

Living with the Threat of Huntington's Disease

A personal report by NBC News correspondent Charles Sabine



A terminal diagnosis can be devastating and even more so when it promises to afflict future generations.

In 1994, Charles Sabine, a distinguished NBC News correspondent, was faced with just that reality when his father was diagnosed with Huntington's disease (HD). In a special *Science for Life* lecture in May, he shared the fear that struck him and his brother when they learned they were at risk of developing this devastating disorder.

“All humans are capable of far more than they believe.”

—Charles Sabine

Gladstone investigators, Paul Muchowski (left) and Steven Finkbeiner (right), flank *Science for Life* guest lecturer Charles Sabine.

HD is a neurodegenerative disease that results in uncontrolled movements, loss of intellectual faculties, emotional disturbance, and certain death. It is an autosomal dominant disease. That means that the child of an HD patient has a 50% chance of inheriting the mutant gene that causes the disease. A person who inherits the HD gene will sooner or later develop the disease. There are no effective treatments.

Mr. Sabine is no stranger to death and tragedy. In his presentation, he drew on his own experiences to provide a refreshing and inspiring perspective on life. From his own life-threatening experiences in battle zones and reporting on the unspeakable horrors people inflict on each other, he learned many lessons. Life is not always fair. And when we focus on our own discomforts, we can easily forget the struggles of others that, indeed, made them stronger. He spoke of the selflessness of the single nurse that stayed with the remaining mental patients in Iraq after their institution had been looted and the inmates ferociously abused. He showed a young Kurdish woman who carried her younger sister

90 miles over mountains—herself without any shoes. He also spoke of the unselfish care that his mother provided to his father throughout his illness.

Finally, with his brother now experiencing the ravages of HD, Mr. Sabine noted that he is constantly evaluating his own behavior and coordination as he waits for the symptoms to begin. Still hopeful, he spoke of the neuroscientists at Gladstone and elsewhere who are working tirelessly to stop HD and many other diseases.

Two of those investigators, Steven Finkbeiner and Paul Muchowski, reported on the progress in their work to understand the origins of HD and to identify possible treatments toward a cure.

“As a practicing physician, my firsthand experience with the suffering of Huntington's patients and their families has given me a great sense of urgency for my research,” said Dr. Finkbeiner. “I am grateful to Mr. Sabine for his insights and for his ability to put this devastating disease into a larger context.”

Huntington's Disease Research at Gladstone

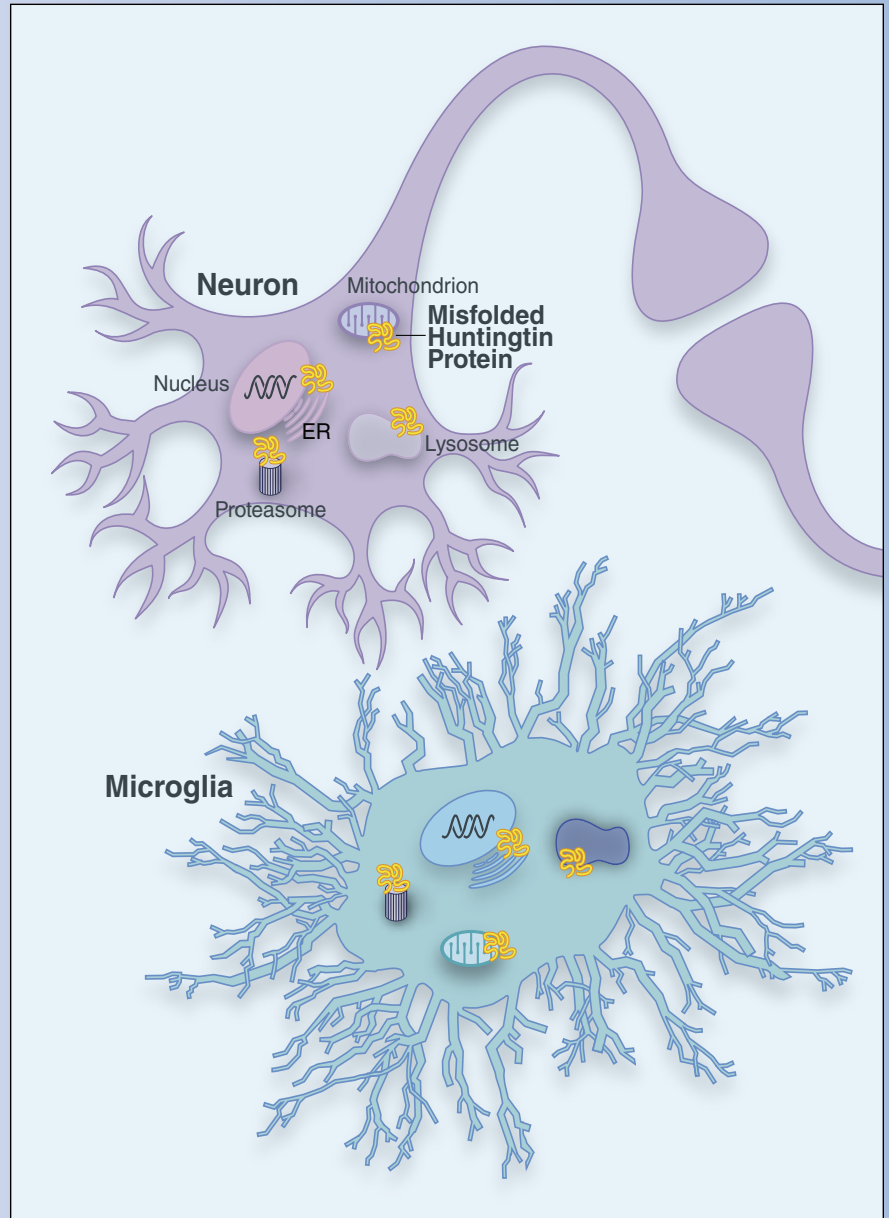
Huntington's disease (HD) is a fatal neurodegenerative disorder characterized by abnormal motor movements, personality changes, and dementia. The disease is caused by a mutant form of a ubiquitously expressed gene. The gene encodes the protein huntingtin (htt), and the mutant form contains a long stretch of glutamines.

