7th UKICRS Conference, January 2001 – London

Speakers and organisers at the 7th UKICRS Conference held in London in January 2001. From Left to right Jayne Lawrence (King's College, University of London), H.S. Aojula (University of Manchester), Kevin Shakesheff (University of Nottingham), Snjezana Stolnik Trenkic (University of Nottingham), Graham Buckton (School of Pharmacy, University of London), Ijeoma Uchegbu (University of Strathclyde), Richard Guy (University of Geneva and Former President of the Controlled Release Society), Antony D'Emanuele (University of Manchester), Robert Hider (King's College, University of London) and Barry Hirst (University of Newcastle upon Tyne).

Another successful UKICRS one day symposium was held at King's College, University of London on Thursday 4th January 2001. The event was generously sponsored by Colorcon, The Controlled Release Society, Elan, GlaxoSmithKline and Wyeth. The UKICRS gratefully acknowledges this support.

An interesting and varied program was organised by Jayne Lawrence and Ruth Duncan, which focused on key issues including tissue engineering, the role of p-glycoprotein in absorption, and gene therapy, with an impressive panel of speakers addressing a packed auditorium.

Richard Guy, president of the Controlled Release Society opened the proceedings with a review of the events of the past year which included an expanded membership, a change to the CRS administrative staff and plans for forthcoming CRS meetings. Dr Tony D' Emanuele, formally resigned his 7 year chairmanship of the UKICRS, welcoming Professor Duncan Craig to the committee as his successor. Professor Craig, of the University of Belfast and one of the founding members of the UK chapter of the CRS will serve the committee as chair for 4 years.

A paper entitled "The concept of Nanoparticulate Systems for the Delivery of Antisense Oligonucleotides" was presented by Patrick Couvreur, of the University Paris Sud, France. Antisense oligonucleotides (ODNs) can selectively modulate the expression of a gene, although their effectiveness is often hindered by the poor biological stability and low intracellular penetration. Experimental data on two nanoparticulate systems were presented, where the ODNs were either associated with the polymer surface or entrapped within the nanoparticle. Polyisobutylcyanoacryalte nanocapsules show great potential for ODN delivery, where the ODNs are entrapped in an aqueous core, prepared from a w/o emulsion. Entrapment into polymeric nanocapsules more efficiently protected the ODNs from degradation by serum nucleases, than adsorption on to the nanosphere surface.

The morning session continued with an overview from David Thatcher of Cobra Pharmaceuticals highlighting "Issues in the Development of Gene Therapy Products". To date non-viral delivery of genes has been difficult to achieve and has not been successful while viral gene therapy vectors have encountered safety problems. Greater biological amplification is required and therefore the delivery needs to be improved. Gene therapy aims to replace defective genes, delete genes to modify disease, deliver novel genes or DNA vaccines. For effective gene therapy the ideal vector must provide sustained and specific gene expression at an appropriate level, whilst targeting efficient gene delivery. The challenges facing gene therapy include inefficient delivery (although this can be increased by the use for a viral promoter), transient gene expression and poor pharmacokinetics. Delivery could be improved by the use of (i) viral promoter systems, which is the most common approach, (ii) non viral systems including endosomal escape and nuclear targeting strategies, (iii) viral systems for example replicating vectors of modified tropism (modification to the viral backbone). Transient gene expression could possibly be overcome by the use of chromatin insulators and the integration into the host’s genome of a persistent virus (e.g. the adeno-associated viruses). The pharmacokinetic profile of the gene product could be enhanced by both viral and non-viral methods of passive or receptor mediated targeting strategies. However, it is anticipated that gene therapy will have its maximum clinical benefit in indications where local delivery with a low level of transient expression is required.

The session continued with a presentation on “Tissue Engineering: The Link with Drug Delivery” by Kevin Shakesheff at the University of Nottingham. Developments in the field of tissue engineering have required the immobilisation of biologically active molecules onto the

surface of polymer based devices. The polymer surfaces are required to present biological molecules that actively promote receptor mediated interactions with cells, or to present molecules that change the distribution of protein absorption *in vivo*. Shakesheff explained how the use of Super Critical Fluid (SCF) Technology could change crystalline polymers into a glassy state. For example poly lactic acid is a liquid at 35°C in a CO_2 environment and particles can be manipulated into a specific shape in the range of 10-50 micrometers. The porosity of the polymer can be altered by changing the rate of CO_2 venting in the systems, a low rate producing a more dense polymer as compared to a high rate of CO_2 venting. Therefore the polymer morphology is controllable and high loadings of guest species (e.g. enzymes or proteins) can be achieved.

