The Newsletter for the Society for Medicines Research

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Smoking-related Lung Disease (COPD): Prospects for New Drug Therapy

by Trevor Hansel

This symposium organised by the Society of Medicines Research was held at the National Heart and Lung Institute (NHLI) in Chelsea, London on 14 March 2001. The meeting involved an audience of some 80 participants in a one-day meeting that included eight lectures on novel therapeutics for smoking-related chronic obstructive pulmonary disease (COPD). The three sessions of the meeting were chaired by Professor Clive Page (Sackler Institute of Pulmonary Pharmacology, London), David Cavalla (Arachnova, Cambridge) and Trevor Hansel (NHLI, London).

The meeting first considered compounds in Phase III clinical studies for COPD (tiotropium, Viozan and Cilomilast), before considering reactive oxidant species, proteases and neutrophil chemotactic as therapeutic targets. The final sessions looked at the exciting potential of monoclonal antibodies and retinoids to retard and even reverse the natural history of loss of lung function in COPD.

Overview of COPD

Professor Peter Barnes (Dept of Thoracic Medicine, NHLI) began the meeting by providing an overview of the pathological and immunological basis of COPD. The increasing prevalence of this disease has resulted in an escalating clinical and economic burden. Indeed, in 1990 COPD was the sixth-most-important cause of mortality in the Global Burden of Disease Study, and is projected to be third by 2020. It was noted that the public profile of asthma is very high, despite there being 26,033 deaths from COPD (UK, 1992) compared with only 1,791 deaths from asthma. Yet COPD remains the poor relation when compared to asthma, with a need for more research on why only a minority of subjects develop COPD after prolonged cigarette smoking.

Prof Barnes stressed that COPD and asthma are separate diseases that do not belong to a single spectrum of lung disease, as propounded in an earlier Dutch hypothesis. COPD involves exposure to cigarettes, an inflammatory response involving macrophages, neutrophils and CD8+ T cells, a lack of airways hyper-reactivity (AHR), and a disease that does not respond to steroids. In contrast, asthma is frequently triggered by allergens, viral infections and exercise; has an inflammatory infiltrate of Th_2 cells and eosinophils, has conspicuous AHR and generally responds well to steroids. The anatomical location of COPD involves both destruction of lung parenchyma (emphysema) and inflammation of the small airways (chronic obstructive bronchiolitis). The architecture of the lung is destroyed by proteases (for example, neutrophil elastase and matrix metallo-protease-9 (MMP-9) and reactive oxygen species released from macrophages and neutrophils, as well as by the direct cytotoxic effects of activated CD8+ T cells.

In COPD there is a loss of alveolar function in exerting tension on bronchiolar walls, in the manner of guy ropes upon a tent, contributing to the obstruction of small airways. Assessment of COPD is based first on spirometry, since the classic studies of Fletcher and Peto (1977) have elegantly delineated the accelerated loss in FEV_1 (forced expiratory volume in one second) that occurs in smokers who are susceptible to development of COPD. This is a fixed obstruction that is only partially reversed by inhaled broncho-dilator therapy. A recent development has been the demonstration of abnormalities in induced sputum in COPD compared with healthy smokers — especially elevated levels of IL-8,

(continued on page 6)

Announcing the 2001 SMR Award for Drug Discovery

by Malcolm Duckworth

Every two years, the Society for Medicines Research makes an award to an individual or small group in recognition of outstanding achievement in the extremely challenging field of drug discovery.

The multidisciplinary nature of the achievement is inherent in the award from a Society that places the whole of the research process at the heart of its belief. With members of the Society from all the related disciplines of drug research, we are proud to recognise the successes of others in order to help the individuals and their host institutions gain the reward and kudos they deserve from the pharmaceutical world.

Diabetes research makes new strides

The 2001 SMR Award for Drug Discovery has gone to Dr Michael Cawthorne, Dr Stephen Smith, Dr Barrie Cantello, Mr Richard Hindley and Dr David Haigh for their recognition of the importance of improving insulin sensitivity as an approach to the treatment of Type 2 Diabetes Mellitus, and for their seminal and enabling contributions in the discovery of rosiglitazone (Avandia), which promises to be an innovative new medicine for treating the disease.

While not the first of this new class of thiazolidinediones to reach the market, it was the first to be approved with an acceptable safety profile and has quickly become established as an important new therapy for Type 2 diabetes.

