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Invited Abstracts

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Biopharmaceutical assessment and performance of coated MR dosage forms

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The oral route is the most common mode of drug delivery, yet it is also arguably the most complex method of administering medicaments to the body. The gastrointestinal tract provides a formidable series of barriers to successful drug delivery, absorption and efficacy. This is not surprising given that the gut has evolved to extract and absorb nutrients from ingested food and keep out foreign materials such as drugs. Orally administered drugs are formulated as immediate-release preparations or more sophisticated modified-release (MR) systems. On passage down the gut, an oral MR product will be exposed to a diverse array of conditions such as surface area (and associated absorptive and efflux mechanisms), pH, bacteria, intestinal pressure, transit time and fluid content. These factors vary from one individual to another and also within the same individual and are also affected by food. This makes oral delivery a challenging proposition, particularly for MR products.

The purpose of this presentation is to provide an overview of the tools that are available to investigate the in vivo behaviour of coated MR dosage forms. These techniques include gamma scintigraphy, capsule endoscopy and pH radiotelemetry. In isolation or combination, these non-invasive techniques provide a powerful approach to understand of the effect of gastrointestinal physiology on MR dosage form performance. Such in vivo human data can be used to develop more meaningful in vitro release tests, which at present are normally based on non-physiological parameters and methodology.

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Personalised medicine: decades away?

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In September 2005, the UK Royal Society has published a report entitled "*Personalised medicines: hopes and realities*" (The Royal Society, September 2005; ISBN 0 85403 620 2). The report concluded that while there were no doubts about the scientific feasibility of the concept of personalised medicine, its implementation is still 'decades away' from reaching the clinical setting. Unfortunately, it was mostly this latter statement which was picked-up by the general media, including the BBC, which heralded its report with the gloomy headline of "*Personalised drugs 'decades away*'" and stated on their web-site that "individually tailored medicines have been "over hyped" and are still many years away". We would like to voice some reservations to this dismal view. Indeed, substantial clinical research, as well as regulatory amendments, healthcare policy adjustments, and ethical guidance are still needed before personalised medicine can become an integral part of standard medical care. Yet, we feel that this pessimistic interpretation by the media is unwarranted. In particular, it is realistic to expect that some recently acquired knowledge on the pharmacogenetics of drug metabolizing enzymes (DMEs), such as the Cytochrome P-450 and UDP-glucoronyltranferase families, could be put to good use much sooner than 'decades away' – hopefully within ten years or so. Rather than expecting rapid implementation in our capacity to tailor novel drugs for patient sub-populations, we can – and should – apply safer and more efficacious pharmacotherapy by better refinement of drug dosage regimens according to the patients' DMEs genomic information.

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Pharmaceutical co-crystals: do they represent a new path to improved medicines?

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The field of crystal engineering (Moulton & Zaworotko 2001; Zaworotko 2001) has evolved in such a way that it has become synonymous with supramolecular synthesis (Desiraju 1995). In the context of pharmaceuticals, it is salient that crystal engineering focuses upon self-assembly of existing molecules or ions and that a wide range of new compounds can be generated without the need to invoke covalent bond breakage or formation. This presentation will be organized as follows: a general introduction to the when, how and why of crystal engineering and supramolecular synthesis, including an overview of the importance of crystal engineering to areas as diverse as nanochemistry, solvent-free synthesis (green chemistry), materials chemistry. The presentation will emphasize how self-assembly of carboxylic acids, primary amides and alcohols can manifest itself in crystalline solids through formation of polymorphs and pharmaceutical co-crystals. Pharmaceuticals are perhaps the most valuable materials known to mankind and there are important intellectual property, regulatory and efficacy implications if one is able to discover new compositions of matter for active pharmaceutical ingredients (API's). Emphasis will be placed pharmaceutical co-crystals, a long known but little unexplored alternative to the three accepted forms of API (polymorphs, solvates, salts). The presentation will detail how one can design and generate novel pharmaceutical co-crystal phases that contain one or more API's. Examples to be presented will include well-known API's such as aspirin (Fleischman et al 2003a), ibuprofen (Fleischman et al 2003a), carbamazepine (Fleischman et al 2003b) and piracetam (Vishweshwar et al 2005a). We shall conclude by addressing the relative stability of co-crystal phases and their tendency to exhibit or promote polymorphism (Almarsson & Saworotko 2004; Vishweshwar et al 2005b; Bis et al 2006).

Almarsson, Ö., Zaworotko, M. J. (2004) *Chem. Commun*., 1889–1896
Bis, J. A. et al (2006) *Crystal Growth Design* **6**: 1048–1053
Desiraju, G. R. (1995) A*ngew. Chem., Int. Ed. Engl*. **34**: 2311–2327
Fleischman, S. et al (2003a) *Chem. Commun*. 186–187
Fleischman, S. G. et al (2003b) *Crystal Growth Design* **3**: 909–919
Moulton, B., Zaworotko, M. J. (2001) *Chem. Rev*. **101**: 1629–1658
Vishweshwar, P. et al (2005a) *Chem. Commun*. 4601–4603
Vishweshwar, P. et al (2005b) *J. Am. Chem. Soc*. **127**: 16802–16803
Zaworotko, M. J. (2001) *Chem. Commun*. 1–9

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Engineering formulation-ready active pharmaceutical ingredients: myth or reality?