The morning session concluded with a presentation by Richard Guy from the University of Geneva, on 'Optimising Iontophoretic Delivery across the Skin by Chemistry and Formulation'. The skin is negatively charged at pH 7.4, therefore when a positively charged drug crosses the skin by iontophoresis, a corresponding negative ion e.g. Glucose is transferred in the opposite direction. Efficiency of drug transport is reduced in the presence of competing ions in a formulation, with transfer of lipophillic drugs e.g. lidocaine being less efficient than more water soluble compounds, the transport of all drugs by ionotophoresis is independent of concentration.

The program continued after lunch with a presentation by Snjezana Stolnik of the University of Nottingham on the Thermodynamics of polymer-DNA interactions using techniques such as differential scanning calorimetry and atomic force microscopy. These studies are aimed at furthering the understanding of the role of carrier-DNA interactions in gene delivery and will ultimately lead to the design of more efficient carriers for gene therapy.

Ijeoma Uchegbu from the University of Strathclyde presented data on the feasibility of enzyme activated polymeric vesicular systems. Polymeric vesicles prepared from carbohydrates, polyethylenimine and amino acids have been developed for drug and gene delivery applications. Dr Uchegbu described the characterisation and feasibility of chitosan based vesicles for use in developing enzyme activated drug delivery systems. These enzyme activated polymeric vesicle systems provide a new means of controlling drug release.

H.S. Aojula continued the session with an interesting presentation on "Bioresponsively-triggered release *in vivo* ". Liposomes are used as carriers in various commercial formulations, however improvements to these systems are restricted by methods to enhance targeting and to prolong the circulation time. Aojula highlighted examples of bioresponsive triggered liposomes by means of pH, thermal, photo and enzyme sensitive mechanisms, indicating that their disadvantages included a lack of plasma stability and absolute sensitivity to control the release. Modifications are required to the amino acids to develop pH sensitivity at a physiologically relevant pH.

The role of "The P-glycoprotein barrier in the gut" was presented by Barry Hirst from the University of Newcastle upon Tyne and evidence of its exploitation for pharmaceutical means was also presented. There are various means by which this endogenous transporter evolutionary designed to limit the accumulation of toxic materials in cells may be exploited for pharmaceutical means.

Graham Buckton from the School of Pharmacy, University of London gave a very interesting and informative presentation on "New Ways of Characterising Amorphous Materials". Pharmaceutical processing, for example milling and freeze/spray drying can introduce amorphous material into crystalline products. Professor Buckton described a method of inverse phase gas chromatography and near infra red + dynamic vapour sorption (NIR-DVS) to quantify the amount of amorphous material present. The measurement of amorphous material is especially important for the characterisation of inhalation drugs and excipients.

The final presentation of the day was by Robert Hider of King's College London on "Controlled Release Goals in the Treatment of Thalasseamia". Hider explained the complex role of iron in and control of iron by the body. Iron is a reactive material which is toxic if not in the correct environment. Two proteins transferrin and ferritin control the toxic effects by limiting the absorption and distribution of iron in the healthy body, however there is no mechanism for excretion e.g. following a blood transfusion. The diverse effect of iron has resulted in many potential applications for iron chelators including: malaria therapies, repurfusion injury, neurodegeneration treatments, cancer chemotherapy, acute iron poisoning, sickle cell and thalasseamia treatments. Sickle cell anaemia patients who require regular blood transfusions require the excess iron to be chelated, currently by an 8hr infusion of the non orally active Desferioximine five times a week. Therefore, there is a great need to develop an orally active agent to improve the method of chelation treatment. Iron chelators are rapidly metabolised, and as a result very high doses are required (1g of CP20 – to be dosed three times a day), although a further new generation iron chelators (CP502) with oral activity and a reduced rate of metabolism have been identified, a controlled release system would be advantageous.

The quality of poster submissions this year was again excellent covering the general area of controlled drug delivery, with a total of 22 posters on display. Two prizes of £500 (towards attendance at the CRS 2001 conference in San Diego) were awarded to the best postgraduate posters presented by Mr Ryan Tomlinson for work entitled “Polyacetals: degradable macromolecular components for biomedical conjugation applications” and Mr John Cleary for work entitled “Electrochemical characterisation of a thermoreversible hydrogel for the controlled release of pharmaceutically active compounds”.

This was an intellectually stimulating meeting with a busy programme and an excellent networking event.

Karen Lewis