The drug discovery spanned a considerable number of years and many organisational changes, beginning initially in Beecham Pharmaceuticals and continuing in SmithKline Beecham and now, finally, GlaxoSmithKline.•

Improving Medicines through Drug Delivery

by David Cavalla

This one-day conference, organised by the Society for Medicines Research (SMR) dealt with a number of aspects of drug delivery, from inhaled methods for peptides and proteins, to polymer-conjugates for cancer and gene delivery. There are two reasons why drug delivery is becoming an increasingly important aspect in new product R&D in the pharmaceutical industry. First, patient acceptability and compliance are dramatically improved when dosing regimens are more convenient; second, new products are increasingly of biological origin, and larger molecules pose a greater challenge to medicine regarding absorption and distribution. As a result of these factors, drug delivery is becoming more a core technology that often operates alongside earlier aspects of product development.

Drug delivery systems

Dr Harry Ferres started the day with an overview of the value of drug delivery systems, emphasising that this technology, by virtue of its visibility to patients, was one of the more obvious improvements in a medicine. While clearly there had been recent success (such as Pulmozyme™ for cystic fibrosis, Procardia XL for hypertension and liposomal amphotericin for fungal infections), there was also much to do in the future. Dr Ferres posited the 'smart tablet', which will be able to produce tailored pharmaco-kinetics and pharmaco-dynamic effects in individual patients. This is an extension of controlled-release technology that has so far delivered chronopharmaceuticals (for example, Corvas, a night time-release version of verapamil from Schering, expected to be on the market in 2002) and should also deliver cascade release (i.e. natural rhythmic) capabilities. The commercial benefits of an improved pharmaco-kinetic profile should not be underestimated: Cardizem DDS, a simple once-daily form of diltiazem, has sold of over $4 billion after expiry of the native-substance-of-matter patent.

The new technical hurdles that need to be overcome in order to realise this promise are substantial, but technology can be borrowed from other areas of high technology, such as freeze-drying techniques (compare instant coffee), electro-spraying (from inkjet printer cartridges) and 3D printing technology (from the ceramics industry).

Two talks then followed relating to inhaled delivery of proteins and other molecules. Professor John Staniforth (Vectura, UK) introduced this area with a presentation on the challenges of deposition and distribution of drugs through the lung. The aim has always been to target the alveoli and conductive airways of the deep lung with a slow-moving cloud of particles containing the active drug. Prof Staniforth's talk focused largely on the use of powders from dry-powder inhalers. In this respect size matters: the benefit of smaller particles is demonstrated with Inhale's insulin, which is able to deliver up to 60% of the dose into the deep lung compared to around 10% available from the earlier metred dose-inhaler device for Pulmicort™. The technology is being driven by a more controlled regulatory requirement, particularly in terms of dose content uniformity, that would have today posed substantial difficulties for the approval of the Pulmicort dry-powder inhaler.

The main factor that governs the delivery of powders is the particle aerodynamic diameter. Fine powders of 1–2 μm in size have high cohesiveness that causes agglomeration and makes them difficult to separate. This can be controlled by coating the active drug on to a lactose carrier, which improves flow and uniformity. The behaviour of carrier particles is governed by their stickiness, which is heterogeneously distributed on the particle surface, and governed by geometry and electrostatics.

Vectura's patented technology includes force control agents to mediate between the active drug and carrier particles to homogenise the interactions

and improve uniformity. Using a modified mouthpiece, which through a static charge causes the release of drug particles from the carrier, the company has delivered around 93% of the active drug into the deep lung.

Despite the benefits of dry-powder inhalers (DPIs), the next speaker offered convincing arguments for the utility of aerosol delivery in some circumstances. Dr Stephen Farr (Aradigm) talked about his company's development of inhaled insulin as a therapeutic treatment for diabetes. Although pressurised metred dose inhalers (pMDIs) and DPIs are the major devices for lung delivery, patient compliance and education is poor. In particular, the way the patient inhales can substantially influence the distribution to the lung: fast inspiration tends to deliver more to the gut; slow inspiration delivers more to the lung. Delivery to the deep lung requires aerodynamic diameters of 1–3 µm. Such small particles have a propensity to aggregate, and Inhale's insulin DPI incorporates a power-assisted disaggregation mechanism. As for insulin, there remains a need for improvement in the accuracy of subcutaneous needle injections, which are susceptible to a patient error rate of around 25% (this can be substantially improved with pen-injector systems). Insulin has an inherent bioavailability of only 20% by the inhaled route, a figure that is low compared to other proteins of similar molecular weight.

