

Exciting developments in Huntington's disease research

By *Monica Frazier*

The NIEHS Keystone Science Lecture Seminar Series continued June 27 with a lecture by [Cynthia McMurray, Ph.D.](#), offering hope that new findings could eventually lead to novel interventions for treating neurodegenerative diseases and a deeper understanding of the role of environmental exposures in the initiation and progression of these diseases.

McMurray, a senior staff scientist at Lawrence Berkeley National Laboratory (LBNL), spoke to a capacity audience on "Genetics and Metabolic Dysfunction in Huntington's Disease."

Funded by NIEHS, McMurray's group conducts research to identify metabolic markers for mitochondrial dysfunction, working toward a detailed understanding of mitochondria-related diseases and new methods of early detection for triplet expansion disorders such as Huntington's. Their results and new technologies (see [text box](#)) have the potential to drastically change disease detection and therapy.

Linked Audio

[Listen to an interview with authors of the January 2011 Analytical Chemistry feature story on NIMS \(06:54\).](#)

When normal DNA repair goes wrong

Huntington's disease (HD), a trinucleotide repeat disorder, results in the progressive neurodegeneration of the brain and death. The disease progression and age of onset are associated with the number of times DNA repair enzymes allow for repeats of the glutamine codon, cytosine-adenine-guanine (CAG).

"One of the most fascinating things about this disease is that DNA repair, which is normally meant to correct our genome, is actually the cause of the mutation," McMurray said.

The disease begins with an inherited predisposition, but is also dependent on somatic expansion that occurs with age. McMurray's research group proposed a mechanism for this expansion, which she calls the toxic oxidation cycle, and, for the first time, linked oxidative damage to the mutation that causes HD.

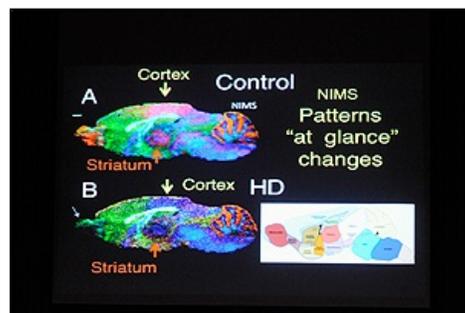
A promising implication of McMurray's discovery is the possibility that specific DNA repair enzymes could be targeted to inhibit somatic mutations in the HD gene. The group has already shown that deletion of the gene coding for a key enzyme in the expansion mechanism suppressed the mutation and delayed disease progression in mice, meaning it is possible that, in the future, HD may no longer be a terminal condition.

Widening the therapeutic window

One major goal of researchers has been to develop a therapy to suppress and remove mitochondria-generated oxidative damage in triplet-repeat disorders. A common effort has been to utilize naturally occurring antioxidants, which, as McMurray explained, have been complete clinical failures due to their non-specificity, inability to reach the mitochondria, and poor pharmacokinetics.



McMurray detailed her group's work during her lecture. (Photo courtesy of Steve McCaw)



The NIMS technology (see [text box](#)) utilized by McMurray's research group allows researchers to visualize regional differences in tissue metabolites. (Photo courtesy of Steve McCaw)



NIEHS Mitochondrial DNA Replication Group biologist Maggie Humble listened, as attendees asked questions after McMurray's lecture. (Photo courtesy of Steve McCaw)

McMurray and collaborators have recently developed a set of hybrid synthetic antioxidants that are made up of a mitochondrial-targeting moiety and an antioxidant in one molecule. These compounds, whose parent molecule is called XJB, are the first to show recovery of mitochondrial copy number, as well as an increase in the stress response of the mitochondria.

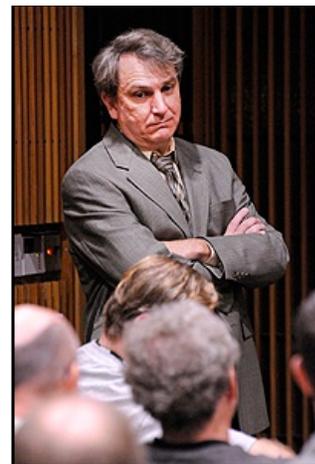
McMurray anticipates the XJB class of compounds will move further into clinical trial, and feels they are promising therapeutics to delay the symptoms of neurodegeneration seen in Huntington's disease, even after disease progression has begun.

Environmental connections

Interestingly, Huntington's disease, a genetic disorder, is very similar in pathology to exposure-related effects of the natural herbal toxin 3-nitropropionic acid (3-NP). The mutant protein involved in HD and 3-NP both induce mitochondrial toxicity, and McMurray and colleagues have found their mechanisms and cellular pathology to be very similar.

Thus, McMurray's research to expand the potential therapeutics for HD and similar genetic conditions may also be applicable to exposures to environmental toxins such as 3-NP.

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)



NIEHS health scientist administrator Dan Shaughnessy, Ph.D., introduced McMurray and moderated the discussion after the lecture. (Photo courtesy of Steve McCaw)

The new anatomy

In their investigation of mitochondrial dysfunction and region-specific brain toxicity in Huntington's disease, McMurray and her colleagues at LBNL found current technology inadequate. Their observation led to the utilization of the breakthrough new technology [Nanostructure-Initiator Mass Spectrometry \(NIMS\)](http://masspec.scripps.edu/publications/public_pdf/172_greving_2011.pdf). (http://masspec.scripps.edu/publications/public_pdf/172_greving_2011.pdf)

NIMS technology enables the profiling of metabolites in specific regions of tissues, for example in brain sections, with very high resolution, opening the door for a new understanding of the cell-specific targets for exposure and disease.

The ability to look at metabolites in single cell types, through NIMS technology, has far-reaching potential for basic research and biomarker development, and may pave the path toward a better understanding of why cell type-specific toxicity occurs, as well as reveal new therapeutic possibilities.

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