Interview: CHDI Management

HDBuzz interviews three top scientists from CHDI, the biggest funder and driver of HD research worldwide

By Dr Jeff Carroll | **February 25, 2011** | **Edited by Dr Ed Wild**

CHDI Foundation, Inc. is a unique drug discovery organization focused exclusively on rapidly developing therapies that slow the progression of HD. It is the biggest funder and organizer of HD research worldwide, but many people affected by HD have never heard of it. During CHDI's Annual Therapeutics Conference in Palm Springs, HDBuzz spoke exclusively to three of its scientific leaders.

Why interview CHDI?

Over the last six years, CHDI has become the major supporter of HD research globally, significantly outstripping governments and commercial contributors alike, and not just funding research but driving it.

CHDI's top scientists: (left to right) Chief Scientific Officer Robert Pacifici, Vice President (Chemistry) Celia Dominguez and Vice President (Biology) Ignacio Muñoz-Sanjuan

Image credit: Gene Veritas

CHDI's annual HD Therapeutics Conference brings together the world's top HD scientists, from both academic labs and the biotechnology and pharmaceutical industry.

In Palm Springs to bring you breaking HDBuzz updates from the conference, Jeff Carroll and Ed Wild sat down to talk to three key CHDI scientists - Drs Robert Pacifici, Celia Dominguez and Ignacio Muñoz-Sanjuan.

Who are these guys?

Robert Pacifici is the Chief Scientific Officer of CHDI: he sets the scientific goals of the entire organization. Celia Dominguez is Vice President in charge of chemistry: it's her job to oversee the actual making of molecules to serve as possible drugs for HD. Ignacio Muñoz-Sanjuan, Vice President in charge of biology, guides what things CHDI should be designing drugs to do in the first place and oversees the biology component of drug discovery programs.

In short, these three scientists are at the cutting edge of the biggest unified effort to develop treatments for HD. We quizzed them to bring you a glimpse of the personalities behind the facade, as well as how the unique ethos and structure of CHDI is driving research forward.

We started by asking how they each became interested in science. Muñoz-Sanjuan explained that he was inspired growing up in Spain by a father who was a medical doctor. "I realized very early on that I wanted to be a scientist" - a goal that was reinforced by the early death of his mother from cancer. Driven to try and understand the problems that contributed to disease, he moved to America to receive his academic training, before being attracted to the world of drug discovery.

The passion that Dominguez has for making drugs is irrepressible. "I love to solve puzzles," she says, "by helping make drugs that work as they're intended". The work of Dominguez and her team is very practical - the others jokingly call her an "electron pusher" for her daily grind of rearranging and honing the chemical structures of molecules. Ultimately, though, it's the chemists who design and make drugs that will provide therapies for HD. Describing her work as much more than just a job, Dominguez says that she "always wanted to be a drug hunter".

Pacifici, the scientific head of the organization, shares this passion for drug discovery but carries a personal insight into the bleak future faced daily by those living with the risk of HD. "I also suffer from a rare genetic disease, which is something that my dad had, and ultimately succumbed to when he was 47". In 1972, the keen observations of a single physician led to the development of a simple, effective therapy that turned the disease that had been ravaging Pacifici's family into a manageable condition. "I went from being a pretty sick kid to taking this little pill, and became cured, basically." This demonstration of the power of scientific knowledge motivated Pacifici to work at developing drugs to fight other diseases.

What is CHDI, and how is it different?

> "Our bottom line is time, not money"

HD families hear about all sorts of drug discovery efforts. How is CHDI different from a regular lab, company, or charity? Pacifici explained to us that there are four features of CHDI that make it unique.

First, CHDI is a not-for-profit foundation. Despite the large sum of money it spends on developing drugs for HD, CHDI's scientists are not driven by making money.

Many companies, even with the best intentions to help patients, have to be focused on what the CHDI scientists call “competitive intelligence”. That means a company working on a drug for, say, Parkinson’s disease has to be constantly aware of what the competition are working on, to make sure they’re not “scooped”.

At CHDI, says Dominguez, instead they value “collaborative intelligence”, as the Foundation tries to connect different researchers together to advance the frontiers of HD research. This is because, as Pacifici points out, “our bottom line is time, not money”. Like HD families, CHDI is motivated only to develop treatments for HD - and the sooner, the better. “For CHDI,” explains Pacifici, “there’s no reason why we wouldn’t want someone else to find the cure. Whoever finds the cure for Huntington’s, we all win”.

Second, CHDI is exclusively focused on HD. It’s all they do. Most drug companies have to place multiple bets, because drug discovery is a very tricky business, in which most efforts fail. Companies have to be guided by commercial interests in deciding which diseases to work on with their limited resources. But CHDI isn’t like that, because they only work on HD, meaning they never have to question whether they’re working on the right thing. It also lets them take the long view, supporting some projects that might take years to bear fruit, without fear of being undermined or embarrassed if another project produces results first.

Next, CHDI is unique because it is privately funded (by donors who wish to remain anonymous). Unlike many charitable organizations, CHDI doesn’t have to spend resources - time or money - on fundraising to maintain its operations. Even most biotechnology companies expend significant efforts raising money for their operations, whether from the stock market or from venture capitalists. CHDI has no need to do that, so it can spend all its time and energy trying to develop treatments for HD.

Finally, CHDI has a very interesting structure. Rather than building its own physical labs, CHDI decided early on to use alliances with and fund existing academic, government, and industrial researchers to get its research done. CHDI also finances what are known as contract research organizations - essentially labs for hire - to carry out research that CHDI directs.

This approach results in great flexibility - CHDI doesn’t need to spend resources building specialized facilities or spend years getting up to speed with new technologies. Instead, it identifies the best teams already working on each target, area or technology and finances them to get the work done. This “virtual” structure lets the Foundation very rapidly get into and out of fields as they need.