Although the gene causing HD is well known, the mechanism of cell death is not. As part of the presentation on HD by Charles Sabine, Gladstone investigators Steven Finkbeiner and Paul Muchowski gave overviews of their research into this puzzling disease.

Dr. Finkbeiner has developed powerful new tools to use in his research. A cell-culture model of diseased neurons developed in his laboratory faithfully recapitulates many of the key features of HD. He devised an automated microscope that enables researchers to obtain images of the same neurons in a culture dish at any desired interval. With these tools, he showed conclusively that so-called inclusion bodies, long thought to be pathological in HD, are actually a protective measure that benefits the neural cells. A monoclonal antibody that he created seems to bind exclusively to a toxic conformation of the mutant htt. Using his automated microscope, Dr. Finkbeiner showed that the binding of this antibody is a very accurate predictor of cell death. He is also examining cell processes (e.g., autophagy and the proteasome) that normally remove defective proteins, such as mutant htt, from neurons.

Dr. Muchowski has developed powerful genetic screens in yeast to identify modifiers of HD. He hypothesized that a degradation pathway for tryptophan called the kynurenine pathway (KP) might be involved in HD. Using his genetic assays, he identified all of the genes that were turned on or off in response to mutant htt. Mutant htt inhibited genes that were ordinarily regulated by an enzyme that deacetylates histone proteins, a common modification in gene regulation. Finally, his team showed that the use of a specific deacetylase inhibitor completely blocked the increases in levels of the KP metabolites in microglia. These findings further implicate the KP pathway in the pathogenesis of HD and provide possible new therapeutic targets for investigation. Histone deacetylase inhibitors are currently in clinical trials in HD patients, so the research at Gladstone is helping to elucidate at least one of the pathways through which they mediate neuroprotection (i.e., by inhibiting the deacetylase, you repress transcription of the KP).

Htt is unlike the gene products that cause many other diseases. It has no known enzymatic or other property that would make it an easy tar-



Shown are intracellular targets in neurons and microglia for the misfolded mutant huntingtin protein that may be involved in HD pathogenesis. Gladstone researchers have helped to elucidate how mutant huntingtin impairs the function of these cellular targets and have shown that mutant huntingtin can have toxic effects in neurons and in other cell types, such as microglia, the immune cells of the brain. The long-term goal of Gladstone researchers is to identify therapies that restore the normal function of the neurons and microglia. ER, endoplasmic reticulum.

get for therapies. The Gladstone investigators have used a comprehensive approach to study HD, attacking its roots from multiple angles. Drs. Finkbeiner and Muchowski have shown that mutant htt may contribute to neurodegeneration directly by affecting neurons as well as indirectly by affecting microglia, and they are developing treatments to block its disease-causing activities in both cell types.