TARGETED THERAPEUTICS

CENTRE FOR DOCTORAL TRAINING

Boots Science Building, The School of Pharmacy, University of Nottingham

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

EPSRC

Engineering and Physical Sciences Research Council

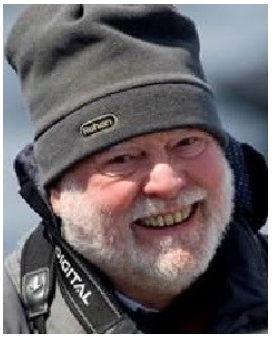
AstraZeneca

The CDT has been an enormous success and a fantastic endeavour in which to be involved. The sustained funding from EPSRC and AstraZeneca has allowed us to develop 30 new research projects, build collaborations linking over 60 scientists from Nottingham and AstraZeneca, and train 6 cohorts of PhDs who are now developing leadership roles in industry and universities with reach across the world. We have seen a culture change in the way PhDs are trained within the University, have developed close and long-lasting research partnerships with AstraZeneca, and are building a sustainable network of PhD scientists who are passionate advocates for pharmaceutical science and the benefits it can bring to society. The extension of the original CDT in Targeted Therapeutics into the new CDT in Advanced Therapeutics and Nanomedicines, in collaboration with the UCL School of Pharmacy, AstraZeneca, Boots Pharmaceuticals, GSK and Pfizer is equally exciting, and should continue to enhance the role of university-industry partnerships in science for society in the future.

Professor Cameron Alexander, Director of CDT

School of Pharmacy, University of Nottingham

Dr Zoe Cotter, Dr Andrew Megarry, and Dr Arpan Desai are now working as Senior Scientists for AstraZeneca in Macclesfield. Dr Helen Angell (not shown) works for AstraZeneca in Cambridge continuing in her field of cancer research.



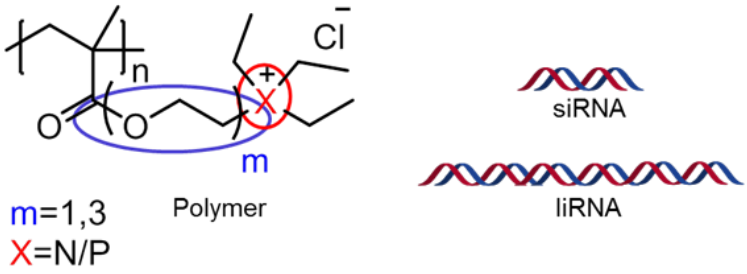
It is my pleasure to reflect on the EPSRC Astra-Zeneca Doctoral Training Centre in Targeted Therapeutics which opened its doors to the first student intake in September 2006. It was a 5 year programme taking in 5 students per year and so its first groups of students completed through 2010/2011 and its last will complete - all being well - in this academic year.

The programme derived from an initiative by academic and industrial pharmaceutical scientists who recognised that the then infrastructure in the UK was inadequate to support the research community which was so important to the pharmaceutical industry but also restricted Universities in their choice of quality trained researchers. I had run an EPSRC/BBSRC/MRC initiative in 2005/2006 to quantify the problem and to seek support from major companies to partner EPSRC in a doctoral training centre. In the event, Astra Zeneca committed to the programme which after initial concerns that it would be seen as a purely AZ project for their specific benefit - which would have been outside the remit of the DTCs (now renamed CDTs) - it was recognised that the students would have an open choice in their career paths and EPSRC agreed to fund it.

It gave me particular pleasure that the programme was initially extended in 2011 and subsequently led to a new programme which was initiated in 2014 with wider academic and corporate support. This was entirely due to the excellence of the programme and the students selected to participate, the strong support from the University of Nottingham and its School of Pharmacy in particular and a very special compliment to Astra Zeneca who were visionary in their commitment to support the programme.

During today you will meet many of the participants in the programme and all the Advisory Board have had great pleasure in interacting with them and watching them flourish, both on the course and in their subsequent careers. I do hope you will enjoy the day and reflect on the success of the programme. Please also store in your minds that there will be a continuing need for these training programmes and if you have the opportunity to support or participate in the future please do so and I hope you will have as much pleasure as I have had from my interaction here.

