

**Dr Mike Webb, Dr Bruce Turnbull, Dr Andrew Macdonald
and Dr Ben Andrews (GSK)**

Using bacterial toxins to deliver macromolecules into cells (BBSRC Industrial CASE Studentship)

The purpose of this project is to investigate the feasibility of using the non-toxic cholera toxin B-subunit as a drug delivery agent.

Cholera toxin is an AB₅ protein toxin comprising a single toxic A subunit (CTA) associated with a non-toxic pentamer of B-subunits (CTB; Fig 1). CTB is responsible for toxin entry into living cells and is sufficient to allow delivery of non-toxic proteins and nucleic acids into cells. Previous studies of cellular entry and trafficking have concentrated on the full AB₅ toxin and it is believed that the A-subunit influences the route taken by the toxin through the cell. However, little is known about the intracellular trafficking of CTB or CTB-macromolecule conjugates, nor has the fate of this protein over time been determined.

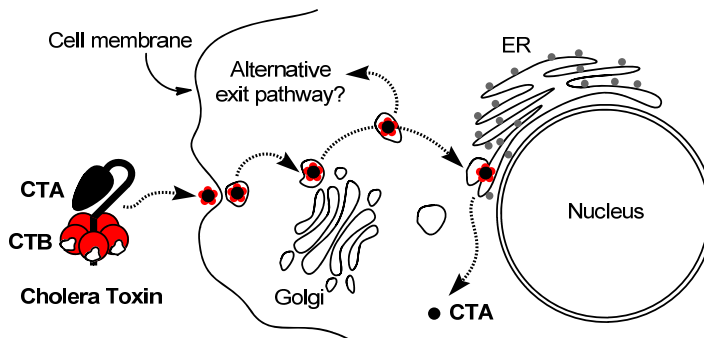


Fig. 1. Cholera toxin enters cells by endocytosis and is trafficked to the ER before toxic A-subunit (CTA) enters the cytosol. What is the fate of CTB? Is there an alternative exit pathway for CTB conjugates lacking CTA?

In this project, we will investigate the trafficking of modified CTB: Is cell entry mediated in the same manner as for the holotoxin? Where does the protein go after entry? Can these pathways be modulated by addition of peptide-targeting tags? Does repeated dosage with CTB have long term effects on the cell? We will address these questions using a combination of protein chemistry and cell biology. We have developed a variety of mechanisms to selectively label and prepare cholera toxin B and larger complexes and the student will apply these methodologies to generate fluorescently-labelled proteins and complexes. These proteins will then be used in a variety of longitudinal imaging studies to address the above range of specific research questions. The project would suit a student with a background in either biochemistry or chemistry and the specifics of the project will be tailored to suit the successful candidate, however it is not anticipated that the project will involve a large amount of synthetic organic chemistry. The project will include at least 9 months spent at GSK Stevenage.

The project is funded through a BBSRC Industrial CASE award with GSK for 4 years from October 2012 and the stipend would be at the standard research council rate (~ £13,895 pa for 2011/12) plus a supplement from GSK. Applications for this studentship, which will be accepted until the studentship is filled, should be directed to Anna Luty, School of Chemistry, University of Leeds, Leeds LS2 9JT and can be made online via the following link: <http://www.chem.leeds.ac.uk/postgraduate-research/how-to-apply.html>

Please contact Dr Mike Webb (M.E.Webb@leeds.ac.uk) or Dr Bruce Turnbull (W.B.Turnbull@leeds.ac.uk) for further details about this opportunity.

Closing date for applications: 7th March 2012.