Title of Project:	Using cryo-EM to quantify the binding of MeCP2 to chromatin
Cell Mechanism Supervisor Name	Adrian Bird
Quantitative Supervisor Name	Marcus Wilson

Summary of project

MeCP2 is a nuclear protein that binds to methylated DNA in the genome. It is highly abundant in neurons and mutations in the *MECP2* gene cause the severe X-linked autism spectrum disorder Rett syndrome. MeCP2 is a DNA binding protein but little is known about how MeCP2 behaves within the context of a chromatinised template.

The aim of this project is to investigate the binding and function of MeCP2 within the minimal building block of chromatin, the nucleosome. Using a combination of cell biology, biochemical and structural biological techniques this project will help to explain how MeCP2 binds to nucleosomes, how this leads to gene repression and how Rett syndrome mutations interfere with these processes. The project will involve:

1) Protein expression and purification of chromatin proteins and histones
2) Chemical biology technologies to generate modified proteins
3) Protein biochemistry and biophysical techniques to understand binding of MeCP2 to modified nucleosome templates
4) Structural biology, in particular cryo-EM, to understand the molecular mechanisms of chromatin interactions
5) Cell biology to extend our in vitro observations to the living cell

The project requires a passionate, motivated student interested in how molecular understanding can help explain fundamental biological processes.

What quantitative skills will the student acquire or develop during their PhD project?

The student will develop a wide range of wet-lab, dry-lab, and transferable skills. This highly cross-disciplinary project involves the development of biochemical and cell biology approaches coupled with quantitative approaches to answer a fundamental biological question. The primary aim of the project will involve the student gaining extensive quantitative and computational skills in single particle cryo-electron microscopy as well as biochemical and biophysical analysis of MeCP2-nucleosome interactions. Observations made in vitro will be tested in vivo using targeted mutagenesis of implicated regions/residues to observe changes in the chromatin structure/localisation and their effect on the biology of cells.