



News from the Hereditary Disease Foundation

We hope that you and your family are safe and well as we enter the final moments of 2020. Certainly, it is a time of challenge, but we are also excited by the promise of Huntington's disease research and what lies ahead as we look toward 2021.

That promise is wonderfully illustrated by the brilliant work of Dr. Ai Yamamoto, who is the recipient of the 2020 Leslie Gehry Brenner Prize for Innovation in Science. The award, which was established by the family of the renowned architect and HDF Founding Trustee Frank Gehry in memory of his daughter, was presented virtually at our [Gala & Symposium](#) in November.



Dr. Ai Yamamoto, Associate Professor of Neurology and of Pathology and Cell Biology at Columbia University
2020 Recipient of the Leslie Gehry Brenner Prize for Innovation in Science

Pushing Boundaries

Dr. Ai Yamamoto made a stunning entrance into the field of Huntington's disease research while she was still a graduate student in the laboratory of her mentor, Rene Hen. She demonstrated that Huntington's disease might be reversible – something no one had shown up to that point. She made this dramatic discovery by taking a mouse containing the first critical “coding” sequence of DNA in the abnormal HD gene and inserted a little switch in front of it. She found that flipping the switch from “on” to “off” was enough to reverse the symptoms of the disease. The mice began to move around as if they were no longer sick—as if the cells of their brains no longer contained abnormal clumps, one of the hallmarks of Huntington's disease. In other words, if you took out the “garbage,” the mouse began to heal.

But where did those clumps go? To what extent did these spectacular results depend upon “disappearing” the clumps? To answer these questions, Ai next focused on what is called autophagy—the recycling system of the cell that eats up garbage and trash and maintains the cell's machinery in tip-top shape. Autophagy plays a crucial role in all cells and is powerful enough to break down the clumps. If the power of this autophagy pathway could be harnessed to go after the clumps, maybe you could prevent them from wreaking havoc inside the cell. Ai reasoned that one way to compel autophagy to eat the clumps might be to make them more appetizing than everything else in the cell.

Ai's search for that mysterious something that could make the clumps tastier led her and her team to a fascinating protein called Alfy. A certain unusual form of Alfy seemed to mark the clumps and make them go away. Then came even more dramatic findings: Alfy had something to do with the age at which HD symptoms started to emerge, what clinicians call age of onset. And that variant Alfy, which seemed to increase the amount of Alfy in the cells, appeared to have a startlingly beneficial effect in staving off the symptoms of Huntington's. In fact, people with the abnormal Huntington's gene who also had this variation of Alfy started to show symptoms many years later—sometimes as many as 23 years later— than their relatives who had the normal form of Alfy.

More recently, Ai has confirmed that in the brains of adult mice, Alfy indeed guides autophagy to eat up the clumps. In mice lacking Alfy, those clumps persist and make HD symptoms much worse. Ai and her team are still testing the theory that the variant Alfy raises Alfy levels in cells. And they are doing experiments to increase the amount of normal Alfy in the brains of their mice to see if higher Alfy levels can delay symptoms. If their efforts prove successful, Alfy may serve as a basis for a radically new treatment for human Huntington's disease—and perhaps for other brain diseases, an exciting prospect for the future!

A Story of Prevailing Hope



In 2017, Nancy Wexler, President of the Hereditary Disease Foundation, participated in the historic meeting of Pope Francis with Huntington's disease families. This special audience with the Pope helped bring international attention to the tremendous suffering of people affected by HD throughout the world, and particularly in South America. Now, during this holiday season, comes an uplifting, heartwarming documentary charting the journey made by some incredibly brave HD families from South America to the Vatican for the meeting. Watch "Dancing at the Vatican" here for free:

<https://www.dancingatthevatican.com/>. To help raise awareness of Huntington's disease, please share this link with two people who have not heard of HD.

Holiday Wishes

Thank you to our friends, supporters and the researchers who are changing the face of Huntington's disease. We wish everyone all the best during this Holiday Season and in the New Year!

Innovating Research...Discovering Cures

[Donate Today](#)

Contact Us:

[Web](#)

[Twitter](#)

[Facebook](#)

Published December 2020