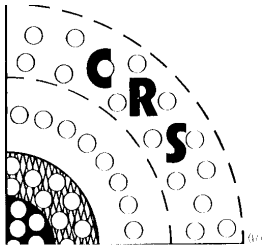
# UKICRS Newsletter



United Kingdom & Ireland Controlled Release Society http://www.pharmweb.net/ukicrs.html
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Welcome to the Fifth UKI Controlled Release Society Newsletter. We are pleased to announce that our newest members from the Republic of Ireland are hosting our millenium meeting in January 2000. In honour of the event, the meeting will be two-days long, instead of the usual one day meeting. Hope to see you all there! As usual, there has been a turnover on the committee and we welcome new faces and say goodbye and thanks for all your hard work to the outgoing people. The committee are looking for nominations for new members, so if you would like to contribute, or you know anyone else with a burning desire to help, please contact one of the existing committee members as soon as possible.

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# A Message from the New Chairman

Into our 6th year and the UKICRS continues to flourish. The 5th Annual Symposium at Aston University was an outstanding success with over 150 delegates, Allan Coombes and Saghir Akhtar are to be thanked for their considerable efforts as hosts of the meeting. We are now looking forward to our next meeting to be held in Dublin. The two-day event is being organised by our Irish partners, David Brayden and Caitriona O'Driscoll, with Allan Coombes passing on his experiences of the 1999 meeting. The theme for the 2000 meeting is Novel Vaccine Formulations and Delivery Systems. We have an outstanding panel of speakers and latest information on the meeting can be found on our web site. We also look forward to our contribution to the British Pharmaceutical Conference in Cardiff. The UKICRS input has been co-ordinated by Anne Brindley with several members of the Committee contributing to the organisation of the joint sessions.

There have been a number of changes on the Committee over the past year. Clive Wilson and Marianne Ashford have stepped down as Chairman and Secretary respectively and have guided myself and Allan Coombes as we take on our new roles within the Committee. Jayne Worlock will also be passing on the treasurer baton to Ali Rajabi-Siahboomi during the coming months. Marianne Ashford, Hiep Huatan and Peter Scholes have left the Committee and are thanked for their valuable contributions over the past few years. We welcome Jayne Lawrence, Caitriona O'Driscoll and Neena Washington as new members, and welcome back Ruth Duncan for a second session on the Committee.

It has been an enjoyable experience being a committee member of the UKICRS since it's inception back in 1994, and the contribution of everyone that has served on the Committee has been recognised by the parent Controlled Release Society. The UKICRS is considered a 'model chapter' and new local chapters are encouraged to follow our lead. It is perhaps not a surprise therefore that Clive Wilson was successful in leading the UK bid for the 2003 CRS symposium. The meeting will be held in Strathclyde and over the next two years we will be busy planning for this major event. We will be looking for 'volunteers' to help us over the next few months, and we are sure that you will all help to ensure that the meeting is a success

**Tony D'Emanuele, Chairman of UKICRS**

# CRS Globalization - What's Ahead

The activities of the local chapters of the CRS have become the focus of the globalization process. There are now 16 local organizations worldwide following the establishment of new chapters, in Slovenia, Turkey, Mexico and the Nordic countries, during the past year. Several new chapters are in the planning phase. The numerous initiatives being taken in the areas of local meeting planning, networking and communications, reflect the energy and vision of these organizations. The build up of local chapters is progressing rapidly. A key challenge is to harness and integrate the many strengths of the local chapter activities into the development of the CRS as a whole. A new forum comprised of all the local chapter heads that will have direct input to the CRS Executive is one initiative aimed towards achieving this goal.

The globalization committee, which consists of all the local chapter heads, will focus on developing an overall strategy and budget to ensure that the local chapter initiatives are coordinated with those of the CRS organization as a whole, and vice versa. In addition to local meetings it is important that we identify and promote initiatives that can encourage student development, engagement with other societies, (the influence of the UKI CRS local chapter on this years BPC agenda is a great example of this), industry, governmental and regulatory agencies, and emerging scientific disciplines relevant to CRS. As the UKI CRS has been at the forefront of setting the agenda for local chapter activities it has a significant role to play in helping take our globalization to the next level. I therefore look forward to working with you on the important agenda ahead. I wish you much continued success!