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The role of the physicochemical properties of active pharmaceutical ingredients (APIs) in formulation design and process robustness is a topic of frequent discussion within the Pharmaceutical Industry. The ultimate objective is to engineer "formulation-ready" API either through controlled crystallization or down-stream processing. The challenges associated with the development of crystallisation processes for APIs are well documented. A range of tools is now available to the crystallization scientist to help address some of the key issues around process development, enabling the acquisition of crucial data early on in development, where material can be scarce and resource constrained. This presentation describes an approach to crystallization development in an industrial pharmaceutical environment, with an intention to review approaches and challenges in particle engineering. Early work focuses on the evaluation of solid form properties including solubilities and some mechanical properties. This provides an indication of typical crystal sizes and morphologies, and highlights – where appropriate – whether any processing is required pre-formulation. The majority of APIs are manufactured through batch crystallization. Following on from solubility measurements, trial experiments are carried out, typically using statistical design of experiments (DoE), to scope out the best crystallisation approach and sketch the range of physical properties associated with variations in the crystallization process parameters. Where possible, API with a range of physical properties (produced during these trials) is progressed through various downstream processes to evaluate the robustness of these to changes in API

properties. Process Analytical Technology (PAT) also plays an important role in our pursuit of data-rich experiments. Focused Beam Reflectance Measurement (FBRM) is a well-established technique for the capture of changes in the number of particles and their size throughout crystallization processes, tracking down nucleation, growth, agglomeration and attrition. At a smaller scale, turbidity measurements can be used in a high-throughput fashion to either aid solvent selection or populate solubility/metastable zone edge curves. Probe-based NIR- and Raman spectroscopies can be used to track polymorph changes, and in addition, substantial progress in the field of real-time image analysis has been achieved in recent years. Scale-up of crystallization processes is also an active area of research, and typically a combination of 1-Litre scale experimentation and computational fluid dynamics (CFD) is employed to predict large scale behaviour. API manufacturers are also actively considering the advantages of non-batch crystallization, and this presentation will briefly discuss progress in this area.

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The need for constant renewal of the antibacterial armamentarium

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The introduction of penicillin into clinical practice in 1943 heralded the dawn of the antibiotic era and rapid advances in the discovery and development of new antibacterial drugs gave rise to the hope that infectious diseases, particularly severe bacterial infections, would be banished to the "dustbin of history". This initial widespread optimism has proven to be premature and major changes in the pattern of infectious disease over the ensuing decades, socio-cultural change and political and economic upheaval have all contributed to a situation where infections remain the second leading cause of mortality worldwide and the major killer in the developing world. The biggest threat, however, to our continued ability to successfully treat a wide range of bacterial infections is posed by the emergence of multi-drug-resistant bacteria. These problematical infectious agents, which initially appeared in hospitals but are increasingly associated with community-acquired infection, have underlined the need for novel antibacterial agents with modes of action different to those possessed by current antibiotics. Unfortunately, at this time of need, there has been a sharp reduction in R&D activity in this therapeutic area. The major pharmaceutical companies, in particular, are perceived to be pulling out of antibiotic development to concentrate on treatments for chronic illness and lifestyle conditions. The number of antibiotic agents approved since the early 1980s has been in steep decline, some recent successes notwithstanding, and the industry has almost certainly exhausted traditional routes of product development such as chemical derivatisation of established structures such as β-lactams and aminoglycosides. I will discuss new paradigms for the development of antibacterial agents that move away from complete reliance on industry-based R&D.

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New targets for antibacterial drug discovery

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The introduction of antibiotics for the chemotherapy of bacterial infections has been one of the most important medical achievements of the past 50 years. However, the emergence of bacterial resistance to antibiotics undermines the therapeutic utility of existing agents, creating a requirement for the discovery of new antibacterial drugs. Several drug discovery strategies have emerged, including incremental improvements to existing antibiotics by chemical manipulation and the search for novel drug targets based on genomic approaches. An alternative strategy seeks to exploit opportunities for drug discovery arising from an understanding of the mode of action of existing antibiotics. Thus biochemical pathways or processes inhibited by antibiotics already in clinical use may nevertheless contain key functions that represent unexploited targets for further drug discovery. Until the beginning of the 1990s the discovery of new antimicrobial drugs relied almost exclusively upon empirical screening programmes to identify antibacterial agents by their ability to inhibit bacterial growth. An additional dimension to this so-called "classical approach" has involved incremental improvements to earlier antimicrobial agents that were themselves discovered by empirical screening. Although classical drug discovery and incremental improvement approaches are still being utilised, new superior genomic based methods are beginning to deliver novel antimicrobial leads that may become the next generation of antibiotics. Paradoxically, at a time when unmet medical needs are growing, many large Pharmaceutical Companies are withdrawing from research on new antibiotics and smaller companies are becoming more involved. Drug development programmes, from both large pharmaceutical firms and smaller biotech companies, are currently in various stages of development encompassing a diverse range of molecular targets involved with cell wall synthesis, nucleotide metabolism, replication, translation/transcription and many more. These programmes in combination with industrial and academic research on essential genes of unknown function show the number of potential target sites is not the precluding factor in the development of novel antibiotics. However many compounds fail in hit to lead development due to factors such as unfavourable toxicity, bioavailability, drug stability or resistance profiles and failure to convert cell-free enzyme activity to whole-cell penetration and killing.

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Changing needs of antibacterial chemotherapy in relation to emerging drug resistance

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Bacteria resistant to most available antibiotics are an increasing problem, especially in hospitals. Despite intensive efforts by the pharmaceutical industry and the availability of new, expensive tools, such as genomic sequencing, combinatorial libraries of chemicals, and high throughput screening, few new antibiotics have been discovered in the last 30 years so alternative approaches are now being investigated.

Phage therapy was first developed early in the last century and has been used extensively in certain countries such as Georgia ever since. The success of antibiotics in the post-war years reduced interest in phage therapy in western countries but this has now started to change with a clinical trial in Germany of phage therapy on infected chronic wounds.

