



ED GRABCZYK, PhD

Associate Professor of Genetics
LSU Health Sciences Center in New Orleans

A POSSIBLE ANSWER TO **AN IMPOSSIBLE DISEASE**

FOCUS: Developing drugs to prevent or delay the onset and progression of Huntington's disease and other DNA repeat expansion disorders.

When possible symptoms of Huntington's disease (HD) appear, a blood test can tell whether a person has inherited the mutant gene. But the prognosis of the disease is so dire that many prefer not to know at all.

HD is a fatal disease that causes certain nerve cells in the brain to waste away. Symptoms usually don't appear until middle age, and may include uncontrolled movements, clumsiness, and balance problems.

HD is caused by a DNA repeat expansion, wherein a segment of repetitive DNA expands within the huntingtin gene, causing disease. HD is one of dozens of progressive neurological diseases caused by DNA repeat expansions.

Nearly a decade ago, Dr. Grabczyk found that one form of a minor DNA mismatch repair protein called MLH3 is responsible for DNA repeat expansion. His discovery was met with skepticism—"For a while, a colleague of mine and I were the only two people who believed it!" Dr. Grabczyk says.

"With help from the Harrington Discovery Institute we aim to inactivate this minor form of the MLH3 protein with splice-switching drugs so that it no longer causes DNA repeats to expand, while perturbing the mismatch repair system as little as possible."

Dr. Grabczyk is hopeful that slowing expansion of the disease-causing DNA repeat will slow or stop the progression of HD, helping patients live longer, more fulfilling lives.

"The Harrington Discovery Institute is amazing, exactly what the world needs."

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