Seminar Series of the
CIHR Training Grant in

# Protein Folding and Interaction Dynamics


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## Protein misfolding in an incurable neurodegenerative disease: Connecting theory and experiment


ALS is a presently incurable and invariably fatal motor neuron degenerative disease characterized by progressive loss of motor neurons, with a lifetime risk by age 70 of about 1/1000. Though most cases are sporadic, over 150 mutations throughout the homodimeric free radical defense enzyme Cu,Zn superoxide dismutase (SOD1) have been found to be associated with a familial form of the disease (fALS), affecting about 1/5 of those with autosomal dominant inheritance. It is presently not clear what unifying features, if any, these mutants share to make them pathogenic. Patients expressing mutant SOD1 may live for over 20 years or less than one year once symptoms are expressed, depending on the mutation. The reasons for this variability have remained mysterious. We have developed a new computational assay to answer this question. We probe the mechanical properties of ALS-associated SOD1 mutants by simulating a series of force spectroscopy experiments with variable tether positions. Such assays would be require extraordinary effort experimentally, but by harnessing the power of computer simulations to manipulate proteins in a virtual environment, mechanical force studies may be designed to directly address those processes critical to the propagation of misfolding and its role in disease. These studies enabled us to quantify a mechanical rigidity “fingerprint” characterizing a given SOD1 variant, and as well to measure the severity of a given mutation upon structural integrity, metal affinity, and dimer stability. Two of these features, when taken together, predict patient survival time to remarkable accuracy once symptoms have been diagnosed ($r=0.94$, $p=5e-8$). Based on these findings, we propose a general scenario for the critical events involved in the propagation of familial ALS, and we rationally predict several novel SOD1 mutant proteins with either protective or deleterious properties.


Host: Dr. Scott Prosser

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