The last step in phage infection is the release of mature phage particles by hydrolysis from within of the bacterial cell wall. This process is mediated by phage-encoded murein-degrading enzymes (glucosaminidases, amidases or endopeptidases) that in some cases exhibit bactericidal activity as purified proteins when added from the outside of the cell, and have been termed enzybiotics. There is good evidence of the activity of enzybiotics in animal models.

Lysostaphin was first described in 1964 and, although not phage-encoded, is an endopeptidase enzybiotic that has completed Phase I and II clinical trials. Lysostaphin rapidly kills *Staphylococcus aureus*, including MRSA, by attacking the pentaglycine crossbridge that is present in the cell wall and is intended for use as a nasal cream by Biosynexus in the USA. In the laboratory, resistance occurs by a shortening of the pentaglycine cross-bridge but this is associated with sensitivity to beta-lactam antibiotics. Lysostaphin-producing cells are resistant due to incorporation of serine residues in the pentaglycine cross-bridge, a resistance mechanism that could spread rapidly on large scale clinical use of this agent but may be overcome.

There are significant problems to be solved before phage therapy and enzybiotics can be introduced clinically but the potential of this technology will be reviewed.

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The Novartis Institute for Tropical Diseases: drug discovery for neglected diseases

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The Novartis Institute for Tropical Diseases (NITD) is a drug discovery research institute dedicated to finding new drugs for the treatment of tropical diseases. The NITD is one of Novartis' contribution to help reduce the global disease burden, and contribute to the solution of the problem of access to medicines to poor patients.
The NITD is set up as a public-private partnership between Novartis and the Singapore Economic Development Board. Its current research projects are mainly focused on Dengue fever and Tuberculosis. However, the institute will extend its research efforts on malaria starting from 2007. The NITD performs basic and conceptual research for identification of targets, develop screening assays, and work on synthesis and optimization of compounds up to readiness for clinical testing.

The NITD intends to become a leading center for knowledge and education by offering exceptional teaching and training opportunities for biomedical scientists in the world and by transferring Novartis' drug discovery know-how to the developing world. Furthermore, the NITD promotes strong partnerships with other institutions and universities on a global scale to leverage its research efforts to bring novel attractive compounds to patients by 2012.

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Steps across borders! What do creativity, intelligence and responsibility have in common?
OR
Historical and current considerations about the socio-political responsibility of science

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At scientific meetings and academic jubilees, results and achievements are always praised but responsibility is seldom discussed. Nevertheless, we know that to be a sound scientist requires more than being able to deliver research results and to teach the subject. Especially those of us located in central Europe should know something about the traps of over-emphasising scientific achievements (Hartshorne, 1937; Kaufmann 2000; Deichmann 2002). Although the autonomy of our universities and research institutions in Europe are no longer endangered in a political sense, they exist today in a turbulent atmosphere, driven by absurd saving plans, sometimes bizarre elitism and influenced by evaluation games and over-bureaucracy. And there is one more problem, surely at the heart of the matter: it is difficult for our universities to avoid being pulled into the only profit-driven speculations of the Neo-liberalism with the sometimes brutally acting stock market as its accomplice. The "absolute open-market economy" and "laissez-faire capitalism" regard research and responsibility only as a money oriented short term amusement for our Fun-Society (Hofmeister & Banerochse 2001). Certainly competition and world-wide activities do change our local situations but many negative economic developments cannot simply be justified by the slogan of globalization (Chomsky 2001; Deans, & Kröger 2002; Stiglitz 2002; Soros 2003). What is the intrinsic value and meaning of knowledge? This question is nowadays often replaced by the question of what type of knowledge do we need to fulfil predetermined functions. This increasing misuse of science (i.e. its transformation to mainly develop and support technology often for purely stock market effects) threatens to destroy its critical, purely truth-oriented function. The increasing connection between KNOWLEDGE and INTEREST — first discussed socio-critically by the german philosopher Jürgen Habermas (Habermas 1968, 1973) — seems to have become the norm to such an extent that the value of science is endangered to vanish in goals and reasons defined outside science: "Truth is what is useful." Does this not demand a response from our universities and research institutions? Where is all this taking us? We are in a transition state: in Europe we are under pressure to restructure our shaking Industrial Societies into Knowledge Based Societies! Because we cannot keep the basic industrial production in our developed countries, knowledge, originality, and richness of ideas are more in demand than ever for further developments. Thus, we need a science education system that is able to nurture creativity, and an uncomplicated fast and open exchange of scientific and technological aspects with industry. We cannot allow our universities to be instrumentalized: neither politically — as in the Third Reich — nor now political-economically (e.g. by "laissez-faire capitalism"). We are all responsible together for what is to come (Popper 1999). What is to come? "The best way to predict the future is to invent it" (Reynman 1965): independent universities and research institutions are a prerequisite for the education of creative, courageous, nonaligned scientists, willing to accept their responsibility as citizens and as professionals. (But isn't every professional a responsible citizen anyhow? Yes, but see the first sentence of this abstract! Too often we scientists exchange our "citizen jacket" against our "lab-coat" as soon as we enter our laboratories and offices.)

