



School of Pharmacy PhD Projects 2014

Project Title Synthesis and evaluation of tetrahydrofolate derivatives to probe the role of folate supplementation in the incorporation of errors in DNA.

Supervisors Dr M. Migaud, Dr H. McCarthy

Description The Migaud group has started a synthetic program in collaboration with a US and an Irish laboratory to investigate the origins of uracil (U) incorporation in DNA, its consequences for carcinogenesis and its potential role in chemoprevention and chemotherapeutic sensitisation. A novel mechanism, recently identified by the US group explains uracil incorporation in DNA, and how it is influenced by B-vitamin supply and offers opportunities for both cancer prevention and treatment.

The research undertaken in the Migaud group is to help understand the mechanism by which N10-formyl-tetrahydrofolate is delivered from the mitochondria, as this 10-formyltetrahydrofolate directly supports the biosynthesis of purines in the cytoplasm and 5,10-methylenetetrahydrofolate in *de novo* thymidylate synthesis in the nucleus, and therefore is key to cellular homeostasis and proliferation. It is predicted that changes in formate supply, through changes in N10-formyl-tetrahydrofolate concentration in the nucleus such as during folate deficiency will impact on thymidine (T) vs uracil (U) incorporation in DNA.

The QUB laboratory will focus on developing modified folate derivatives, which will be key-reporting tools, to be used by the partnered laboratories. The synthetic work will focus in particular on the preparation of some isotopically labeled (non-radioactive) tetrahydrofolate derivatives to conduct LC-MS-MS quantification in collaboration with the US and the Irish groups. Other folate-based chemicals will be designed to answer specific biological questions and will report either through chemical derivatisation of the biological targets or via fluorescence labeling.

This project will help transform our fundamental knowledge of *de novo* nucleotide metabolism in the nucleus, establish the fundamental mechanisms whereby uracil is incorporated into DNA, determine the role of dietary folate, vitamin B12 and nucleoside supplements in regulating uracil accumulation in DNA, and help establish the role of uracil in carcinogenesis, chemoprevention, and sensitizing cells to chemotherapeutics.

Start Date 1 Oct 2014

Keywords Synthetic organic chemistry, Chemical biology, Enzymology

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How to Apply

Postgraduate applications should be made using Queen's Online:

<http://go.qub.ac.uk/pgapply>

Please note that there are two application processes: one for admission to the university and another for postgraduate awards.

Further Information

Additional information for prospective postgraduate students can be found on the School of Pharmacy website:

<http://www.qub.ac.uk/pha>

and the Queen's Postgraduate website:

<http://www.qub.ac.uk/home/ProspectiveStudents/PostgraduateStudents/>