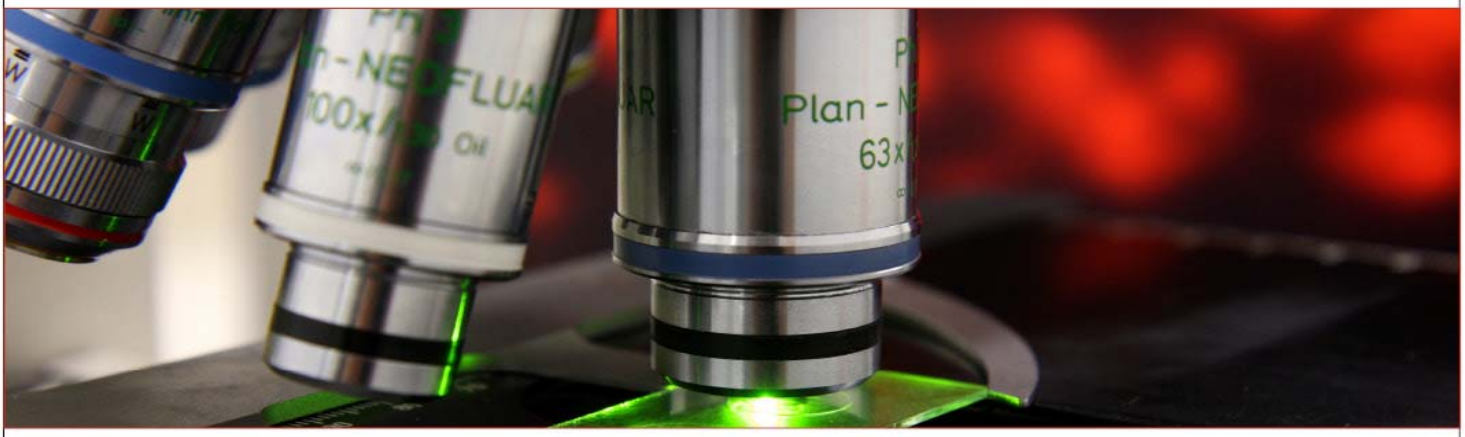
SÉMINAIRES ET CONFÉRENCES



Wei Yang

Laboratory of Molecular Biology, NIDDK, National Institutes of Health USA

« Seeing is believing: the secret of enzyme catalysis»

Enzyme catalysis has been studied for over a century. How it actually occurs has not been visualized until recently. By combining in crystallo catalysis with X-ray diffraction analysis of reaction intermediates, we have observed the processes and reaction intermediates of DNA synthesis and RNA degradation at unprecedented atomic details. Contrary to the canonical view that enzyme-substrate, transition state, and enzyme-product states have identical atomic composition and catalysis occurs by a two-Mg2+-ion mechanism with rearranging of electrons, protons and electrostatic charges, we have discovered that it is essential for enzyme-substrate complexes to capture a third Mg2+ ion en route to product formation. Unlike the canonical two metal ions, which are coordinated by DNA polymerases and nucleases, this third metal ion is free of enzyme coordination and is liganded by nucleic acid substrate/product only. Its location between the □- and □-phosphates of dNTP in the case of DNA synthesis suggests that the third metal ion may drive phosphoryl-transfer by breaking the existing phosphodiester bond in dNTP. In contrast, during RNA degradation, the transiently bound third Mg2+ ion appears to activate the nucleophilic water. Experimental data indicate that binding of the third metal ion may be the rate-limiting step in DNA synthesis, and the free energy associated with metal-ion binding may overcome the activation barrier to the DNA synthesis reaction.

Faculté de médecine
Département de biochimie et médecine moléculaire
Université de Montréal

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Pavillon Roger-Gaudry
Salle : G-1015
Invité James Omichinski

Tél : (514) 343-7341 courriel mailto: jg.omichinski@umontreal.ca