Hartshorne, E. Y. (1037) *The German Universities and National Socialism*. London: Unwin Ltd. 1937
Deichmann, U. (2002) *Angew. Chem. Int. Ed.* **41**: 1310–1328
Kaufmann, D. (2000) "*Das Blut von Auschwitz und das Schweigen der Gelehrten", S. 189–226 in Band I der Geschichte der Kaiser-Wilhelm-Gesellschaft im Nationalsozialismus. Bestandsaufnahme und Perspektiven der Forschung*. Two volumes ordered by the Max Planck-Society, Wallstein Verlag
Hofmeister, K., Banerochse, L. (Hrsg.) *Machtworte des Zeitgeistes*. Würzburg: Echter Verlag
Chomsky, N. (2001) *Profit over people*. Hamburg: Europa Verlag, 6. Aufl.
Soros, G. (2003) *The bubble of American supremacy*. NY: Public Affairs
Deans, G. D., Kröger, F. (2002) *Merger Endgames – Strategien für die Konsolidierungswelle, St. Zeisel*. Wiesbaden: Gabler Verlag
Stiglitz, J. (2002) *Globalization and its discontents*. New York: W. W. Norton Comp.
Habermas, J. (1968) *Technik und Wissenschaft als Ideologie*. Frankfurt: Edit. Suhrkamp
Habermas, J. *Erkenntnis und Interesse*. Frankfurt: Edit. Suhrkamp
Popper, K. (1999) *Alles Leben ist Problemlösen. Über Erkennen, Geschichte und Politik*. München: Piper Verlag
Feynman, R. (1965) A quote of Richard Feynman, Physic Nobel Prize 1965

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Mechanistic understanding of mucoadhesive principals for polymeric materials

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Mucoadhesion is said to occur when two surfaces, one of which is a mucous membrane, adhere to each other. This has been of interest in the pharmaceutical sciences to enhance localised drug delivery, or to deliver 'difficult' molecules (especially proteins and oligonucleotides) into the systemic circulation. Most mucoadhesive materials described in the literature are hydrophilic macromolecules containing numerous hydrogen bond forming groups; carbomers and chitosans being two of the best known examples (Smart 2005a). The mechanism by which mucoadhesion takes place, when applied in formulations with low moisture contents, is said to be by a two stage process. The first is the contact (wetting or adsorption) stage, followed by the second consolidation stage (establishment of adhesive interactions). The relative importance of each stage will depend on the individual application. For example, adsorption is a key stage if the dosage form cannot be applied directly to the mucosa of interest, while consolidation is important if the formulation is large and exposed to significant dislodging stresses. Adhesive joint failure will inevitably occur, either by overhydration of a dosage form, failure of the mucus layer or epithelial or mucus turnover. The retention of aqueous gels and liquids on mucous membranes has also been described as mucoadhesion, although retention is our preferred term. Here, the formulation rheology, ability to 'wet' the mucous membrane and interaction with the biological milieu will affect its retention. Deposition of macromolecules onto mucosal surfaces from solution, in a similar fashion to the way that mucin glycoproteins adsorb on to epithelial cells in the eye and mouth has also been described as mucoadhesion (Smart 2005b). All larger polymers tend to adsorb onto surfaces due to interfacial phenomena and the ability to form a range of weak co-operative bonds. The presence of functional groups (such as amine or carboxyl groups) favours this process. New mucoadhesive materials with optimal adhesive properties are now being developed. One method involved adding thiol groups to existing bioadhesives that can in-situ interact with each other and the cell surface/mucus gel by the formation of disulphide bonds. Other examples include: the incorporation of ethyl hexyl acrylate into a copolymer with acrylic acid in order to produce a more hydrophobic and plasticized system; the use of poloxomers that show phase transition from liquids to adhesive gels at body temperature and will therefore allow in-situ gelation at the site of interest; the chemical combination of pluronics with poly(acrylic acid)s to produce systems with enhanced adhesion; and the use of dihydroxyphenylalanine (DOPA), an amino acid found in mussel adhesive protein that is said to lend to the adhesive process. The generation of new therapeutic products from the 'new biology' has led to a renewed interest in mucoadhesion, although the potential of this technology is still to be fully exploited.

Smart, J. D. (2005a) *Expert Opin. Drug Deliv*. **2**: 507–517
Smart, J. D. (2005b) *Adv. Drug Deliv Rev*. **57**: 1556–1568

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Carbohydrate-based therapeutics

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There has recently been a resurgence of interest in the biological roles of carbohydrates (Bertozzi & Pratt 2005). Thus, while carbohydrates were traditionally considered to be of importance as energy sources, and as skeletal components, recent advances in analytical techniques have now suggested that carbohydrates are involved in a wider range of biological processes, including cell recognition and cell differentiation processes, and cell-external agent interactions. Carbohydrates are found on the surfaces of all cells, and as each type of cell displays different carbohydrates this allows the cell surface carbohydrates to act as distinguishing markers for each cell type. Carbohydrates of even short sequences are used for carrying biological information, for example, the human blood groups are differentiated by relatively simple changes in oligosaccharide structure. Interactions between carbohydrates and lectins (carbohydrate binding proteins) can initiate beneficial biological events, such as immune responses and cell growth and differentiation events (e.g. during embryogenesis), as well as detrimental disease processes, such as inflammation, viral and bacterial infections, and cancer metastasis. By deciphering the roles carbohydrates play within both natural and disease pathways it has proved possible to identify new opportunities for the development of carbohydrate-based therapeutics of interest for treating a wide range of diseases. This presentation will provide an overview of the roles of

carbohydrates in disease processes (Evans et al 2004; Seeberger & Werz 2005; Doones et al 2006) and will detail research projects that are currently ongoing within our laboratories for the synthesis of carbohydrates of biological and therapeutic interest (Osborn 2005). Thus the roles of carbohydrates within cancer, viral and bacterial infections will be outlined, and examples of carbohydrate-based therapeutics that offer potential for treating specific diseases will be discussed. In particular, the synthesis and analysis of glycopolymers of use for probing the specificity of binding of different strains of the influenza virus, anti-infective agents of interest for treating bacterial infections caused by *Enterobacter sakazakii*, and inhibitors of glycosidase enzymes, which are involved in the synthesis of cancer associated carbohydrates, will be described.

