

## CONFÉRENCE

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### Dr. Tommy Alain

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#### Translation control of innate immunity and implication for viral oncolysis

The innate immune response constitutes the first line of defense against viral infection and type-I interferons (IFNs) are critical for this process. A key regulation of innate immunity occurs at the level of translation, and we have demonstrated that the kinase mTOR (mammalian target of rapamycin) and its downstream targets, 4E-BPs and S6Ks, are directly implicated in this control. Oncolytic viruses constitute one of the most promising novel anti-cancer therapies, however virus-induced type-I IFN greatly limits the clinical application of oncolytic viruses against malignant gliomas (MGs). We proposed that reducing type-I IFN production through the inhibition of mTOR and its downstream targets would augment viral oncolysis of MGs. We found the highly specific inhibitor of mTOR, rapamycin, in combination with an IFN-sensitive VSV-mutant strain (VSV<sup>ΔM51</sup>), dramatically increased the survival of immunocompetent rats bearing MGs. Importantly, VSV<sup>ΔM51</sup> selectively killed tumor, but not normal cells, in MG-bearing rats treated with rapamycin. These results demonstrate that reducing type I IFNs through the inhibition of mTORC1 is an effective strategy to augment the therapeutic activity of VSV<sup>ΔM51</sup>. The recent discovery of novel active-site inhibitors of mTOR with inhibitory effects more potent than those of rapamycin are presently studied in the lab, and we anticipate that their combination with oncolytic viruses will have an increased therapeutic benefit against MGs.

**Vendredi 15 avril 2011 à 11 h 30**  
**Pavillon Claire McNicoll, salle Z-300**

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