Aradigm's approach involves the control of the inspired flow rate through a breath-activated guiding system. Droplets of insulin are produced through a multilaminate strip precisely in the size (2 µm) required for deep lung penetration, and capable of delivering free particle fractions in the 80% range (see Figure 1). The inter-subject variability is similar to the s.c. insulin pen injector, however, it has recently been found that smokers absorb substantially more than non-smokers. This could become a problem for a molecule with as narrow a therapeutic range as insulin.

Moving from the top to the lower half of the body, Dr Richard Palmer (Alizyme, UK) talked about the use of the colon as a delivery site, both for local therapeutic effects, and for systemic delivery. There have been many approaches to colonic delivery over the years, from thick enteric coats, time-dependent release mechanisms, pH-dependent formulations and degradable pro-drugs. All of these have produced very variable release profiles, often because the transit time through the colon can vary substantially, from as low as six to as high as 30 hours. In the case of pH-dependent release, gastrointestinal pH is different in different people, and also depends greatly on food intake. These elements can cause the drug to be released very quickly or not at all. The pro-drug approach, which has variously been based on glucuronidases, glycosidases, azo-reductases, dextranases and others, involves the creation of a new chemical entity which must undergo all of the toxicological examination required for such a species.

Alizyme's approach is based on technology that originated at the Institute of Food Research at Norwich, and involves the incorporation of the drug behind a glassy amylose coat which is broken down by colonic bacterial amylases. The system can use conventional film-coating equipment, can be used with most solid oral dose forms and can provide a pulse or controlled release. It can also be applied for local or systemic delivery. The amylose is not broken down by pancreatic amylases, and is mixed with ethyl cellulose to provide robustness. In proof-of-concept studies, the system was used to dose volunteers with ranitidine, salbutamol, glucose or ATL2502 (pro-drug of prednisolone). There was no substantial inter-subject variability, and although food delayed the onset time, this was because of delayed stomach emptying, with no effect on AUC of the drug (see Figure 2). For the prednisolone delivery system, there is a marked reduction in systemic absorption of prednisolone; Phase II results are expected to be avalable in the second half of 2001.

The next two lectures dealt with the technology of polymer-conjugation, both for small molecule anti-cancers and for large proteinaceous therapeutics. Dr Ruth Duncan (Welsh School of Pharmacy) has been working in this area since the 1980s on the polymer-conjugated doxorubicin code named PK1. Polymer-conjugated successes have greatly stimulated interest in this area which was until recently treated with some scepticism by the mainstream pharmaceutical industry. One of the first examples in the cancer field was the polymer-conjugation of neocarzinostatin to polystyrene maleic acid by Prof N Maeda, which showed efficacy in liver cancer. Developments on this theme have highlighted the importance of the polymer itself, which should be non-toxic, non-immunogenic and around 40kDa in molecular weight to avoid renal elimination. N-hydroxypropyl methacrylate (HPMA) is a preferred polymer which has been used as the basis for a number of anti-cancer therapeutics. Since PK1, which was discovered by Pharmitalia and is now in Phase II investigation under development by Pharmacia, other conjugates have been investigated for platinate (Access Pharmaceuticals, in Phase I), paclitaxel (Cell Therapeutics, in Phase I) and camptothecin (Enzon Inc, in Phase I).

Figure 1. Multi-laminate dosage form holding liquid insulin formulation (left) in Aradigm's AERx inhaled insulin system (right)

(continued on page 4)

(continued from page 3)

Polymers offer the ability to target extracellular regions of tumours because of the greater permeability of the vasculature around such areas. As a result, the doses of polymer-conjugate anti-cancers can be increased. In Phase I examination of PK1, the maximum tolerated dose reached 320 mg/m^2 compared to the normal maximum tolerated dose of 60 mg/m^2 of doxorubicin itself. Chemical targeting is another means of producing additional selectivity. In PK2, an additional galactose moiety is attached to the doxorubicin-HPMA conjugate in order to enhance liver targeting. Another development in polymer targeting is to co-administer the polymer-conjugate with a monoclonal antibody conjugate of an enzyme, which is capable of cleaving the covalent bond linking the polymer to the active drug. Finally, polymers also offer an ability to deliver oligo-nucleotides. Certain amphoteric poly-amido-amines are taken into cells by endocytosis and this offers the possibility of a non-viral gene vector able to deliver genes into the cytoplasm of a cell.