Professor Bill Dawson, Chair CDT Advisory Committee



Formulation design (polymer and dsRNA)	Physico-chemical and biological properties
Length of linker Nature of the atom Type of dsRNA	Polymer binding Binding strength Size and charge Biological efficiency

Phosphonium salt-containing polymers have recently started to emerge as an attractive alternative to ammonium-based gene delivery systems. Throughout the research project it was investigated how structural parameters – such as polymer design (nature of atom and length of linker) as well as RNA structural parameters (length of RNA) affect physico-chemical properties and biological behaviour.

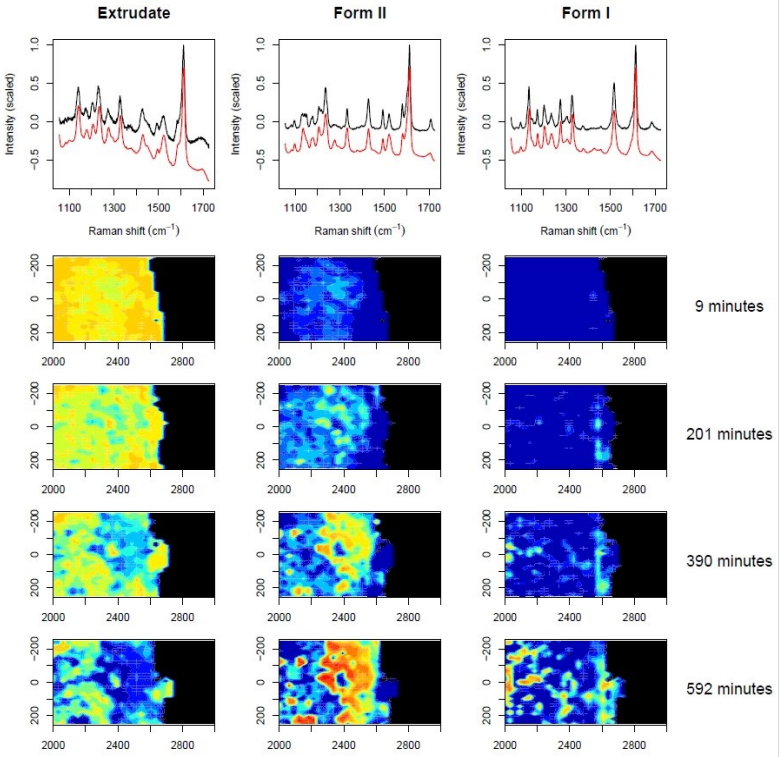
Dr Vanessa Loczenski Rose now works in RNA research for Syngenta and is a member of the CDT Advisory Committee.

Instruments (fluid bed dryer and roller compactor) used in Macclesfield for tablet making.

Achieving scientific leadership is a key ambition within AstraZeneca and the long standing collaboration with the University of Nottingham through the CDT has contributed to this. The collaboration has strengthened our relationship with a leading School of Pharmacy within the UK and delivered projects that have been applied to our drug development projects. At the initiation of the collaboration a key goal was in the training of students who would be ideally equipped for a career within academia or the pharmaceutical industry. Evidence of the success of this training is that 4 of the students are now employed by AstraZeneca and others have found employment as academics or with other companies. We look forward to building upon the success of the original CDT as it evolves into the new CDT in Advanced Therapeutics and Nanomedicines involving UCL and other leading pharmaceutical companies.

Professor Mark Purdie, AstraZeneca

We have employed real-time Raman mapping to investigate the dissolution of bicalutamide:copovidone amorphous solid dispersions. Our data indicate that amorphous bicalutamide present in the 50% drug loading transforms first to metastable crystalline form II and then stable form I. Form I crystallizes preferentially from the amorphous form in a random nucleation mechanism, rather than from the crystalline form II. The crystallization behaviour observed here has significant implications for drug delivery and bioavailability optimization, and is likely to apply to a wide range of molecular dispersion formulations.



Tres & Patient *et al.,* Journal of Molecular Pharmaceutics **2015,** 12 (5), 1512–1522.

Francesco Tres, and Jamie Patient, final year CDT PhD students.

