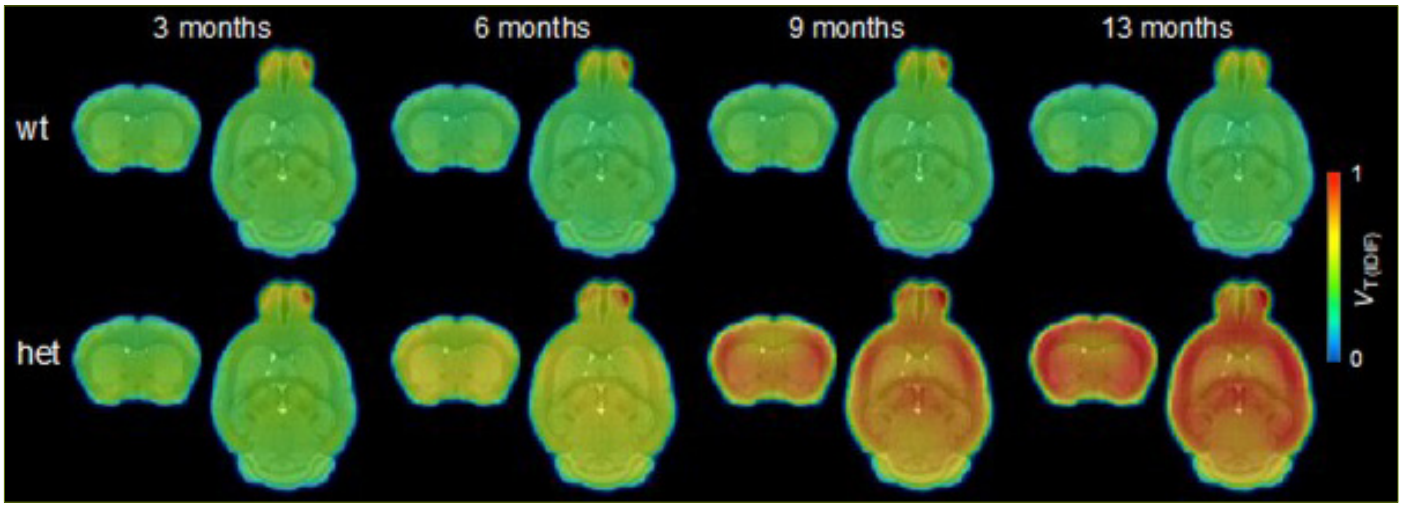

Figure 1: Mean [^{11}C]CHDI-180R V_T parametric images taken at stated intervals and co-registered with MRI templates from zQ175DN wt and het mice (an HD animal model) to assess longitudinal disease characterization of mutant huntingtin using novel imaging ligands. Figure taken from Figure 2.b; additional details can be found in the Materials and Methods section and figure legend of https://www.biorxiv.org/content/10.1101/2021.07.09.451725v1.full (article is pre-print, submitted for peer review)

Understanding HD: the earlier, the better

The Human Genome Project, completed in 2003, allowed researchers to pinpoint genes that cause or play a role in many diseases, including neurological disease, but the underlying cause and mechanism for many diseases is still unknown.

HD is difficult to treat because once a patient shows symptoms, the disease has already progressed substantially and treating the underlying cause, even if doctors could, is difficult at such a late stage. That's why Muñoz-Sanjuan's research is also focused on identifying and developing novel technologies that can detect early HD biomarkers that would be able to indicate if a patient is at the early onset of disease progression. Like most diseases, if detected earlier, the chances for better treatment and longer survival are higher.

Another large facet of his team's work is developing methods that can give clinicians an understanding of the biological effect a treatment is having (or not having) on a patient and their disease progression. The development of translational and disease progression biomarkers is a key goal for the organization.

"In support of the huntingtin lowering therapies, we need to understand how to measure the impact of lowering mHTT in a translational manner to help companies interpret results from the clinical trials and that involves measuring the huntingtin (HTT) protein itself," he says. "We have an active program where we developed novel PET imaging tracers for mHTT and that's being tested clinically right now."