**Glynn Wilson, Ph.D**
**Chair Globalization Committee**

# UKICRS Committee for the Millenium

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# The 5th UKICRS Symposium "Polymeric Drug Delivery into the New Millennium"

**8th January 1999, Aston University School of Pharmacy**

Around 150 delegates from all parts of the U.K, from academia and industry, were welcomed to the 1999 UKICRS meeting at Aston Pharmacy School by the meeting organisers, Dr Saghir Akhtar and Dr Allan Coombes. Professor David Billington Head of the School of Life and Health Sciences at Aston University drew attention to the meeting venue. Birmingham's location in a region steeped in history, the city's manufacturing traditions, the exciting urban regeneration programme and the growth of new hi-tec industries. Professor Billington hoped that the attractions of Birmingham as a conference venue would bring the International CRS Symposium to the city in the next decade.

Professor Clive Wilson performing his last duty as Chairman of the UKICRS before handing over to Dr Tony D'Emanuele recounted some of the history of the CRS. The society was conceived in 1973 to represent members in the agrochemicals sector and has expanded to incorporate controlled delivery of pharmaceuticals, cosmetics and agriculture/veterinary applications. The CRS and its influence continue to grow : 1500 delegates attended the 1998 International Symposium in Las Vegas and strong links exist with the AAPS and BPC. The aim of UKICRS to develop contacts with organisations in related scientific areas was shown this year by the high attendance of delegates from the biomaterials field and the inclusion of a keynote Institute of Physics and Engineering in Medicine/ UKICRS lecture on polymers for tissue repair.

The scientific session was opened by Professor Etienne Schacht from the University of Gent, Belgium. His talk on "Biodegradable Polyphosphazines for Biomedical Applications' clearly conveyed the versatility of this class of polymers in that the possible physical forms range from water soluble polymers, to hydrogels, elastomers and solids and the degradation rates (due to hydrolysis) are controllable from weeks to months. Blending of polymers and the incorporation of depsipeptide side groups in the polyphosphazine (PPZ) chain enables fine tuning of degradation characteristics. Controlled drug delivery had been achieved using 'reservoir or matrix—type' systems (for Mitomycin C) and polymer-drug conjugates. Long-circulating colloidal delivery systems were also feasible since PPZ nanoparticles, surface modified using PEO-PPZ conjugates, have shown reduced RES uptake after intra-venous administration.

Professor Neil Graham from the University of Strathclyde discussed controlled drug delivery from polyurethane/ PEO hydrogels which can be designed to swell in aqueous environments under pH control. The hydrogels, produced by radiation crosslinking of PEO/PU polymers, can be produced as nanogel or microgel-structured particulates for further processing into coatings or drug-containing matrices for solid dosage forms. Drug release profiles can also be adjusted to provide constant delivery rates over a required timescale and the hydrogels allow controlled release of high and low molecular weight actives. One of the earliest commercial applications of the technology involved controlled delivery of prostaglandin $E_2$. Current research is exploiting non-water soluble and water soluble hydrogels for drug delivery, the latter form providing a promising material for controlling the release of protein therapeutics.

Dr Julian Blair of Quadrant Healthcare described the company's novel group of oligosaccharide ester derivative (OED) glass-formers for oral and pulmonary delivery of pharmaceuticals. These materials are welcome additions to what is still a relatively small number of options for controlled drug delivery (cf polylactides, polyorthoesters, polyanhydrides). The

active is encapsulated in an amorphous OED matrix and released by a composite mechanism involving diffusion and controlled devitrification of the matrix. Drug release profiles can be varied by OED selection, control of formulation technique, particle size, drug loading and excipient composition. Drug loadings in excess of 40% w/w are achievable and drug release can be sustained over hours or days.

Lunch and poster viewing extended over 2 hours to allow adequate time for consuming, at leisure, an excellent meal, for appreciating the 40 posters on display and enjoying the social occasion which has become an integral part of the UKICRS national meetings.