Bertozzi, C. R., Pratt, M. R. (2005) *Chem. Soc. Rev*. **34**: 58–68
Doones, K. J. et al (2006) *Chem : Eur. J*. **12**: 656–665
Evans, P. G. et al (2004) *J. Pharm. Pharmacol*. **56**: 691–702
Osborn, H. M. I. (2005) *Synlett* **17**: 2571–2587
Seeberger, P. H., Werz, D. B. (2005) *Nature Rev. Drug Discov*. **4**: 751–763

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One for all and all for one: true for phytopharmaceuticals?

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Medicinal substances do not affect everyone to the same extent and the range of pharmaceuticals available to treat a condition may not all be necessary in a particular condition. In recent years this has become a matter of much debate and interest with the introduction of the concept of individualized pharmacotherapy. This may be new in Western medicine but is common in most established traditions where plants are used as therapeutic agents. In these situations, the agents selected are prescribed as part of a more comprehensive and holistic examination of the patient. The extreme reductionism of many treatments in 'orthodox' medicine does not take into account the variations that can exist in a defined disease state, the patient and in the nature and relative amounts of compounds present in plant material used. The same symptoms displayed in a patient can be due to one or more of a number of different underlying factors so medicines given for symptomatic relief may give only a transient relief. Although not always based on objective scientific research, a skilled practitioner may be able to choose effective herbs through experience and the mechanism responsible may be elucidated only subsequently. There are many differences between human populations, which may determine that one drug or herb is not always the best for a particular person. These differences may be intrinsic and connected with gender and genotype, or they may be extrinsic and caused by factors such as environment, occupation and concurrent medication. With phytopharmaceuticals, a third dimension exists, which is generally not so important with single chemical entity drugs. Much variation can occur in the plant material because of its genetics, growing and harvesting conditions, collection, storage and preparation. All of these can have a great effect on efficacy and toxicity. These points will be illustrated by examples from the use of plant materials and products in Western and other cultural forms of herbal medicine.

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Herbal medicines and bone health

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Osteoporosis, a disease characterized by low bone mass and deterioration of the micro-architecture of bone tissue, leading to increased fractures, occurs most commonly in post-menopausal women and patients on long-term oral corticosteroids. It is more prevalent in Asian and Caucasian women, and other genetic factors are important in its pathogenesis: family studies suggest that these account for 70–85% of individual variance in bone mass. Most current anti-osteoporotic drugs (e.g. bisphosphonates) inhibit bone resorption, leading to an increase in bone mineral density (BMD), but may have serious adverse effects. Some natural products, such as herbs and salad vegetables, inhibit bone resorption, but little is known of their effects on bone formation. This is a multifactorial process that is difficult to recreate in vitro, but by using the calcifying fibroblastic-colony forming unit assay (CFU-f) in combination with an established bone organ culture assay, it is possible to identify most agents known to have bone anabolic activity (Miao & Scutt 1998). We have screened several traditional herbal medicines, reputed to aid bone healing, for their ability to stimulate colony formation in the CFU-f assay. One of these, the stem of *Cissus quadrangularis* (traditionally known as 'Bone Setter'), was toxic at high concentrations, but *Cestrum diurnum* leaf and *Zingiber officinalis* (ginger) rhizome showed promising activity. *Cestrum* produced a significant increase in the proportion of alkaline phosphatase positive colonies at 0.1, 1 and 10 μg/ml and then was toxic at 100 μg/ml, which is a typical profile for an agent that stimulates osteoblastic differentiation and very similar to that seen with 1,25-dihydroxyvitamin D_3. This plant causes calcinosis in grazing animals and has been reported to contain a glycoside of 1,25-dihydroxyvitamin D_3 (Hughes et al 1977); it may therefore show potential in cases of vitamin D deficiency. Ginger also stimulated the proportion of alkaline phosphatase positive colonies at 0.1 μg/ml, followed by a progressive dose-related decrease in colony number. This reduction followed the log of the concentration suggesting a receptor mediated event and not simple toxicity. The remaining herbs tested were devoid of activity. Other food supplements and herbal medicines which claim to enhance BMD (Putnam et al 2006) will be described in the presentation, and their suitability for therapeutic use and evidence for efficacy discussed.

Miao, D., Scutt, A. (1998) *J. Bone Miner. Res*. **23**: S537
Hughes, M. R. et al (1977) *Nature* **268**: 347–349
Putnam, S. E. et al (2006) *Phytother. Res*. In press

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Targeting intestinal epithelial tight junctions: an open and shut case

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Tight Junction (TJ) structures play several critical roles in the normal structure and function of epithelial barriers, including those of the gastrointestinal tract. Of particular interest for the pharmaceutical industry are efforts to understand the complexities of the TJ to the extent that they might be manipulated to increase the intestinal uptake of therapeutic proteins and peptide drugs. Studies from several laboratories have now defined many of the critical TJ components. Currently, efforts are underway to better define how these TJ components are organized to produce the unique barrier properties that define the intestinal epithelium and to better understand factors that regulate the function of these components. Importantly, it is well-established that TJ structures of the intestinal epithelium are dynamic, a feature essential for the normal repair of any epithelia that turns over rapidly and which can be insulted by ingested compounds and pathogens. Examination of normal mechanisms of TJ opening and closing have led to the discovery of several paradigms: TJ protein components can signal the presence and status of TJ structures; the function of TJ protein components can respond to changes in phosphorylation events; and a variety of intestinal pathologies correlate with diminished chronic dysfunction of TJ structures. Application of materials and agents that regulate TJ opening and closing are now being examined not only for the potential oral delivery of therapeutic protein and peptide drugs but also in the treatment of intestinal conditions where TJ dysfunction can be corrected to reverse a pathological state.