The practical demonstration of the use of polymer conjugates for proteins was expounded in the next talk from Dr Stephen Charles (Shearwater Polymers, now part of Inhale Therapeutics). Shearwater offers a one-step drug-enhancement capability for PEGylation of proteins, small molecules, peptides and oligonucleotides. Polyethylene glycol, as a highly water-soluble molecule can enhance the bioavailability of water-insoluble and poorly soluble drugs. Shearwater has successfully developed two compounds through FDA approval, three more are in pre-registration and more than a dozen are in various other stages of development. In addition to PEGylated interferon α for hepatitis-C virus, other major projects have included polymer conjugates of IFN-α (with Roche), HGF (Pharmacia) and neupogen. As a polymer, PEG presents a large hydration volume and is a highly flexible structure. It is present in ointment, shampoo and some food and is entirely non-immunogenic, FDA-approved for i.v., topical and oral use and readily cleared from the body. PEG conjugates have improved solubility, stability (from months to years), reduced immunogenicity, proteolysis and increased bioavailability from the injection site. Despite the advantages, in early chemistry of PEG conjugates, problems were found in stability and low selectivity of conjugation. Shearwater's approach involves the conjugation of one molecule of active per molecule of PEG, the use of a narrow range of molecular weights of PEG (around 30kDa), and with a low proportion of the diol impurity which has the potential for producing a cross-linked conjugate. The chemical link can incorporate an amide, or carbamate, or a Michael adduct of a sulfur on to an α, β-unsaturated carbonyl system. The PEG polymer wraps around the protein to stabilise it with respect to proteolysis and immunogenicity.

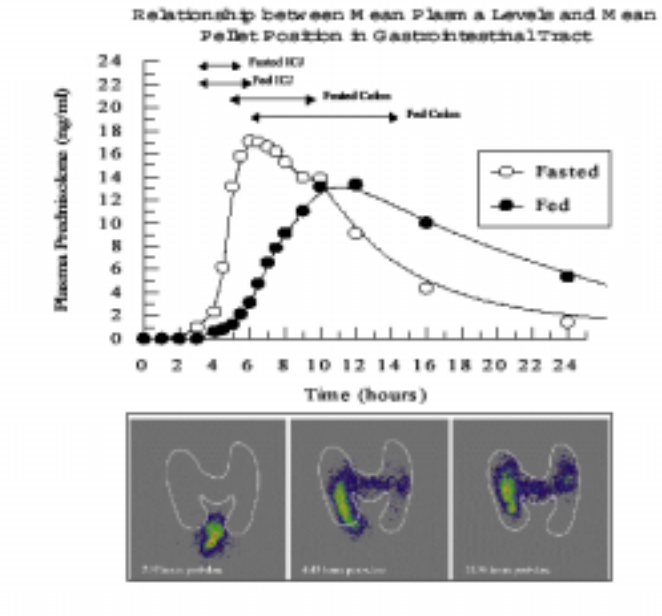


Figure 2. Alizyme's COLAL™ colonic delivery system releases prednisolone into the colon in fasted and fed volunteers to a similar extent but at different times

Shearwater's collaboration with Schering Plough resulted in Pegasys™, a PEGylated version of interferon α for hepatitis-C virus, with improved clinical efficacy. The percentage of patients with sustained reduction in viral levels was increased to 40% compared to the 10% achieved with conventional interferon α therapy. At the same time there was reduced immunogenicity. Pegasys™ is marketed as a pre-filled syringe and FDA-approval is expected in the second half of 2001.

Oral delivery of proteins and peptides

Perhaps the philosopher's stone of the drug delivery scientist is the oral delivery of proteins and peptides, which in the absence of an enhancer can only expect bioavailabilities of the order of a few per cent. There have been numerous attempts in this area, but obtaining efficacy without compromising safety has proved a substantial challenge. Recently, Emisphere Technologies has seemed to succeed where others have failed, and it fell to Tim Corless to tell the symposium how this had been achieved. Emisphere's technology is organised around a number of carrier molecules, which, in combination with the native protein itself seems to promote oral absorption through the stabilisation of alternative conformations which are more amenable to passive transportation through the transmembrane route. There is no evidence from the work carried out so far that the system produced any damage to cells of cellular junctions. The carriers themselves are new chemical entities which have molecular weights in the region of 300. The particular carrier that is good for one molecule may not be particularly good for another, although there are some physical chemical characteristics which seem to be associated with good carrier properties, based on logP and some other (non-defined) measures, and some carriers work well for more than one protein.

