

CONFÉRENCE

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Understanding and targeting the oncogene eIF4E in cancer

My laboratory focuses on determining the molecular basis for the oncogenic activity of the eukaryotic translation initiation factor eIF4E. eIF4E is upregulated in 30% of human cancers including a subset of acute myeloid leukemia (AML) patients. In order for eIF4E to oncogenically transform cells it modulates the mRNA translation and mRNA export of a specific subset of mRNAs involved in proliferation and survival. Our studies focus on determining the molecular basis for eIF4E dependent mRNA export. We have determined that eIF4E dependent mRNA export occurs through a pathway distinct from bulk mRNA. Further, we have determined that eIF4E can act both upstream and downstream of Akt signaling, and this activity is in part mediated by its mRNA export functions. We have used structural methods to understand the regulation of eIF4E including how the promyelocytic leukemia protein PML is able to potently inhibit the nuclear mRNA export activity of eIF4E and thereby suppress oncogenic transformation by eIF4E. Our studies suggested that targeting eIF4E could lead to clinical benefit. In this regard, we identified the anti-viral drug ribavirin as a competitive inhibitor of the natural ligand of eIF4E (m7G cap). In a phase II clinical trial, ribavirin monotherapy led to remissions and hematological responses in patients with poor prognosis AML.

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Pavillon Claire McNicoll, salle Z-300

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