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A new approach to deliver drugs across the blood-brain barrier

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Many brain diseases (such as multiple sclerosis, stroke, brain tumors, epileptic seizures, meningitis, Alzheimer's disease, AIDS related dementia, Parkinson's disease) are undertreated or cannot be treated at all. Limited blood-brain barrier (BBB) passage of most CNS-active biopharmaceutical drugs presents a problem. A possible solution is receptor-mediated drug delivery/targeting of biopharmaceuticals including enzymes, RNAi and genes, by a non-viral technology comprising a carrier molecule that fits to the receptor. Recently, we have identified a novel human applicable carrier protein (known as CRM197) for the delivery of conjugated proteins across the blood-brain barrier. Uniquely, CRM197 has already been used as a safe and effective carrier protein in human vaccines for a long time and recently also systemically in anti-cancer trials. This has resulted in the accumulation of a large body of knowledge on the carrier protein, including its transport receptor and mechanism of action, receptor binding domain, conjugation and manufacturing process, and kinetic and safety profile both in animals and man. We have found that CRM197 can deliver biopharmaceuticals across the blood-brain barrier by a well-characterized, safe and effective mechanism called receptor-mediated transcytosis. From literature (Raab & Klagsbrun 1997) it was already known that CRM197 uses the membrane-bound precursor of heparin-binding epidermal growth factor (HB-EGF) as its transport

receptor. This precursor is also known as the diphtheria toxin receptor (DTR). In fact, CRM197 is a non-toxic mutant of diphtheria toxin. Membrane bound HB-EGF is constitutively expressed on the blood-brain barrier, neurons and glial cells. Moreover, HB-EGF expression is strongly up-regulated on the cerebral blood vessels in diseases with inflammatory events like Alzheimer, Parkinson, MS, stroke/ischemia, tumours, seizures, encephalitis. This will provide disease induced drug targeting to the brain. Research sofar has shown in-vitro and in-vivo (animals) proof of principle for the transport of biopharmaceuticals across the BBB (Gaillard et al 2005a,b). Overall, the CRM197 carrier protein as a novel brain drug delivery technology holds out a great promise, especially since CRM197 is already safely applied to man, where other technologies involve potential safety hazards in human application.

Gaillard, P. J. et al (2005a) *Exp. Opin. Drug Deliv*. **2**: 299–309
Gaillard, P. J. et al (2005b) *Int. Congres Series* **1277**:185–195
Raab, G., Klagsbrun, M. (1997) *Biochim. Biophys. Acta* **1333**: F179–F199

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Personalised herbal medicine in the management of cancer: benefits and potential risks

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The use of complementary alternative medicines (CAMs) in cancer patients is well documented, but their effectiveness is often not established. They may be less harmless than commonly assumed and can interfere with conventional therapies. In the first part of this presentation, CAMs commonly encountered in oncology practice will be reviewed. They can be divided into the following categories: single or combined anti-carcinogenic remedies, anti-carcinogenics and immunostimulants, antioxidants, remedies with endocrine properties, psychoactive remedies, and other remedies used by cancer patients. Many of the potential side effects and interactions described are based on hypothesis about pharmacokinetic and pharmacodynamic properties, which frequently have only be demonstrated in vitro, but could have significant clinical implications if found in vivo. Particularly, the potential for interactions with the cytochrome P 450 system and the p-glycoprotein pump for drug interactions can be significant. The second part of this presentation will explore psychological aspects of CAM use and the implications for clinical practice. Clinicians need to be aware of CAM-induced side effects or interactions and should be able to identify hazards, advising patients accordingly and avoiding uncritical encouragement of potentially harmful use. Ignorance in this area, given the independent usage of CAMs, may lead to criticism and possibly litigation. Equally, patients should be encouraged to disclose information about CAMs to health care professionals. Such discussions need to be conducted sensitively to avoid alienating patients who may feel that they have not been taken seriously or have been criticised for using CAMs. Challenges and potential pitfalls based on cognitive-behavioural principles under consideration of different personality profiles will be discussed. A communication style combining educational elements with strategies to explore patients' potential anxieties and to maximise their sense of self-determination and control is proposed.

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Remembering the past: the history of sage from the 1st to the 17th century

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Personalizing medicine requires an appreciation for the increasing interest and demand for herbal medicine. Patients expect therapeutically useful, individualized treatment, and the outcome of treatment depends in part on how practitioners respond to patients' needs and feelings. Herbal Medical Products (HMPs) are consumed along or in place of standard medical treatments, and health care practitioners should be aware of the possible advantages and risks of such treatments including potential interactions with chemically defined medicines. Simultaneously, there is a renewed interest in the potential of using ancient texts as ethnobotanical sources. They are an important research tool documenting traditional uses of plants through the centuries, and can be a very helpful instrument to understand a species' current use and their future trends. By surveying ancient herbals and secondary sources from the 1st until the 17th century, we studied the historical development of sage (*Salvia officinalis* L. and closely related species, such as *S. lavandulifolia* Vahl or *S. fruticosa* Mill), one of the most relevant European medicinal plants. Although they differ in their chemical composition, they have been used indifferently and dispensed as sage. Historically, *S. fruticosa* and *S. officinalis* have been cultivated, although nowadays *S. fruticosa* and *S. lavandulifolia* are mainly gathered from the wild (Eastern and Western Mediterranean, respectively). In Europe where it has been considered a panacea, sage has been a celebrated medicinal plant since earliest times. Its Latin name *Salvia* derives from *salvare*, to save, in reference to its curative properties. Hippokrates, Theophrastus and Dioscorides refer to their wonderful properties and in the Middle Ages it was an essential element of monastery gardens. On the other hand, in historical Arabic medicine it seems to be of limited importance at least under cognate names of *salvia*, or *salima*, its Arab-translated name. In Europe, the range of traditional applications is endless. It has been used as a medication against respiratory disorders, as a carminative, an antiseptic, for healing wounds, in skin and hair care and many other complaints as well as a food seasoning. Today, it is still commonly used as a domestic medicine for a variety of purposes, although due to the toxic effects of camphor and thujone, major components of *S. officinalis*, its use has been restricted (Kintzios 2002). Specifically, there is renewed interest in sage due to its effects against Alzheimer's disease (Perry et al 2001). It has shown strong antioxidant properties and acetylcholinesterase-inhibitory effects. Interestingly, long before the mechanism of the CNS was understood, sage was used to treat CNS related disorders. Most early English herbals (e.g. Gerarde 1633) make reference to such uses while these properties are neither mentioned by the classic Greek authors nor by many Renaissance herbals. In conclusion, the historical study of the medicinal uses of sage demonstrates the potential of using historical texts to contextualize the demand for 'personalized medicines' and may also offer ideas for novel therapeutic uses of this important European medicinal plant.

Gerarde, J. (1633). *The herball or general historie of plantes*. London: A. Islip, J. Norton & R. Whitackers
Kintzios, S. E. (2002) *Sage. The genus* Salvia. Boca Raton: CRC
Perry, N. S. L et al. (2001) *J Pharm. Pharmacol*. **53**: 1347–1356

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Personalized Ayurvedic medicines: science meets traditional practice

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The Indian subcontinent, with one of the oldest civilizations, harbours many traditional healthcare systems. Ayurveda, with a history that goes back to 5000 B.C., is one of the ancient healthcare systems. Ayurveda was developed through daily life experiences with the mutual relationship between humans and nature. The knowledge on use of natural resources for healthcare is transmitted from generation to generation and also noted in ancient texts like "Sushrut Samhita", Charak Samhita", "Nakul Smhita" etc. Development of this traditional system of medicines with a perspectives on safety, efficacy and quality, will not only help to preserve this traditional heritage, but also help to rationalize the use of natural products in health-care (Mukherjee 2002). Ayurveda is a holistic system of medicines where functional principle is based on "Tridosh" theory – Vata, Pitta and Kapha; any imbalance or disturbance in these basic principles of body causes disease. Various methods of treatments including "Panchakarma" and allied therapy are known for developing personalized medication from Ayurveda, based on individual disease condition. Due to certain inimical interferences with the Indian system of medicine (ISM) over the centuries, a need has arisen to unify the entire system and codify it. In this context, laying down the standards of Ayurvedic drugs is of paramount importance. This is more so because these days the Ayurvedic drugs increasingly come from the industry rather than the Ayurvedic physician compounding them impromptu (Khan & Balick 2001; Mukherjee & Wahile 2006). For assuring the therapeutic efficacy, safety and to rationalize their use in healthcare, quality control of Ayurvedic medicine is very important parameter. To achieve those in personalized traditional medicine, the traditional methods are procured, studied, documented and then the traditional information about identification and quality assessment is interpreted properly in terms of modern assessment. The marker compound analyses may play an important role in the quality control and standardization of traditional medicinal formulations, where the concentration of the secondary metabolites can provide valued standardization procedures. This technique not only helps in establishing the correct botanical identity but also helps in regulating the chemical sanctity of the herbs and also may be useful in the validation of dose of traditional formulation. Integrated approaches for drug development from traditional medicines can lead to better Ayurvedic products, improved understanding on their mechanism of action, modified compositions at molecular level and better understanding of interactions among various molecules for their synergy or adverse reaction. Thus, development of the Ayurvedic and other traditional Indian Systems of Medicine may help to tap the traditional ethnopharmacological knowledge through modern approaches.

Khan, S., Balick, M. J. (2001) *J. Altern. Complement. Med*. **7**: 405–515
Mukherjee, P. K. (2002) *Drug Information J*. **63**: 635–644
Mukherjee, P. K., Wahile, A. (2006) *J. Ethnopharmacol*. **103**: 25–35

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Pulmonary delivery of nucleic acid derived therapies

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The development of effective gene therapy aerosol formulations is an important goal due to the non-invasive ease of access of DNA to a vast localised surface area of tissue and pre-conceived patient acceptance of inhaled drug delivery. A host of pulmonary conditions could potentially benefit from this approach, including cystic fibrosis (CF), lung cancer and potentially chronic diseases such as asthma. Respiratory delivery of genes not only obviates any potential adverse consequences of non-localised administration (e.g. intravenous), but conversely offers an opportunity to exploit epithelial cells of the lung to produce, and transfer to the circulation and other tissues, therapeutic gene products such as hormones and enzymes. To assist DNA interaction with, and gene processing within, lung cells synthetic non-viral gene delivery agents offer substantial advantages over viral systems, as they are less immunogenic, potentially permitting repeated delivery. The gene delivery scientist has three basic options for administering non-viral gene vectors to the lung; nebulisation of liquid-suspended gene particles, aerosolisation of dry powders of gene vector with carrier particles or pressurised expulsion of DNA-complex from a propellant dispersion. Jet nebulisation is currently the most exploited method (37 PubMed hits for 'gene therapy' AND 'nebuliser') for introducing synthetic gene vectors into the lung in animal models and in the clinic. Indeed, in the case of CF, nebulisation is the only pulmonary delivery method currently under consideration in the strategic research plan of the UK CF Gene Therapy Consortium. Nebulisation of gene therapy formulations is, however, inefficient; shearing forces, preferential nebulisation of the solute and adhesion to plastic can mean that as little as 10% of DNA in the nebulisation chamber is emitted through the mouthpiece (Birchall et al 2000). These limitations are particularly important to expensive gene transfer pharmaceuticals and also partly explain the limited success of previous CF gene therapy clinical trials. While newer nebuliser technologies and improved vectors are under development, the less commonly investigated dry powder inhaler (DPI; 6 hits for 'gene therapy' AND 'dry powder') and pressurised metered-dose inhaler (pMDI; 3 hits for 'gene therapy' AND 'metered dose') devices may provide advantages including improved stability, rapid administration and ease of transportation. We have gained unique expertise in preparing and characterising spray-dried gene vectors for delivery via DPI (Li et al 2005a, b). For example, a novel DPI formulation comprising trehalose, dimethyl-β-cyclodextrin and a synthetic lipid:polycation:pDNA (LPD) gene vector was found to comprise small (3–4 μm), spherical particles of uneven surface morphology with a low tendency to aggregate. These powders demonstrate excellent stability, gene expression efficiency following 6-months storage comparable with freshly prepared systems, and efficient pulmonary deposition. Currently, we are also developing a novel technology for producing DNA nanoparticles amenable to delivery via pMDI. DNA is loaded into the aqueous pool of a surfactant-stabilised water-in-oil microemulsion. Following removal of water and organic solvent the dimensions of the surfactant-coated nanoparticles and their ability to disperse in hydrofluoroalkane (HFA) propellants allows for the production of stable medicinal aerosols potentially capable of efficient pulmonary delivery by pMDI.