The afternoon started with a joint Institute of Physics and Engineering in Medicine/UKICRS lecture : 'Biological recognition of synthetic and natural polymers in wound healing'. Professor Jeffery Hubbell from the University of Zurich presented a fascinating account of biomimetic approaches to material design for medical applications. In particular, much attention is currently being directed towards manipulating cell adhesion in both two and three dimensions in order to reduce specific adhesive interactions (eg blood platelets with cardiovascular implants), to target the adhesion of particular cell types (eg endothelial cells) and to induce specific adhesion-related cellular responses (eg migration of smooth muscle cells). Hydrogels formed by *in situ* photopolymerisation of PEG-based methacrylate macromers, for example, have been surface modified using bioactive peptides to promote adhesion of cell types desirable in wound healing. Biomimetics was also directing research in the area of enzyme-degradable materials which allow cell penetration after breakdown by locally active proteases such as plasmin, collagenase and elastase. Biomimetic signalling effects have also been incorporated into biological materials (such as fibrin) by using bi-domain peptides to influence their properties and biological function. One segment provides attachment to the fibrin matrix, the second (eg RGD cell adhesion sequence) supplies the required bioactive property.

The first lecture of the session on 'Polymers for CNS delivery' was presented by Professor Henry Brem from John Hopkins University School of Medicine Carmustine (BCNU)-impregnated polyanhydride gliadel implants for brain tumour therapy is the first new therapy to be approved by the FDA in 23 years. The wafer implants are implanted directly at the site of tumour resection and provide high local concentration of drug with minimal system toxicity. A linear dose response has been measured, with a drug loading of 20% proving to be the optimum dose. The success of the delivery system in improving survival of patients treated for gliomas, both at initial presentation and recurrence, indicates an important role for local delivery of other therapeutic agents such as cytokines, immunotoxins and anti-angiogenesis agents.

Dr Saghir Akhtar from Aston Pharmacy School continued the theme of CNS drug delivery with a talk on 'Sustained Polymeric Delivery of Antisense Nucleic Acids to the Brain'. The potential use of Ribozymes to specifically cleave the RNA component of the tumour-associated ribonucleoprotein, telomerase was presented. Other studies suggested that implantable biodegradable polymer formulations present an attractive strategy for improving site-specific delivery of antisense molecules within the brain.

The concluding lecture of the scientific session was delivered by Dr Adam Smith from Oxford University on the subject of 'Localised delivery to the cerebral cortex using Elvax slices : reversible silencing of intrinsic activity'. Sub-dural implants of Elvax polymer giving sustained release of the GABAA receptor agonist muscimol were used to achieve inactivation of cortex over a period of weeks or months so as to identify behavioural consequences. Autoradiographic tracing revealed a highly localised distribution of muscimol directly beneath the implant. Within 2 hours of implantation, no visual cortical responses were recorded throughout


*Ladies and Gentlemen - I present the Speakers!*

the 1500 μm depth of the underlying cortical layers. This level of functional blockade could be maintained for 6 weeks and was reversible; normal cortical responses could be recorded within 9 hours of implant removal.

A highly enjoyable and stimulating meeting was drawn to a close by the Chairman of UKICRS, Professor Clive Wilson who commented on the fascinating options for polymer controlled drug release which had been presented by the speakers and poster exhibits. The high standard of work and quality of presentation made judging of the posters extremely difficult this year and the final choice was made from five excellent submissions. Julia Nwachuku from the Department of Pharmacy and Pharmacology at Bath University was awarded one of the £500 prizes for her poster on 'Gene transfer using a bifunctional peptide comprising a membrane translocating sequence coupled to a cationic DNA-binding domain'. Amelia Petch from Aston Pharmacy School won £500 for her poster on 'DNA chip technology as a novel technique for designing effective antisense oligodeoxynucleotides against the epidermal growth factor receptor mRNA'. The prizes will assist Julia and Amelia to attend the 1999 International CRS Symposium in Boston.

Finally the committee of UKICRS wishes to thank elan Pharmaceutical Technologies, Pfizer Central Research, ZENECA Pharmaceuticals and Skye-Pharma for their generous sponsorship which helped to ensure the high quality of the 1999 meeting.