We wondered whether not having its own research space had turned out to be limiting. Pacifici explained that the policy has always been that if there was something CHDI wanted to do but couldn’t, it would build a lab. That hasn’t happened yet, and doesn’t look likely to.

Robert Pacifici: The biggest thing HD-affected people can do to help the search for treatments is "enroll in every single trial they're eligible for".

Image credit: Lev Blumenstein

CHDI and the unique challenges of HD

So CHDI has a unique structure. How does it fit into the HD community? Dominguez and Muñoz-Sanjuan agree that the close connection between HD families, researchers and clinicians is a truly unique, and essential, part of the HD research effort. As Pacifici says, this means "we never forget why we're doing this". It's clear that the effects of HD on families have sunk in to these scientists. Pacifici suggested that "if you started out with a blank piece of paper and tried to design a disease that was most horrible … you'd be hard pressed to do better than HD". Despite this terrible situation HD families find themselves in, Pacifici feels there's a scientific upside to HD, too: "That's the bad news. The good news is that there's this sense that this is a very difficult but solvable problem, so it attracts really smart people … we're going to make it happen."

CHDI's 'discovery pipeline'

The Therapeutics Conference often heard mention of 'pipelines', a concept drug companies talk about a lot. A pipeline is just the list of drugs that a company is working on at a given time, organized by the fact that some of the programs will be more advanced (closer to human trials) than others. Drug-hunters use the word 'target' to mean a gene or protein whose activity is important in HD, so it's a 'target' for drug development.

Why have a pipeline - why not just pour all your resources into the most promising drug? "Unfortunately," says Pacifici, "the drug discovery process is incredibly inefficient. You never want to end up in the situation where you're a one trick pony".

Having multiple projects targeting different aspects of HD gives a greater chance of success in having an impact on the disease. Also, Pacifici points out, "you want to be diverse across time. It may be that in 20 years you could have a 'cure', but what do you do for people now? We need something that we can deliver in the shorter term".

So, CHDI is working on a 'pipeline' of projects that are at various stages of development. Wondering just how big this endeavour is, we asked how CHDI's efforts on HD compare with those of commercial drug companies' operations trying to cure other diseases. "We spend more on HD

than a large pharmaceutical company spends on neuroscience," says Pacifici. That's all the more remarkable given how rare HD is, compared with diseases like Alzheimer's that have much larger potential markets. To give an idea of scale, CHDI is likely focusing more resources on HD than all other organizations combined.

But how does this break down? How many different programs can this small organization advance at one time? According to Pacifici, Dominguez and Muñoz-Sanjuan, CHDI has about ten drug development programs happening in parallel at any one time - each program typically examining dozens of potential ways of hitting a particular target.

Are these always the same programs, we wondered? No, says Pacifici, programs have to be ruthlessly prioritized according to the latest findings. "One of the really important differences between a traditional scientific researcher and a drug hunter is the mentality of trying not to perpetuate something, but to kill it." Or, as Dominguez puts it, "my goal is to kill it. If it survives, it's worthy". Pacifici reckons more than half the targets that have been in CHDI's pipeline have been "killed" on that basis.

> "This is a very difficult but solvable problem, so it attracts really smart people… we're going to make it happen"

That may sound brutal, but it means that CHDI is not interested in following up on a drug just for the sake of prestige, or because they first discovered it, or because they might be able to make money from it to treat something else, like Parkinson's disease or obesity. At the end of the day, they only want to put drugs into people that work for HD. By trying their hardest to prove that a particular drug they've developed doesn't work, the ones that survive have really been put through the wringer.

The importance of clinical research

Turning our attention from basic research to the idea of testing drugs in people, we asked CHDI about human research. Inspired by a question from HDBuzz reader Michaela in Germany, we asked "what can patients and young people at risk of HD do to help the efforts of CHDI in looking for treatments?". Pacifici answered that people can "enroll in every single trial they're eligible for". Expanding on this, he said that "there is nothing more precious to a drug hunter than an observation that's made in the patients we want to treat".

"Does it really matter if one person is or isn't involved in a study or trial?" we asked. Immediately, Muñoz-Sanjuan and Dominguez emphatically replied "Yes!". Pacifici went on to explain that all treatment trials have what are known as inclusion and exclusion criteria. These are rules such as 'people with high blood pressure can't participate in this trial' or 'this trial is for people with a CAG repeat between 42 and 50'. These criteria are essential for a trial to run efficiently, but they limit the potential pool of recruits for each trial. Having the largest possible range of patient volunteers means that future clinical trials, whether from CHDI or anyone else, will be recruited and run with the maximum speed. And we'll have effective therapies for HD sooner.

Closing thoughts

CHDI's work is hugely exciting for HD families. It's hired some of the best people working in drug discovery and got them focused exclusively on HD, leveraging a vast network of top collaborators around the world.

Equally importantly, there's a fire that burns in the eyes of scientists who've met HD family members and become hooked on the tantalizing notion that effective treatments to reduce the suffering wrought by HD are within reach - and that working towards them is a worthwhile and fulfilling way to devote their time and expertise. We saw that fire in the eyes of these CHDI scientists, and we're hopeful that some of the programs they've talked about at this meeting could rapidly progress to being therapies for HD families.

Dr Carroll and Dr Wild have conducted scientific HD research sponsored by CHDI but have received no honoraria outside that scientific funding. Their attendance at the CHDI conference is supported by the European HD Network, an independent network of HD professionals, from funds entirely independent of CHDI. For more information about our disclosure policy see our FAQ...

GLOSSARY

Parkinson's Disease A neurodegenerative disease that, like HD, involves motor coordination problems

therapeutics treatments

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD