Joint Seminar - Department of Anatomy and Cell Biology & McGill Cystic Fibrosis Translational Research Centre (CFTRc)

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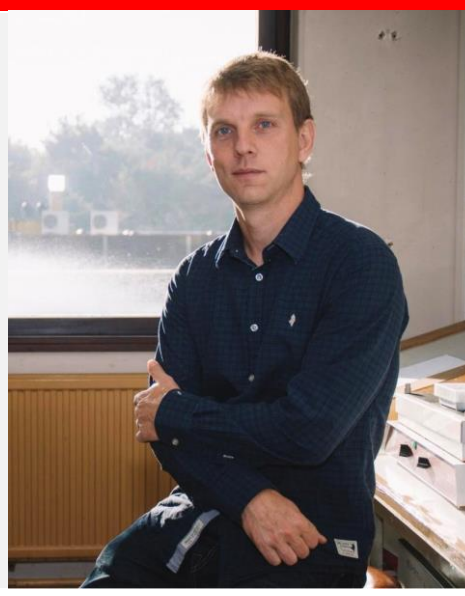

Permanent researcher (Senior Associate Professor)
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Hosted by: John Hanrahan , PhD
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Cystic Fibrosis Translational Research CENTRE de Recherche Translationnelle sur la Fibrose Kystique

Thursday, March 17, 2022
11:30 a.m.

"Nanobodies against CFTR : from discovering novel conformations to new therapeutic routes"

Functional impairment cystic fibrosis transmembrane conductance regulator (CFTR) anion channel by mutation causes Cystic Fibrosis (CF). The most frequent mutation is the deletion of phenylalanine 508 (F508del) in the first nucleotide-binding domain (NBD1) that affects the thermodynamic stability of the domain. We have developed nanobodies targeting NBD1 of human CFTR and demonstrate their ability to stabilize both isolated NBD1 and full-length protein. Crystal structures of NBD1-nanobody complexes provide an atomic description of the epitopes and reveal the molecular basis for stabilization. These stabilizing nanobodies, promote maturation and cell-surface expression of F508del-CFTR. This effect is highly synergistic with that of approved correctors indicating that their modes of correction are different. Subsequently, we have shown that this rescue leads to recovery of CFTR activity in cellular assays but also forskolin-induced swelling of organoids derived from CF patients.

Our nanobodies also revealed that NBD1 can spontaneously adopt an alternative conformation that departs from the canonical NBD fold previously observed for CFTR and related transporters. Crystallography studies reveal that this conformation involves a topological reorganization of NBD1. Single-molecule fluorescence resonance energy transfer microscopy shows that the equilibrium between the conformations is regulated by ATP binding. However, under destabilizing conditions, such as the prominent disease-causing mutation F508el, this conformational flexibility enables unfolding of the β-subdomain. Our data indicate that in wild-type CFTR this conformational transition of NBD1 regulates channel function, but, in the presence of the F508del mutation, it allows domain misfolding and subsequent protein degradation. Our work provides a framework to design conformation-specific therapeutics to prevent noxious transitions.