**A. Coombes**

# Report on the 26th International Symposium on Controlled Release of Bioactive Materials

**June 20th 1999, Boston, Massachusetts**

The 26th International Symposium on the Controlled Release of Bioactive Materials took place in the attractive and historic city of Boston and was attended by over a thousand delegates from all over the world. Early arrivals, of whom there were many, had the opportunity to attend the appropriately named "soapbox sessions". These provided an opportunity for drug delivery companies to tout their wares, and Bob Sparks of Particle and Coating Technologies to make the most of his final slot of the day by delaying coffee and biscuits for a further five minutes. Thomas Kissel opened the first day proper with a welcoming address and introduced Robert Langer whose opening plenary set the scene for this lively, high quality meeting.

The topics addressed by the symposium were many and varied and multiple parallel sessions made keeping track of the when and whereabouts of the numerous presenters something of a challenge. This was highlighted by the apparent deification of Joseph Robinson whose alleged omnipres-

ence was eventually left untested when his simultaneous opening of the sessions on Clinical Experience with Controlled Delivery, and the Forum on Drug Delivery and Biotechnology in the New Millenium was judiciously rescheduled.

Monday also saw Jean-Paul Behr co-chair a minisymposium on the Mechanisms of Gene Delivery by Synthetic Systems and his lecture highlighted some of the associated problems. The greatest barrier to gene delivery remains the nuclear membrane, however the group at Strasbourg have shown that a single nuclear localisation signal peptide covalently bound to a reporter gene can enhance gene expression up to one thousand fold. They hypothesise that the 3nm-wide DNA present in the cytoplasm is initially docked to and translocated through a nuclear pore. After entering the nucleus, the DNA is thought to collapse to a chromatin-like structure thereby providing a mechanism for threading the remaining DNA through the pore.

There was plenty of interest for those of us with an interest in self-assembly, and polymeric block copolymers featured in a number of the presentations. Flamel Technologies, for example, described the use of biodegradable linear block copoly(L-leucine-L-glutamate) which forms stable complexes with a variety of proteins including insulin and self-assembles to form sustained release colloids up to 400nm in diameter. Block copolymer micelles for controlled delivery was also the topic for Kataoka whose group has previously reported the use of doxorubicin-conjugated poly(ethylene glycol)-poly(a,b-aspartic acid) in the treatment of solid tumours. The use of block copolymer micelles as targeted non-viral gene vectors is currently a key focus area. The plenary lecture by Helmut Ringsdorf also considered the applications of polymer conjugates and other supermolecular systems in drug delivery. An interesting feature of the lecture was the description of multicompartment micelles and the possibility of developing heterogeneously organised polymeric micelles with differentiable, individually functionalised surface regions.

The Capsugel Graduate Student Minisymposium was well attended and the audience was suitably rewarded with a number of excellent presentations which included an elegant piece of work described by Chun Wang in which coiled protein domains were used as physical crosslinks for thermally responsive hydrogel-forming synthetic polymers. Notably, the proteins used to crosslink the gel are genetically engineered segments of the stalk region of motor protein kinesin. Below the transition temperature the protein crosslinks are thought to exist as $\alpha$-helices, whilst above the transition temperature the proteins are thought to adopt a random coil configuration that results in a reduction in gel volume to just one tenth of the original equilibrium volume. The potential of these systems for controlled release of drugs is presently under evaluation.

As would be expected, targeted drug delivery had a high profile and selecting just one or two highlights from so many high quality papers has proven difficult and necessarily rather subjective. Nonetheless the presentation by Ronit Satchi on the novel use of Polymer Directed Enzyme Prodrug Therapy (PDEPT) was of particular interest. PDEPT involves the use of a polymeric prodrug and a polymer-enzyme conjugate to generate a cytotoxic agent selectively at a tumour site. The two are separately administered and accumulate in solid tumour by the enhanced permeability and retention (EPR) effect. The present study used a HPMA-doxorubicin drug conjugate administered intravenously to mice. Several hours later, the polymer-enzyme conjugate (HPMA-cathepsin B) was administered which accelerated the release of doxorubicin in tumour tissue leading to superior antitumour activity in the B16F10 melanoma model employed in the study. The PDEPT approach would appear to offer advantages over alternative related combination methodologies by virtue of reduced immunogenicity and in some cases, enhanced specificity.