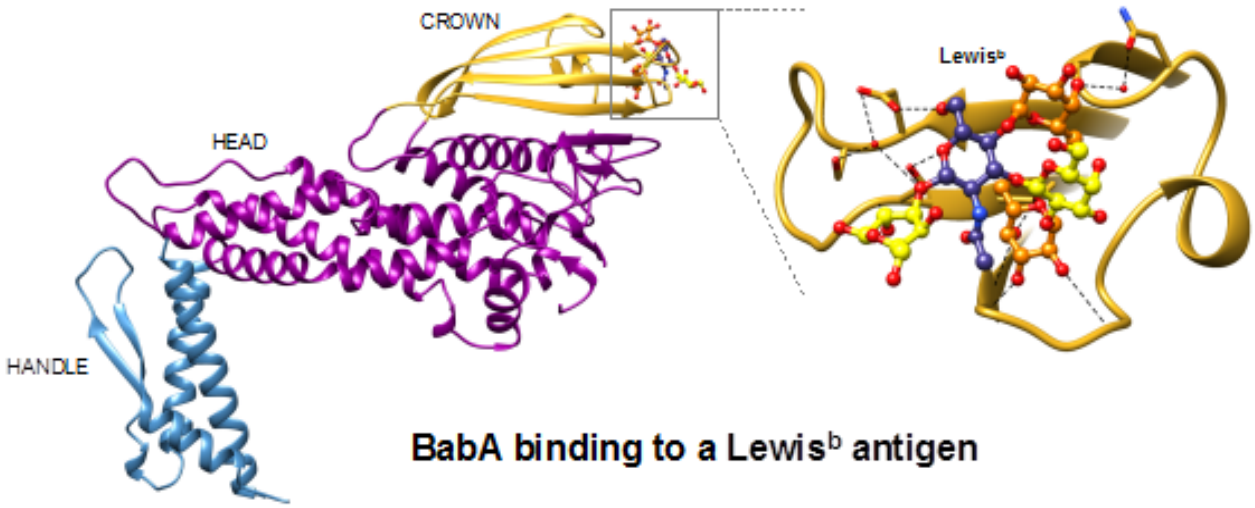
The Centre for Doctoral Training in Targeted Therapeutics was established through our Life Sciences Interface programme. Since its launch the CDT has delivered multidisciplinary postgraduate training to cohorts of engineers and physical scientists, equipping them with the skills to become future leaders in the pharmaceutical sciences. The new EPSRC CDT in Advanced Therapeutics and Nanomedicines has expanded beyond the initial collaboration between the University of Nottingham and AstraZeneca and now also includes University College London, Boots Pharmaceuticals, GSK and Pfizer. I look forward to seeing how this new team will build on the previous experiences from the CDT in Targeted Therapeutics, continuing to evolve their multidisciplinary training programme throughout the lifetime of the new EPSRC CDT in Advanced Therapeutics and Nanomedicines to meet the needs of the health and life sciences sector.

CDTs are one of the three main ways that EPSRC provides support for Doctoral Training. The other routes are the Doctoral Training Grant and Industrial Case Studentships.

In March 2014 the Chancellor of Exchequer announced the latest investments in Centres for Doctoral Training bringing the total number of CDTs to 115.

Mr Osborne said: "Our £500 million investment in Centres for Doctoral Training will inspire the next generation of scientists and engineers, ensuring Britain leads the world in high-tech research and manufacturing."

Dr Victoria Marlow, EPSRC



The gastric pathogen *Helicobacter pylori* adheres to human stomachs by using the outer membrane protein BabA to attach to Lewis^{b} antigens - an oligosaccharide found abundantly expressed on the gastric epithelium. Our crystallographic study[1] revealed, for the first time, that BabA binds to a single Lewis^{b} antigen through an intricate network of hydrogen bonds mediated by its Crown region.

Hage *et al.,* Science Advances **2015**, 1(7), e1500315.

Naim Hage, final year CDT PhD student.