"This is a program that we started in 2010 and have developed internally as CHDI, in collaboration with tthe contract research organization, Evotec," he explains. "The application of that tracer, if it works in humans as well, would be to show if and where the drugs are affecting mHTT expression in the brain."

Muñoz-Sanjuan's team has also been developing HTT protein quantification assays. By tracking HTT protein abundance along with other biological markers, doctors can monitor molecular disease progression in tandem with clinical progression. These data could help doctors predict disease progression prior to the emergence of physical symptoms and potentially lead to earlier treatment plans for patients based on biological markers.

In addition, those assays are being used in clinical trials for treatments that target mHTT expression to track pharmacological effects in the brain.

Muñoz-Sanjuan has been working on these research projects at CHDI since he joined over a decade ago. These large-scale projects take time and speeding it up at any part of the process is vital.

"It's been instrumental for us to be able to run high-throughput screens to identify small molecules that affect HTT expression during drug discovery campaigns," he says. "We've screened over a million compounds using PerkinElmer instruments and these assays have enabled other companies to pursue similar approaches. Another big aspect of our research that we use PerkinElmer instruments for is developing phenotypic readouts in both small- and large-scale projects using relevant human cell systems."

The whole patient

By being part of the HD community as a scientist for many years, Muñoz-Sanjuan has had first-hand experience with patients and their families. He has witnessed their struggles living with an incurable and inherited disease; over the years, he inevitably developed a personal connection to many patients and the overall community. While traveling and giving seminars about his work in Latin America, Muñoz-Sanjuan met many HD patients and relatives who were excited to understand more about their disease and talk to someone who understood what they were going through.

Those patient connections are part of what led Muñoz-Sanjuan to start his non-profit organization, aimed at helping HD patients in towns in Venezuela, Colombia, and Peru—places that not only have the highest incidences of HD in the world, but where people are also living in extremely vulnerable conditions.

Establishing a separate, rights-based humanitarian foundation was important to Muñoz-Sanjuan, who felt there was more that researchers like himself could do today for these families living in regions with a high prevalence of HD. He felt compelled to act on this urge and knew that there were like-minded people who wanted to do more with him.

"I spent time in Colombia, Venezuela, and Brazil between 2012 and 2013 seeing families, and I just couldn't forget what I saw," he says. "I felt I had a moral responsibility to not ignore what I had seen. And I decided, even if it was just on my own, that I would do something to raise awareness and help them. And that idea kind of grew over time into the organization that I started."

Many of these families with prevalent HD have little to no medical or social support; in fact, there is one area of Venezuela that is believed to have the highest percentage of people diagnosed with HD with 700 in 100,000 people affected.

"I also connected very well with the people that were in those communities," he says. "And I felt that if somebody could do something, maybe I was that somebody who had enough connections in the HD community and enough visibility, to raise awareness to this problem. And on a personal level, I just felt like I couldn't ignore what I had seen and not do anything about it."

Dr. Muñoz-Sanjuán in Venezuela with a child sponsored under Factor-h's Kids program

He remembers, early on in his Factor-h journey during his first visit to Colombia, a time when a man who had traveled hours to attend one of his talks stayed after to enthusiastically thank him for coming and shedding light on his and others' situation. The next year when Muñoz-Sanjuan visited the same area, he spent the day driving around to visit and deliver gifts to people he had connected with during his past trip. He didn't make it to that man's village until late in the evening, and he was stunned to see the man waiting for him out in the streets when he arrived.

"As soon as I got out of the car, he says 'I've been waiting for you all day, I knew you would come back to see me.' And I still get emotional about it because this man, whom I met only once, somehow sensed that I was not going to abandon them, that I would come back," he says.

"We sat outside his house, on the porch with his family, and we just talked for an hour, and he just kept saying, 'I knew you would come back.' These are the little things that matter. Each one of us has the ability to change people's lives in very significant ways, just by being present and caring for people," Muñoz-Sanjuan says.

"There's nothing unique about what I do here," he says. "It's just a matter of saying, I'm going to spend a little bit of my time with you today. And that's good enough sometimes."

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