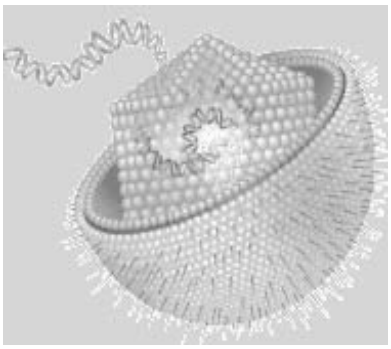
One of the most stimulating papers in the Targeted Drug Delivery session was given by Ban-an Khaw and addressed the principal obstacle to successful mitochondrial gene therapy, which is the absence of a suitable mitochondrial transfection vector. The authors have recently investigated vesicles prepared from the bola-amphiphile dequalinium (DQA) as a novel DNA delivery system. The interest stems from the intrinsic ability of DQA to selectively accumulate in mitochondria and they propose that DQAsomes may act as a cationic liposomal vector for mitochondrial DNA transfer. The present study reports the release of DNA from DQAsome/DNA complexes on association with cardiolipin-rich liposomes which mimic the mitochondrial membrane. Importantly, DNA is not released from the complex in the presence of an excess of anionic lipids other than cardiolipin. The results show that DNAsome/DNA complexes should be stable on association with the cytoplasmic membrane but able to selectively release DNA at mitochondrial sites.

The importance of alternative routes of drug delivery which avoid first pass metabolism was exemplified by the large number of contributions in the area of transdermal delivery. Iontophoresis and sonophoresis featured in a number of the papers and Gerald Kasting highlighted the increasing importance of computational aids in assessing delivery of drug, cosmetic and personal care ingredients through the skin. Deficiencies in existing models were noted and new approaches which estimate factors such as follicular delivery rates were described. Of particular interest was a report by Devin McAllister regarding the use of solid microneedles for transdermal protein and peptide delivery. The microneedles are just 150 μm in length which is sufficient to penetrate the stratum corneum barrier but not to trigger pain receptors in the underlying tissue. The authors demonstrate transdermal delivery of BSA and calcein, but in addition can now fabricate arrays of hollow microneedles of similar dimensions which it is hoped will aid the delivery of drugs across the skin at therapeutic rates.

In conclusion, I should in fairness point out that this brief review cannot do justice to the many excellent papers presented at this symposium, and has not even touched on the many hundreds of supporting poster contributions which made fascinating reading if slow progress around the extensive display areas. I could of course spend the next ten months getting to grips with the presentations I missed at the meeting, or relating the incident involving Sandy Florence and a large pot plant. However next July heralds the 27th International Symposium in my favourite European capital Paris, and given my by no means unique linguistic inability, I guess now would be about the right to time to start brushing up on my French.

**Gareth D. Rees**
**SmithKline Beecham**

# UK-Ireland CRS: Dublin 2000 Vaccine Delivery Symposium



Preparations are at an advanced stage for what will be one of the most prestigious branch conferences ever held by the CRS. The Special Symposium *on "Novel Vaccine Formulations and Delivery Systems*" will be held in historic Trinity College Dublin on January 6th-7th, 2000. The programme is complete and 20 distinguished experts in the field have confirmed their participation. Professor Bob Langer will give the keynote lecture and topics on the programme include advances in non-injected vaccine delivery, new polymeric approaches, DNA vaccination, use of live attenuated vectors and global and strategic vaccine priorities. Speakers will give academic and industrial perspectives. It is worth remarking that only a few years ago a drug delivery conference devoted to vaccines. This scenario has all changed as a result of significant research breakthroughs, an expanding commercial rationale which estimates a market of $8b for vaccines in 2004 and progress in non-injected vaccine delivery.