CDT Students and Alumni

2011 Cohort

Naim Hage

Andreea Iuraş

Lee Moir

Jamie Patient

Kathryn Skilling

Francesco Tres

2010 Cohort

Dr Karen Beech

Dr Delyan Ivanov

Dr Vanessa Loczenski Rose

Dr Robbie Mackenzie

2009 Cohort

Dr Jason Cheung

Dr Arpan Desai

Dr Andrzej Gallas

Dr Katarzyna Nurzyńska

Dr Sarah-Jane Rymer

2008 Cohort

Dr Rosemary Adsley

Dr Fabrice Bayard

Dr Paulina Cygan

Dr Andrea Domingues Gonçalves

Dr Andrew Megarry

Dr Catherine Pereira

2007 Cohort

Dr Helen Angell

Dr Matthew Freddi

Dr Gavin Hackett

Dr Victoria Hutter

Dr Adnan Khan

Dr Klára Lovrics

2006 Cohort

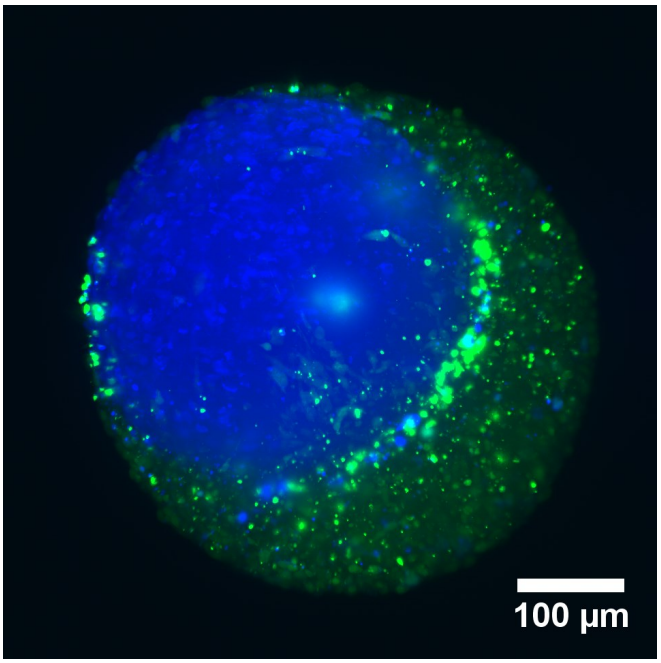
Dr Zoe Cotter (Langham)

Dr Catherine Rogers

Dr Nikolaos Scoutaris

Over the past ten years, projects in the EPSRC Centre for Doctoral Training with AstraZeneca have put the CDT at the cutting-edge of research in the pharmaceutical sciences.

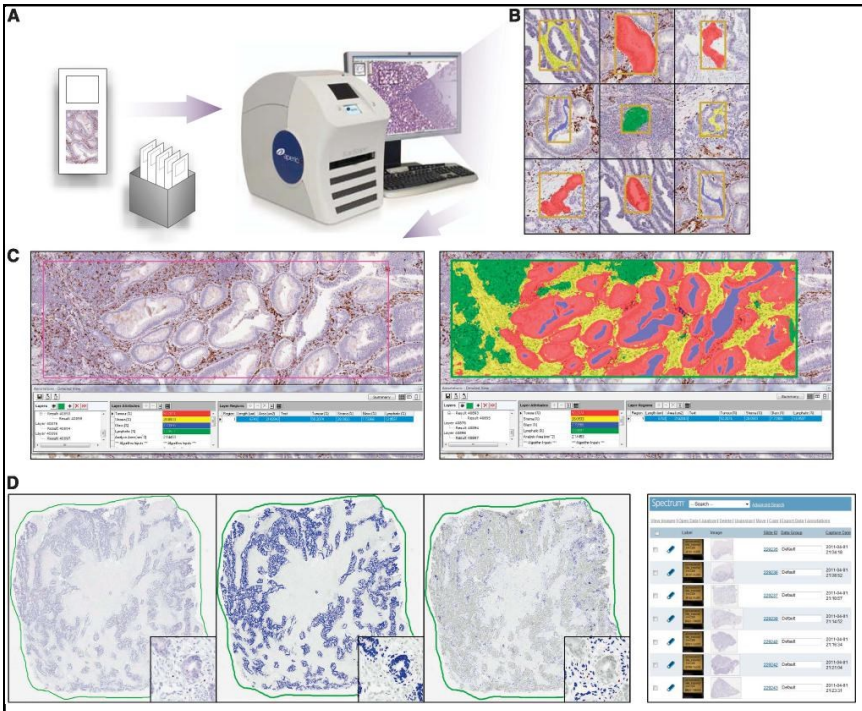
CDT teambuilding weekend in the Lake District



Co-culture spheroid made up of human neural stem cells (green) and human medulloblastoma cells (blue).

This three-dimensional in vitro model was used to identify safer and more effective medicines for children's brain tumours. The human neural stem cells represent the developing child's brain and the medulloblastoma cells - the growing tumour. The model was used to test nanoparticle-based chemotherapy in the hope of decreasing side effects and improving efficacy of treatment for brain tumours in childhood. Successful therapies would eliminate the blue (tumour) cells without affecting the green (normal) tissue. The image is a maximum intensity z-stack taken with the Zeiss Z1 light-sheet microscope.

