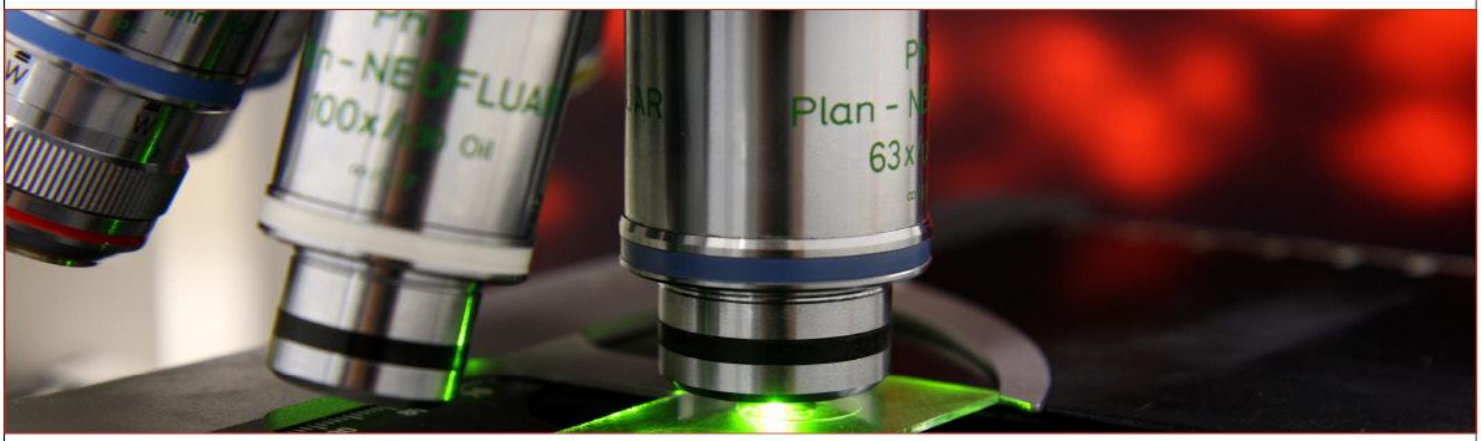
SÉMINAIRES ET CONFÉRENCES



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'' Activation of the relaxin receptor by chemically divergent agonists''

The RXFP1 relaxin receptor is a key mediator of physiological adaptation of the cardiovascular system to pregnancy, and its vasodilatory and anti-fibrotic effects have made it an attractive target for development of drugs to treat severe cardiac and pulmonary diseases. A number of RXFP1 agonists are currently in Phase 2 clinical trials, including both small molecule drugs and engineered peptides. We sought to understand the molecular basis for activation of RXFP1 by these diverse ligands using cryo electron microscopy, hydrogen deuterium exchange mass spectrometry, and other methods. Collectively, our data show that the small molecule drug candidate AZD5462 activates RXFP1 quite differently from peptide agonists, stabilizing a distinct conformation by interacting with the membrane-embedded surface of transmembrane helix 7. In contrast, the native hormone triggers a series of conformational rearrangements beginning with the receptor's ectodomain, culminating in selective activation of G protein relative to arrestin. Together, these data show how chemically divergent agonists can induce distinct conformations and signaling outcomes in a clinically relevant GPCR.

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Le lundi 23 février, 11h30

Pavillon Joseph-Armand-Bombardier, Salle : 1035
et
Zoom

invité de Pascale Legault
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