Oxidative stress in Huntington disease, protection by the MTH1 hydrolase
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In the present project, we propose to investigate a possibly new mechanism of protection against HD based on the over-expression of the oxidized purine nucleoside triphosphatase hMTH1. This enzyme hydrolyzes purine nucleoside triphosphates to monophosphates, thus protecting cells from damage caused by their incorporation into DNA or RNA (Mo *et al.,* 1992).
We propose to investigate the molecular basis for our preliminary findings that expression of an hMTH1 transgene protects mice against 3-nitropropionic acid (3-NP) -induced striatal neurodegeneration in a mouse model for HD. Since the most firmly established role for hMTH1 is protection of DNA and RNA against incorporation of oxidized precursors, we will focus attention on this. Furthermore, since hMTH1 is known to exist in both nuclear and mitochondrial forms, and mitochondrial dysfunction and oxidative damage may play a role in the pathogenesis of HD, we will consider oxidative damage to the mitochondrial as well as to the nuclear genome.
We plan to test the hypothesis that high levels of hMTH1 expression may attenuate or slow-down the neuropathological process triggered by the HD mutation. By extension, based on current ideas about the role of hMTH1 in protecting DNA we will investigate whether the reduction in the steady state levels of oxidative DNA damage provided by hMTH1 can attenuate the CAG expansion responsible for the disease. In order to examine this hypothesis, we will use a transgenic mouse that has been recently generated in our lab.