Dr Delyan Ivanov, EPSRC Postdoctoral Research Associate, University of Nottingham.



Digital pattern recognition-based image analysis (DPRIA) software was developed to segregate distinct regions of colorectal cancer (CRC) tissue, including tumour, stroma and the invasive margin. Image analysis algorithms were constructed to quantify prevalence of immune cells, such as CD8+ cytotoxic T cells and Foxp3+ regulatory T cells. By combining immunohistochemistry with DPRIA, we demonstrated a potential metastatic phenotype in CRC. The study accelerated the wider acceptance and use of automated systems as an adjunct to traditional histopathological techniques.

Genie analysis workflow. (A) Digitally acquired images were achieved using a ScanScope digital scanner (Aperio ePathology Solutions). (B) Genie pattern recognition software (Aperio ePathology Solutions) was used for automated assessment of specific tissue regions, to identify patterns by manually marking up example areas. (C) Genie classifiers were generated for the separation of: tumour (red); stroma (yellow); lymphatic aggregates (green); non-neoplastic tissue (not shown) and glass (blue) and then tested for accuracy. (D) For each slide, the area of interest was manually marked (green line). Genie classifiers were combined with a nuclear algorithm to quantify the percentage positive number of immune cells (brown) in each area.

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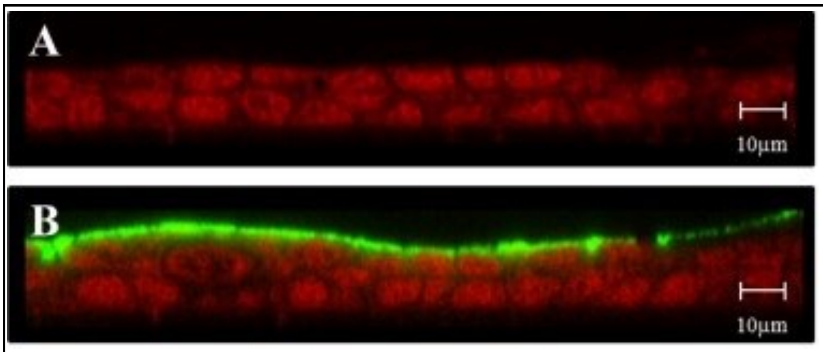
Dr Helen Angell, Senior Scientist, AstraZeneca.



Confocal images of layers of the rat bronchial epithelial cell line, RL-65 immunolabelled for P-glycoprotein (green) and counter-stained with a nuclear dye (red). Image A is the background control and image B is the P-glycoprotein stained sample. In vivo rat models are widely used for predicting how new inhaled medicines interact with human lungs and are required for regulatory approval. However, there are many instances where drug permeability studies in human in vitro models are not predictive of pulmonary absorption in in vivo rat studies. This work aimed at developing and characterising a rat in vitro model of the bronchial epithelial barrier to understand interspecies differences between rat and human airway epithelia. The expression and functionality of the transmembrane transporter P-glycoprotein was assessed in human and rat in vitro models to elucidate the differences in drug permeation between the two species. A suitable in vitro culture system was developed to further validate new inhaled medicines in development for the treatment of airway diseases.

Hutter *et al.,* European Journal of Pharmaceutical Science **2012,** 47, 481-489.

Dr Victoria Hutter, Senior Lecturer in Pharmaceutics and Pharmacy Practice, University of Hertfordshire.

The foresight of AstraZeneca and the EPSRC to support the School of Pharmacy in founding one of the first CDTs in the country has, I think, paid rich dividends to all those involved and, I hope, especially the many students who have benefited from this programme. The quality and breadth of research that has resulted has created real impact, impact that will continue to grow in the years to come. The innovative methods of postgraduate training developed within the CDT in Targeted Therapeutics have also greatly enhanced the quality of training that other postgraduates receive in the School. Success breeds success, and it is very pleasing to see that for the future our new CDT in Advanced Therapeutics and Nanomedicines is even more ambitious in its goals and now has a wide range of leading industrial partners, as well as the UCL School of Pharmacy. This new consortia brings together some of the very best training and students and I very much look forward to seeing new generations of students being challenged by the new CDT, the outcomes of their research, and the careers they embark upon.

Professor Clive Roberts, Head of School

School of Pharmacy, University of Nottingham

Links:

www.advancedtherapeutics-cdt.ac.uk

www.epsrc.ac.uk

www.astrazeneca.co.uk

For further information please contact:

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