

Seminar Series of the
CIHR Training Grant in

Protein Folding and Interaction Dynamics

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Protein Knots: Which? Where? How and Why?

Since 2000, when they were first identified by Willie Taylor, the number of knotted proteins within the pdb has increased and there are now nearly 300 such structures. The polypeptide chains of these proteins form topologically knotted structures – either a simple 31 trefoil knot or a 41, 52 or 61 knot.

We have been studying the structure, folding and function of two types of knotted proteins – the bacterial 31-trefoil knotted methyltransferases and the eukaryotic 52-knotted ubiquitin C-terminal hydrolases. The first part of the talk will focus on our folding studies on knotted methyltransferases and will include our work on (i) equilibrium and kinetics of unfolding experiments in chemical denaturants, (ii) protein engineering on both the small scale and large scale (iii) circularisation experiments which establish that the polypeptide chain remains knotted even in the chemically denatured state, and (iv) recent *in vitro* translation work which shows that knotting is rate limiting and also shows how GroEL/GroES play a role in the folding of these proteins *in vivo*.

The second part of the talk will focus on our studies of knotted ubiquitin C-terminal hydrolases – UCH-L1 and UCH-L3. This will include equilibrium and kinetic unfolding and folding studies as well as recent work on the effect of point mutants associated with Parkinson's Disease on the structure, folding and dynamics of UCH-L1. Recent work on the effect of oxidative damage on the structure of UCH-L1 will also be described and evidence that this protein adopts a partially unfolded form (PUF) on modification with the reactive aldehyde and by-product of cellular oxidative stress, HNE.

The final part of the talk will address the question of why proteins with knotted structures exist and what, if any, evolutionary advantage they have over unknotted structures. In particular, recent degradation assays have established that knotted proteins can be very resistant to mechanical unfolding and degradation by the bacterial ClpP/X machine.

The talk will KNOT assume knowledge of protein folding mechanisms.

Host: Dr. Lewis Kay

Thursday, November 14 - 12:00pm
Medical Sciences Building, Rm. MSB 4171
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