The conference is co-chaired by Dr. David Brayden of Elan Pharmaceutical Technologies, Dr. Caitriona O'Driscoll of the Department of Pharmaceutics at Trinity and by Dr. Allan Coombes of Aston University, UK. The conference now has an excellent up-to-date web-site, which was created by the chairman of UKI-CRS, Dr.Tony D'Emanuele. The web-site is located at: http://www.pharmweb.net/ukicrs.html. It gives the full programme (see below), registration on-line facility, details of hotel availability, local maps and hyperlinks to tourists sites in Dublin. Posters are very welcome by the set date of December 1st and two graduate student prizes of Ir£500 have been donated as bursaries towards attendance at CRS Paris 2000 for best poster awards.

The Conference has been very reasonably priced for a 2 day meeting to promote attendance by UK delegates getting over their post-Millennium blues and who require rejuvenation in the Emerald Isle. Significant sponsorship has already been obtained and further sponsorship is still being sought at various levels from companies. A special Banquet Dinner has been arranged in the Old Dining Hall of Trinity College, to help continue the excellent social occasion which has been a hallmark of the UKICRS national meetings.

Further details can be obtained from Emma Clarke, UKI CRS Conference Co-ordinator, c/o Elan Corporation, Lincoln House, Lincoln Place, Dublin 2, Ireland. Tel; +3531-709 4401; fax; +3531 709 4108, Email; claremma@elancorp.com.

**David Brayden**

**UK-Ireland CRS 2000 Programme:**

***January 6th, 2000***
Welcome (UKI CRS Chairman, T. D'Emanuele, U. Manchester)
National and global vaccine priorities for the year 2000 (D. Salisbury, Department of Health, UK)
Overview of current vaccine delivery strategies (R. Langer, MIT)
**Advances in Non-Injectable Vaccine Delivery**
Transcutaneous immunisation with cholera toxin adjuvant (G. Glenn, IOMAI Corporation, Washington DC)
Mucosal vaccination using non-pathogenic bacteria (J. Wells, Cambridge)
Potential of the saponin QS21 as a mucosal vaccine adjuvant (C. Read-Kensil, Aquila, USA)
Mucosal delivery of DNA vaccines using novel biodegradable particulates (O. Alpar, Aston U.)
**Polymeric Advances in Vaccine Delivery**
PLGA-entrapped antigens as viable oral vaccine delivery systems (D. Brayden, Elan Pharmaceuticals)
Microencapsulated antigens:protection against breakdown (E. Lavelle, Rowett Institute, Scotland)
Oral vaccine delivery: targeted polymerised liposomes (R. Brey, Innovax Delivery Systems, USA)
Stability, sustained release and delivery of carbohydrate-based particle systems (J. Kampinga, Quadrant, UK)

***January 7th, 2000***
**Vaccination Strategies**
Interaction of *H. pylori* antigens with gastric epithelia (Dermot Kelleher, U. Dublin)
Novel approaches for the nasal delivery of vaccines (Lisbeth Illum, West, UK)
Oral vaccination using live and dead bacterial systems (Gordon Dougan, Imperial College, London)
Live attenuated salmonella for mucosal vaccination (Steve Chatfield, Microsciences, UK)
Isolated milk proteins as delivery systems for DNA vaccines (Majella Lane, U. Dublin)
Stimulation of mucosal immunity by LT and CT mutants (Rino Rappouli, Chiron Biocine, Italy)
**Hurdles and Priorities in Vaccine Research**
Intestinal physiology: epithelial-immune cell interaction (Alan Baird, University College Dublin)
The vaccine requirement for TB prevention (Martin Vordermeier, Vet. Labs Agency, Surrey)
Recent advances and new approaches for development of a malarial vaccine (Adrian Hill, U. Oxford)
The pros and cons of DNA vaccination (Kingston Mills, U. Maynooth, Ireland)

# CRS Poster Prize Winners

*The prize winners each received free registration to the next International CRS meeting and £500 towards travel costs. Congratulations to Amelia Petch and Julia Nwachuku!*

