



White Rose HIP Health Technology Bulletins

The White Rose Health Innovation Partnership (WRHIP) aims to accelerate new health-related technologies by facilitating interactions between academia, industry and the NHS using an *open innovation* approach.

The new projects funded as part of this initiative are built upon a foundation of excellence in health innovation by the Partnership's members. This series of Health Technology Bulletins offer an introduction to this research excellence and cover a broad range of clinical and technology areas.

Each bulletin is written to give a general introduction to the topic area along with short case studies of clinical applications of new knowledge. Information is also presented on where to learn more about these new technologies and health challenges, and how to access the network of health innovation professionals established by the Partnership.



Targeted drug delivery

Drug delivery is the science of optimizing the administration a pharmaceutical or biopharmaceutical product. The aim is to maximize the therapeutic effect in the patient whilst minimizing the potential side effects of the intervention and increase patient compliance and satisfaction with the therapy.

Historically therapies were administered via an oral route (tablets, pills and oral liquids) or via injections. These traditional drug delivery systems have certain disadvantages:

- The drugs are delivered to the entire body via the blood circulation and only a small proportion of the total dose reaches the site where it is required
- The high doses often required to achieve the requisite therapeutic effect at the site of action has the potential to cause toxic side effects

Targeted drug delivery can overcome these shortcomings by delivering the drugs right where it is needed, with minimal side effects.

The development of targeted drug delivery accelerated dramatically when the first biopharmaceuticals products were launched in the 1980's. These protein-based drugs could not be delivered by the oral route because the physiological conditions in the gut would cause their destruction. Many academic groups worked to develop innovative ways of delivering these new medicines and these innovations have been widely adopted.

Categories of targeted drug delivery

Targeted Drug delivery comprises two main categories:

Active targeting

These drugs are designed to target and interact with specific biological sites e.g. cancer specific antigens. The drugs are designed to select and interact only with the intended target, minimizing side effects. Monoclonal antibodies and RNA interference therapies are examples of this category.

Monoclonal antibody therapy is used to treat a wide range of diseases such as cancer, multiple sclerosis, cardiovascular disease, inflammatory disease and transplant rejection. The antibodies bind only to the specific cells they were designed to target and they induce an immunological response against these target cells. Some monoclonal antibodies have been modified to deliver toxins, radioactive isotopes and other biologically active substances to the site of cancer cells in order to enhance the killing effects.

RNA Interference (RNAi) therapies are still in development but hold great promise for the treatment of viral infections, cancer and macular degeneration. These therapies work by blocking gene transcription by targeting messenger RNA and blocking the synthesis of specific proteins. Ironically, the first clinical trials of this class of therapy in macular degeneration involved

injecting the RNAi drugs directly to the diseased tissue in the eye. This direct delivery ensured that the RNAi drugs can reach their target intact. Local delivery also makes it less likely that the drugs will have unanticipated, harmful effects elsewhere in the body. This was therefore a case of an active targeted therapy delivered by a passive targeting.

Passive targeting

These are drugs that have been designed to be delivered to a specific site of action generally using innovative drug delivery devices. In order to be effective the drugs may have to be specially formulated for sustained delivery of the drug or to enhance their permeability.

Methods of delivery include: nasal sprays, inhalation systems such as nebulizers, dry powder inhalers and metered dose inhalers, transdermal patches and creams, ophthalmic creams and suspensions and inter-uterine devices.

Nanomaterial technologies are seeing increased use the development of these systems as nanoparticle engineering can help to maximize drug bioavailability at the sites of action.

The main advantage of passive technologies compared to the active ones is to require a smaller dose of drug to be delivered directly to the site where it is needed.

Targeted drug delivery - Case Studies

The following case studies were all funded by the White Rose Health Innovation Partnership and demonstrate the range of expertise in targeted drug delivery available in Yorkshire.

Case Study 1 Molecular drug delivery device for cancer chemotherapy

Conventional chemotherapy for the treatment of cancer has significant side effects because of the high doses required to treat the patient. This project is developing a novel platform technology which will allow specific tumor targeting which will allow a far lower dose of drug to be used. This has the potential to reduce the side effects associated with conventional chemotherapy.

The project has managed to chemically couple existing epigenetic cancer drugs to a molecular device. The molecular device significantly enhances the penetration of the drugs into the tumors. This allows far lower doses to be used in order to achieve the same therapeutic effect.

