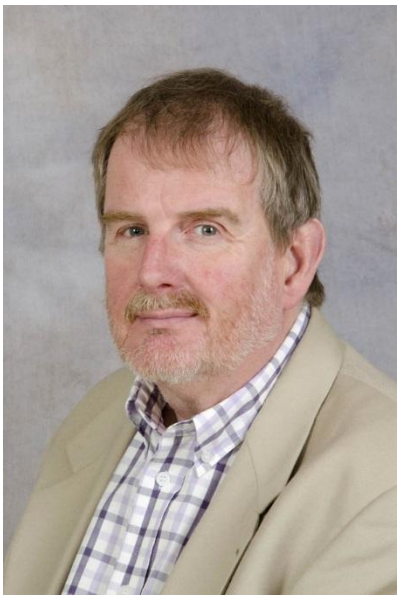
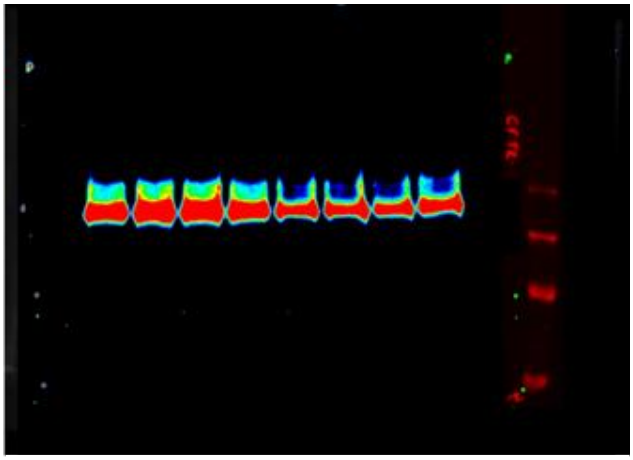


Clifford Lingwood, PhD

- Research Institute, Molecular Structure & Function, Senior Scientist
- University of Toronto, Laboratory Medicine & Pathobiology, Professor
- University of Toronto, Biochemistry, Professor

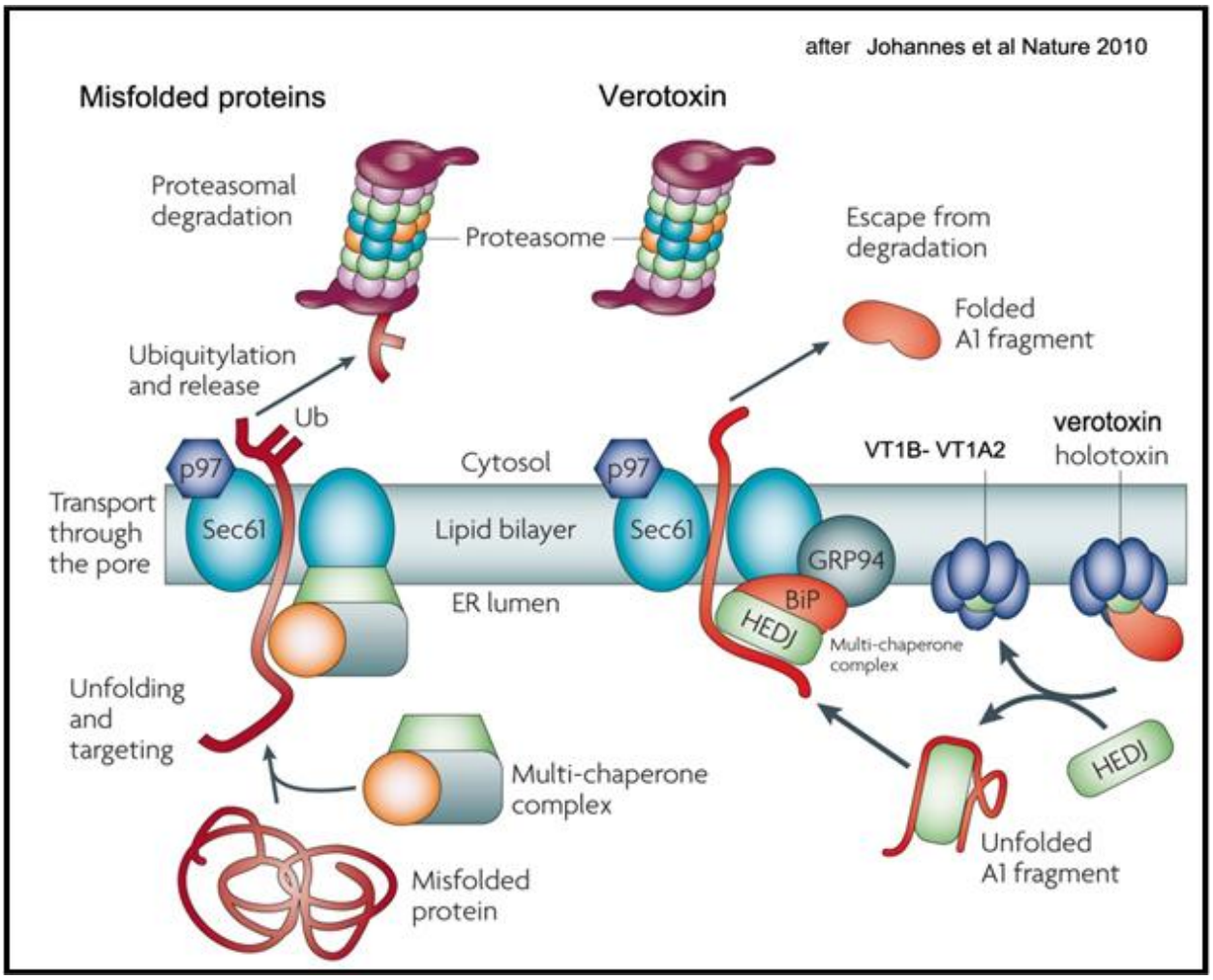
My research focuses on glycosphingolipids (which are aberrant in Cystic fibrosis (CF)), and how glycosphingolipids can play a role in protection of delta-F508 CFTR (Cystic fibrosis transmembrane conductance regulator) against Endoplasmic Reticulum-Associated Degradation (ERAD). Glycolipids are involved in the mechanism entry of many bacterial pathogens, including some bacterial subunit toxins, such as cholera toxin and verotoxin.