**DNA Chip Technology as a Novel Technique for Designing Effective Antisense Oligodeoxynucleotides against the Epidermal Growth Factor Receptor mRNA.**
A.Petch[1], M.Sohail[2], E.Southern[2], S.Akhtar[1].
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We have been investigating the antisense-mediated inhibition of epidermal growth factor receptor (EGFr) mRNA, which has been found to be widely overexpressed in glioblastoma multiforme (GBM), a highly aggressive and malignant form of brain cancer. Patient survival rates for GBM are less than one year and at present, there is no effective treatment for this condition. Antisense oligodeoxynucleotides (ODNs) are short synthetic pieces of DNA that can bind sequence-specifically to a particular mRNA species allowing cessation of its transcription into the respective protein. In this way antisense has the potential to down-regulate oncogene expression and potentially inhibit cell growth and tumour progression. For antisense ODNs to function effectively they need to be designed to accessible sites on the mRNA. In the past, computer algorithms have been used to determine mRNA

structure from the primary nucleotide sequence. However the tertiary and secondary structure of RNA is not readily predicted by this method and thus leads to inaccurate antisense sequences. In collaboration with Oxford University we have used a novel DNA chip technology which allows the accessible sites of mRNA to be determined more effectively and thus will hopefully provide more efficacious ODNs to be designed. DNA chip technology allows all conceivable overlapping antisense ODNs of every length, up to a defined maximum, to be synthesised on a glass polymer support. Optimal sequences from this defined array were then by hybridisation of the radiolabelled EGFr mRNA transcript and subsequent sequence identification by computer. Using this technique to look at the first 120bp of the EGFr mRNA we determined two sequences (AS1 and AS2). These were synthesised as both phosphorothioates and 2'O-methyl modifications and were tested for their efficacy in vitro. ODNs were delivered to A431 cells, which greatly over-express EGFr, using an optimised cationic lipid and their effect upon cell proliferation was tested using the crystal violet assay.

Results show that both AS1 and AS2 were able to inhibit cell proliferation by approximately 60% in 24 hours compared to control cells that received lipid treatment alone. Further more this effect was not found with control ODNs that consisted of scrambled sequences. A third sequence (AS3) designed to be complimentary but not selected to target a hybridisation accessible site did not exhibit an effect on cell proliferation. This data indicates that DNAchip technology is a reliable way of determining hybridisation accessible antisense sequences. Array designed antisense sequences are being further investigated for their clinical applications in the treatment of glioblastoma multiforme.

**Saghir Akhtar**

**Gene transfer using a bifunctional peptide comprising a membrane translocating sequence coupled to a DNA-binding domain.**

J.N. Nwachuku[1], M. Ashford[2] and C.W. Pouton[1],
*[1]Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, [2] Zeneca Pharmaceuticals, Alderly Park, Macclesfield SK10 4TG*

Non-viral gene delivery systems are being improved for the transfer of genes to mammalian cells and consequently efficient uptake into the nucleus. There are several intracellular barriers for gene transfer and it is well established that escape from the endosomal compartment following internalization of transfection complexes is one of the rate-determining steps. 16 amino-acid Penetratin peptides, based on the *Drosophila* homeoprotein (pAntp), are reported to be membrane-active and the mechanism of internalization possibly involves the formation of inverted micelles. Various cationic polymers and polyethyleneimine (PEI) exhibit very efficient levels of gene transfer *in vitro*. This study examined the interaction of pAntp peptides with plasmid DNA and determined the ability of pAntp peptides to mediate transfection in mammalian cells. The work also investigated whether the use of multi-component complexes, with the inclusion of pAntp peptides, improved transfection efficiency in mammalian cells.

The penetratin sequence was synthesized as follows:
$H_2N$-RQIKIWFQNRRMKWKK-COOH
The penetratin derivative with an oligo-lysyl chain ($K_{25}$-JNN1) was synthesized as follows:
$H_2N$-KKKKKKKKKKKKKKKKKKKKKKKKK-RQIKIWFQNRRMKWKK-COOH

This study showed that Penetratin has considerable potential for delivery of small polypeptides (and possibly oligonucleotides) by direct transfer of the molecule across the plasma membrane, although the process is not efficient for larger species such as plasmids used in this study. Also, the $K_{25}$ moiety helps to anchor penetratin to DNA which does not display as high endosomolytic activity as amphipathic helical peptides. Furthermore, $K_{25}$JNN-1 appears to be membrane-active but most of the DNA is taken up by endocytosis.
The cationic polymer, polyethyleneimine shows very effective DNA-binding, mediating efficient gene transfer (without the addition of chloroquine), although no significant synergy was seen in the prsence of penetratin. Finally, whether penetratin can facilitate DNA delivery to the nucleus remains to be tested (pAntp is known to target the nucleus).

