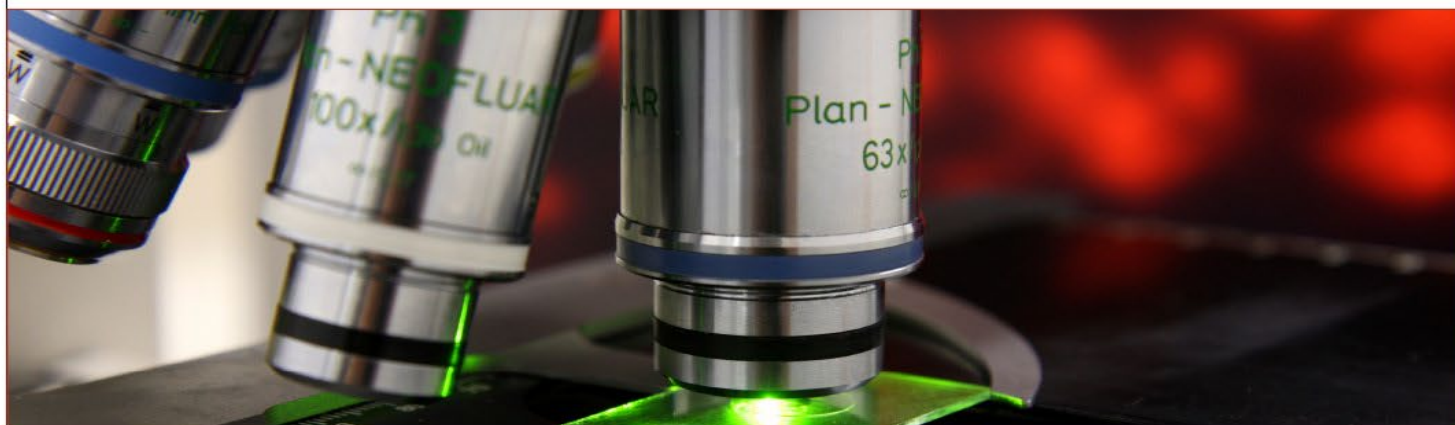


SÉMINAIRES ET CONFÉRENCES



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“The Structural Basis of SERM and SERD Efficacy in Y537S ESR1 Breast Cancer Cells”

Activating somatic mutations to *ESR1* arise under therapeutic selective pressure to enable hormone resistance in luminal breast tumors. The tyrosine to serine missense mutation at position 537 (Y537S) within the estrogen receptor (ER) ligand binding domain (LBD) confers the greatest therapeutic resistance. Initial studies suggested that the ER-degrading activities of selective estrogen receptor degraders/downregulators (SERDs) was required to achieve full anti-transcriptional efficacy in Y537S *ESR1* breast cancer cells but next generation SERDs often showed variable efficacies. While, lasofoxifene and elacestrant, which are poor ER-degraders, are effective anti-tumoral agents. To reveal the molecular basis of efficacy, we first evaluated a panel of SERMs, SERM/SERDs, and SERDs for their potency and efficacy of ER-degradation using a novel live cell assay. Y537S mutation increases ER lifetime and reduces the potency and efficacy of SERD-induced degradation. Transcriptional reporter gene and cellular proliferation assays in WT/Y537S *ESR1* cells reveal highly potent and effective SERMs, SERM/SERDs, and SERDs. High resolution x-ray co-crystal structures show that the most effective molecules enforce a WT-like therapeutic antagonist conformation by favoring the formation of a new S537-E380 hydrogen bond. These findings informed the development of new tetrahydro-6-isoquinoline-based SERMs, designed to probe the S537-E380 hydrogen bond. The lead SERM, T6I-29, engages distinctive structural features while favoring the S537-E380 hydrogen bond. It achieves effective anti-tumoral activities in Y537S *ESR1* MCF7 ectopic xenografts with fulvestrant-like effects on the transcriptome. Together, these studies show that the most effective antiestrogens use the Y537S mutation to their advantage to favor the therapeutic LBD antagonist conformation.



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Pavillon Joseph-Armand-Bombardier, Salle : 1035

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