We are looking at the role of glycolipid trafficking in mediating the pathology of these toxin-induced diseases. These toxins undergo a process of retrograde transport – they bind to a glycolipid on the cell surface, they internalize, and are transported into endosomes, the trans-Golgi network, and then into the Golgi and endoplasmic reticulum (ER). In the ER, the A-subunit separate from the B-subunits. The A-subunit hijacks ERAD by pretending it is a misfolded protein. It uses the host cell mechanism for the translocation of proteins from the ER to the cytosol. Once the A-subunit is in the cytosol, it can kill the cell.



delta-F508 CFTR Western Blot, cells ± toxin.

ERAD is a quality control mechanism consisting of many chaperones by which nascent polypeptides are screened for their three-dimensional structure. Only those proteins folded into their correct three-dimensional structure are wanted for functional use and may translocate from the ER into the Golgi and then to their site of function.



VT-ERAD scheme for new potential CF treatment.

There are some genetic diseases in which the mutation in the affected protein does not cause a great loss of activity, but causes a minor but significant change in the protein's three-dimensional structure. This is the case for delta-F508 CFTR, and ERAD causes the cytosolic degradation of the delta-F508 CFTR protein.

Bacterial subunit toxins such as cholera toxin and verotoxin can enter cells to traffic to the ER and use the same ERAD membrane translocation process to access the cytosol, but avoid degradation because they have no lysines required for cytosolic degradation. Therefore, the method of rescue we are developing involves exogenous supply of an inactivated toxin A-subunit that will occupy the ERAD channel and compete with the endogenously produced delta-F508 CFTR, decreasing delta-F508 CFTR breakdown. This form of treatment can synergize with other approaches designed to help the misfolded delta-F508 CFTR protein achieve its correct three-dimensional structure.

I became interested in glycolipids and their fascinating function when I began my post-doctoral fellowship at the Fred Hutchinson Cancer Research Center in Seattle. Glycolipids have been structurally

characterized for many years but they are insoluble and therefore it is difficult to study their function. There are also no genes that encode them. With the toxins that we had been working on, I realized that they were a potential treatment for cystic fibrosis. These toxins have evolved over thousands of years to hijack cellular processes of protein synthesis and protein folding, and thus their "evolutionary mimicry" can be utilized to help treat diseases such as CF.

Click here for a complete list of Dr. Clifford Lingwood's publications at NCBI PubMed.

Trainees:

Zenbo Zhang (post-doctoral fellow) originally designed the constructs that we now use – cholera toxin and verotoxin – containing an inactivated A-subunit. **Humaira Adnan (post-doctoral fellow)** purified mutant toxoids and studied effects on delta-F508 CFTR levels and maturation in cultured cells.

SickKids Hospital > Clifford Lingwood Profile

SickKids Hospital > Research > Lingwood Lab

University of Toronto > Department of Biochemistry > Clifford A. Lingwood Profile

University of Toronto > Collaborative Program in Neuroscience (CPIN) > Clifford Lingwood