The project has managed to produce the new coupled molecules which maintain their anticancer activity. These have been successfully tested *in vitro* and the next steps are to test these *in vivo*. Further work will look at using the same technology applied to a wide range of cancer drugs.

This project has been led by Dr Klaus Pors and Professor Laurence Patterson from the University of Bradford, with the expert clinical input from Professor Chris Twelves of Leeds NHS Foundation Trust

Case Study 2 Novel delivery of paediatric asthma drugs

5.2 million people in the UK are affected by asthma, and the disease accounts for NHS costs of £996M per annum. The most common treatments for asthma are inhaled drugs, particularly nebulised systems. Patient compliance amongst children using nebulizers is however often difficult to achieve as standard nebulisation treatment takes 15 minutes. Compliance can be improved significantly by reducing nebulisation time.

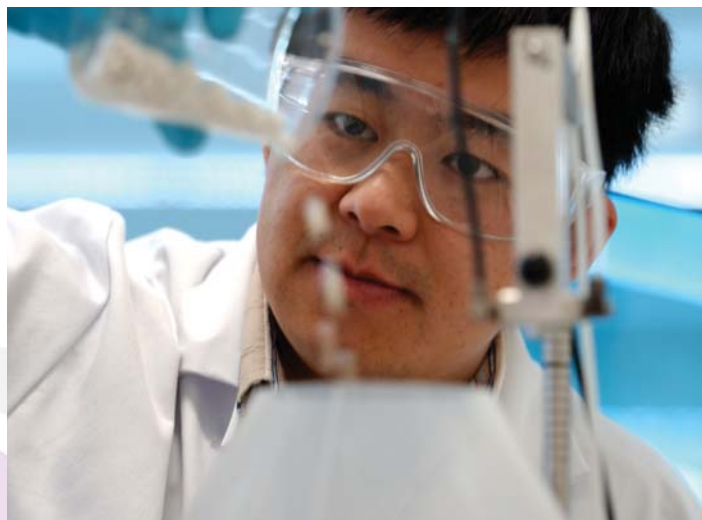
Previous studies by AGT and the University of Bradford showed that it was possible to solubilise and nebulise budesonide at concentrations significantly higher current therapy doses by using AGT Science Ltd novel Nanagel technology.

The project aimed to establish the relationship between drug loading and delivery kinetics, in order to prove that increasing the concentration of the drug in the formulation translates to comparable increased drug availability to the lung, and therefore a reduced treatment time.

Results from these studies have showed that the Nanagel formulation has the potential to significantly reduce nebulisation time of the steroid budesonide. The formulation was shown *in vitro* not to be harmful to the epithelial barrier, thereby increasing the acceptability of inhaled treatments and improving the quality of life of these patients.

The project combined the Universities of Bradford and Huddersfield's expertise in pulmonary delivery and drug analysis with AGT Science Ltd novel Nanagel technology.

This project has been led by Professor Peter York and Dr Marcel de Matas from the Institute of Pharmaceutical Innovation at Bradford University and Professor Henry Chrystyn from Huddersfield University. AGT Sciences Ltd supported the project.



Case Study 3

Development of a depot system for sustained pelvic drug delivery

Prof Peter O'Donovan, a Consultant Gynecologist from Bradford NHS Foundation, identified a need to improve the administration of drugs to the pelvic region. Current treatments for many gynecological conditions have serious side effects due to their methods of administration employing either systemic routes or drug-loaded intrauterine devices.

This innovative project aims to develop a new depot system for sustained pelvic drug delivery. The aim was to explore the feasibility of developing a polymer drug matrix that would release small amounts the drug levonogesterol in a linear manner over a long period of time. It was essential to demonstrate a slow release combined with chemical stability in the polymer matrix over many months. It is anticipated that the depot could be inserted if required during diagnostic laparoscopy procedures in the pelvis of patients.

The initial clinical indication for this technology would be endometriosis. The clinical benefit of this system would be that unlike current treatments using drug loaded intrauterine devices the depot system would allow the patient to become pregnant.

In addition to the vital clinical input, experts from multiple departments at the University of Bradford were involved. These included Dr Marcel de Matas from the Institute of Pharmaceutical Innovation; Kay Marshall, Professor of Pharmacology ; and the Polymer Centre of Industrial Collaboration. The project was backed by Femcare Ltd.