Birchall, J. C. et al (2000) *Int. J. Pharm*. **197**: 221–231
Li, H. Y. et al (2005a) *J. Gene Med*. **7**: 1035–1043
Li, H. Y. et al (2005b) *J. Gene Med*. **7**: 343–353

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Therapeutic biomolecules and key pharmaceutical challenges in developing NBE

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New biological entities (NBE), especially proteins, continue to gain increased market share and represent a growing part in the pharmaceutical industry's portfolio. Proteins are very large, complex and heterogeneous molecules as compared with the traditional small molecules (NCE). NBEs consist of unique amino acid sequences that fold into secondary structure elements (e.g. alpha helices and beta sheets). The tertiary structure is formed by packing such structural elements into globular units (domains). The final protein may contain several polypeptide chains arranged in a quaternary structure. It is this defined three-dimensional structure that is the prerequisite for biological activity. In addition, the heterogeneity is further increased by post-translational modification such as glycosylation. Since this complex and dynamic three-dimensional structure is held together by weak non-covalent forces only, proteins are inherently unstable. They are susceptible to physical degradation (such as adsorption, denaturation, aggregation, precipitation) as well as chemical degradation (such as deamidation and oxidation). Degradation is affected by many different parameters, namely pH, temperature, ionic strength, light, metal ions, oxygen, other excipients, surfaces and shear forces. It is critical that the protein maintains its stability throughout all processes (i.e. during production, storage, transport as well as handling in the clinics), therefore the challenging task of the formulator to understand these degradation pathways and thus design a robust formulation to ensure a high quality drug product. To achieve this, a variety of analytical methods need to be applied. Proteins are easily destroyed and eliminated by the body, therefore the majority of biological products are in either a liquid or freeze-dried formulation for either intraveneous, sub-cutaneous or intra-muscular application. However, a lot of effort and research is ongoing to explore alternative routes of administration for biotherapeutics.

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Delivery technologies for biopharmaceuticals: new challenges and needs

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Addressing the ongoing changes in the development of biopharmaceuticals, and assessing their impact on the selection of effective delivery strategies has been a major challenge for the biotech/pharma industry. In recent years, the growth of biopharmaceutical products approvals has represented one of the most significant trends (Tufts 2005). Recombinant proteins, monoclonal antibodies and peptides have been opening new possibilities for the treatment of many pathologies, such as cancer, neurological, endocrine and autoimmune diseases. Nevertheless, biomolecules present peculiar issues that affect every stage of pharmaceutical development; for instance, physicochemical and biological instability, challenging doses and therapeutic regimens, immunogenicity (Hermeling et al 2004). Newer classes of biopharmaceuticals (Shire et al 2004), and the increasing focus on long term therapies are significantly impacting the "traditional" delivery concepts, essentially limited to the lifecyle management of protein drugs. While this area remains highly relevant, and expanding with the new opportunities of non invasive administration (FDA 2006), the delivery aspects for proteins, peptides and MAbs need often to be considered at early stages of development programs, to allow reliable proof-of-concept studies and significant clinical development, to ultimately increase the possibility for a successful product. Special considerations on the choice of delivery technologies, based on established or innovative formulation and processes, on the physical status modification of the biologic drugs, and on protein conjugation or engineering will be made, briefly analyzing the positive aspects and the main drawbacks of each approach. Case studies focused on the rational development of biopharmaceutical products will be presented. For instance, the use of accessible, characterized excipients such as cyclodextrins (Banga et al 1993; Otzen et al 2002; Del Curto 2005a), will be discussed in late discovery and early development phases of new therapeutic proteins, as well as in the development of injectable hydrogels for controlled release of rh-β-interferon (Del Curto et al 2005b). Also, an overview of the possible delivery approaches for the lifecycle management of this therapeutically and market-relevant protein will be provided, as an example on how to address the unique issues related to biopharmaceuticals development.

Banga, A. K. et al (1993) *J. Drug Target*. **1**: 341–345
Del Curto, M. (2005a) *Pat. Appl. WO2005/058346*
Del Curto et al (2005b) *Pat. Appl. WO2005/110466*
FDA News (2006) http://www.fda.gov/bbs/topics/news/2006/NEW01304.html
Hermeling, S. et al (2004) *Pharm. Res*. **21**: 897–903
Otzen, et al (2002) *Protein Sci*. **11**: 1779–1787
Shire, S. et al (2004) *J. Pharm.Sci*. **93**: 1390–1402
Tufts Center for the Study of Drug Development, Outlook (2005)