# Thinking of starting a new chapter of the CRS?

Over the past four years, CRS has expanded world-wide, with the emergence of new groups in Germany, Scandinavia, Slovenia, Turkey and a student chapter at Purdue, just to mention a few. Our own chapter also grew and gained impetus from the Dublin based groups (today Dublin, tomorrow the world) to form the UKICRS chapter. A couple of potentially strong local chapters have yet to spawn (Switzerland and France, are you listening?) which seems odd in view of their vaulted position in controlled delivery - they certainly have the talent - and perhaps the industry could benefit from the enthusiasm.

Last February, I attended the Indian chapter's controlled release society meeting in Goa: the event was hosted at one of the bigger hotels at Ciadad de Goa and the banners proclaimed the second international meeting to the confusion of the holidaymakers. Quite a few assumed "Controlled Release" was something to do with the parole board and that we were all prison psychiatrists which made me wonder if we have an identity crisis. What then is controlled drug delivery research and who joins in? In the first days of controlled drug delivery, the agriculture and veterinary sections of the department were quite well represented: this is still true at the international conferences but at grass roots level, i.e. within local chapters, there's nary a sign.

Last December, Tony and I attended a controlled release seminar organised by the Royal Institute of Chemistry at DTI headquarters. To say this was different to our ordinary business was an understatement: scientists at this meeting were dealing with what you would think of the mundane in a truly exotic way. I learned more about mordants for controlled release smells in laundry and the formulation of perfumes- it really was fascinating stuff, and we couldn't help commenting that conventional drug delivery would learn a lot from this kind of interaction. The enthusiasm for hearing about the controlled release society was extremely encouraging and the leaflets were gone within minutes of the tea break. The committee has always looked outwards towards collaboration with societies from every walk of medicine, chemistry and physics : according to Glynn Wilson (a.k.a. Clive's little bro' ) this is fairly unusual and a feature that the parent organisation would like other local chapters to emulate. In Glynn's new post as co-ordinator of the CRS local chapters, he has indicated that chapters will have to be self-sufficient and strategic monies will not be used to bankroll each local chapter's summer conference. He wants to target the money more effectively towards expanding the breadth of the society. Clearly to grow, the society has to network extensively, keeping its vitality and adapting to the new disciplines which it encompasses. In doing so, we must also not forget from where we came. Some of those roots are developing concepts which might provide solutions for more esoteric problems and it would be a pity to re-invent the wheel. In development and expansion of UKICRS, the next phase should not be to start a Channel islands local chapter but to look at possible new interactions with colleagues in the food, household and cosmetic industries.

**Clive Wilson**

# Symposia Dates for your Diary

- November 29th-December 1st, 1999, Asian Conference and Exhibition on Controlled Release, Hong Kong, China
- December 12th-December 17th, 1999, 5th US-Japan Symposium on Drug Delivery Systems, Hawaii, USA
- January 6th - January 7th, 2000, 6th United Kingdom-Ireland Controlled Release Society Symposium on: "Novel Vaccine Formulations and Delivery Systems".
- July 7th - July 13th, 2000, 27th International Symposium on Controlled Release of Bioactive Materials, Paris, France.
- June 23rd - June 27th, 2001, 28th International Symposium on Controlled Release of Bioactive Materials, San Diego, USA.

# Want to know more?

If you want to find out the latest news about the UKICRS, why not join our mailing list on the Internet? The mailing list is used to let readers know UKICRS news, elections, conferences etc. If you would like to join, please go to our website at http://www.pharmweb.net/ukicrs.html. We only send out a few messages a year (and no adverts!). If you have any questions on matters relating to controlled release. why not use the Controlled Release discussion group. Its link can also be found on the home page.

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