Case Study 4

Developing electroporation as a clinical tool for cancer therapy

When short, high-voltage electrical pulses (electroporation) are applied to a cell membrane, temporary pores are formed allowing drugs to easily pass through membrane and enter the cell.

Medical applications of electroporation are currently under-developed, but they have the potential to offer a powerful alternative for targeted drug delivery, particularly for the treatment of difficult to reach tumors.

This project involved development and evaluation of a specialised electroporation approach designed to work in cancer tissue. The aim has been to improve the effectiveness of chemotherapy by solving the problem of the poor permeability of cancer drugs through the cell membranes of tumors. The aim of the project has been to devise a method to inject small doses of anticancer drugs close to tumor sites and using the optimised electroporation technique to target the tumor cells. This technique could allow far lower doses to be used in order to achieve the same therapeutic effect, therefore minimising side effects of the treatment.

The project has demonstrated that it is possible to get drugs into the target cells in vitro. The technique has been proven not to interfere with the nervous system and the cells that were treated remained viable.

This project has been led by a team of researchers from the departments of Electronics and Biology and University of York, together with the University of Leeds and Leeds NHS Trust. The main contact for this project is Dr Martin Robinson at the University of York.



Founding partners in the Programme include:

University of Leeds
 University of Sheffield
 University of York
 University of Bradford
 Medipex
 Medilink Yorkshire & the Humber
 The Leeds Teaching Hospitals NHS Trust
 Sheffield Teaching Hospitals NHS Foundation Trust
 Bradford Teaching Hospitals NHS Foundation Trust
 Yorkshire Forward
 Health Technologies Knowledge Transfer Network
 New Jersey Biotechnology Life Science Coalition
 Rutgers, The State University of New Jersey
 University of Medicine and Dentistry of New Jersey
 New Jersey Institute of Technology
 Princeton University
 International ARI Institute, University of Toledo, Ohio
 Polymer Centre for Industrial Collaboration
 Biomaterials and Tissue Engineering Centre for Industrial Collaboration
 Pharmaceutical Innovation Centre for Industrial Collaboration
 Wireless Technologies Centre for Industrial Collaboration
 Particles Centre for Industrial Collaboration

Regional Centres of Expertise

Points of entry	Expertise	Contacts
Pharmaceutical Innovation Centre of Industrial Collaboration University of Bradford	Drug formulation and analysis, inhaled drug delivery, tableting, poorly soluble drugs, extended release formulations, nano suspensions	www.ipi.ac.uk Piers Lincoln 01274 236160 p.lincoln@bradford.ac.uk
Polymers Centre of Industrial Collaboration University of Bradford	Polymers for extended drug release, material characterisation	www.polycic.com 01274 233624 Dr John McGrath j.c.mcgrath@bradford.ac.uk
Institute of Cancer Therapeutics University of Bradford	Cancer medicines development: from concept to clinic. Pre-clinical drug testing	www.cancer.brad.ac.uk 01274 233226 Dr Stuart Nelson s.nelson@bradford.ac.uk
School of Pharmacy University of Huddersfield	Therapeutics of inhaled drugs	www.hud.ac.uk 01484 472783 Prof Henry Chrystyn h.chrystyn@hud.ac.uk
Particles Centre of Industrial Collaboration University of Leeds	Particle characterisation and engineering	www.particlescic.com 0113 343 2376 Simon Lawson s.lawson@leeds.ac.uk
BITECIC Ltd	Medical devices, cell and tissue engineering	www.bitecic.com 0113 397 0325 John Egan john.egan@bitecic.com
Skin Research Centre University of Leeds	<i>In vivo</i> and <i>in vitro</i> testing of therapeutic agents for skin conditions	www.leeds.ac.uk/src 0113 343 5615 Dr Richard Bojar src@leeds.ac.uk
Leeds Institute of Molecular Medicine University of Leeds	Targeted drug therapy testing in ovarian cancer models	http://limm.leeds.ac.uk/contact.htm 0113 343 8517 Phil Burns p.a.burns@leeds.ac.uk
Enterprise and Innovation Office The University of York	<i>In-vivo</i> electroporation for drug delivery	www.york.ac.uk 01904 435289 Joe Ross jr23@york.ac.uk



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