Emisphere is working with a number of major pharmaceutical companies including Lilly (HGF,

humatrope), Novartis (salmon calcitonin), Regeneron (ciliary neurotrophic factor for obesity) and Cubist (cyclic antibiotic peptide). In addition they have applied their technology to oral heparin by themselves (although it was nearly licensed to DuPont before their acquisition by BMS) and this is in Phase III evaluation. Preclinical success has also been determined for LMWH, rhGH and EPO among others. The projects are typically started by administration of a number of candidate carrier molecules in association with the protein of interest by oral gavage in the rat. Blood levels are determined and bioanalysis used to identify the most successful candidate. In collaboration with a partner, the company aims to identify the optimal carrier within six months of starting the collaboration, and begin toxicological trials and enter into man within 15 months. The optimal carrier can reduce the dose of the biomolecule as well as increase the efficiency of absorption. For instance, in the case of heparin, the carrier is sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC) (see Figure 3), and the resulting complex has a bioavailability of 17%.

Emisphere predicts a substantial opportunity with this product, since the market for heparin is currently $2 billion and growing 15% annually. Emisphere is developing both a liquid oral form and a solid dose form (about 18 months behind). In addition to the anti-coagulant use, heparin also has some anti-inflammatory properties and Emisphere is investigating their formulation in these indications.

The final talk of the day, delivered by Dr Kari Airenne (Ai Virtanen Institute and Ark Therapeutics, Finland) concerned gene delivery, a subject which remains controversial despite the approval in 1999 of the first antisense therapeutic (fomivirsen sodium for treatment of cytomegalovirus retinitis from Isis Pharmaceuticals). Gene therapy in its widest sense involves the transfer of genetic material into somatic cells of a host to treat or prevent an inherited or acquired disease. The main targets are to eliminate, repair or replace a mutated gene, to regulate gene expression and signal transduction to achieve a useful therapeutic effect, to regulate the immune system or to target malignant and other cells for destruction.

Although non-viral of naked DNA or plasmid-liposomes or cationic polymers has been contemplated, most approaches to gene therapy involve delivery via a viral vector, of which there are multiple types. Adenoviral vectors have been advocated because of their high efficiency in terms of incorporation of the inserted gene into the target cell or organ, however, they also have high immunogenicity.

By contrast, the retroviral vectors have reduced immunogenicity but also reduced efficiency. Dr Airenne advocated the use of the baculovirus vector because they are not known to infect invertebrate hosts (and are safer), and are currently used as biopesticides (and therefore have a known toxicity profile). By including a mammalian promoter in the BCV gene, a large amount of foreign DNA can be incorporated.

The system's ability to transfer a gene successfully into a mammalian system was demonstrated by the transfer of galactosidase into a rabbit carotid artery. The transfection efficiency was similar to that of adenoviral transfer, but the presence of galactosidase enzyme was not observed beyond two weeks after the experiment. While the system also has applicability for skeletal muscle, choroid plexus of brain and endothelial cells, the long-term expression of the transferred gene remains a problem to be solved.

In conclusion, this represented a timely review of the advances in drug delivery that will increasingly become part of future medicines. The existing technology is wide ranging, from controlled-release formulations to permit reduced dosing frequency through to polymer conjugates to target anti-cancer drugs to their site of action. The future technology is even more exciting, with the realisation of orally delivered proteins from biotechnological processes and the improved use of the lung as a route for large molecules to enter the body. •

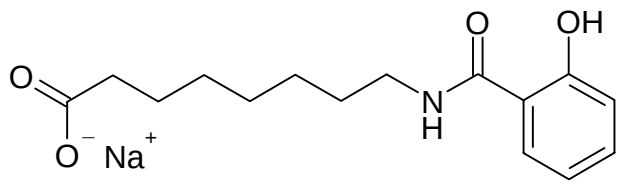


Figure 3. Emisphere's carrier molecule for oral delivery of heparin, SNAC

SMR Bursary Receives Cornerstone Donation from AstraZeneca

The SMR has a broader purpose than professional development. A significant proportion of our meeting attendees are students, normally post-graduates. We believe our meetings stimulate good-quality entrants into the pharmaceutical industry and strengthen the intellectual base of the employment pool. We have been faced with increasing costs for running our meetings associated with rising prices for lecture hall hire and catering. In some cases the incremental cost per delegate is more than the student registration fee, which we have had to increase to reflect commercial realities. We now believe this charge is stretching the budgets of academic bodies and restricting student registrants to our meetings. It is unlikely that alternative, more cost-effective training opportunities are open to such people in this country.

We have therefore set up a student bursary fund, supported by those likely to benefit from a strong pool of university leavers eager to enter the pharmaceutical industry. We are very pleased to report the donation of a cornerstone contribution of £5,000 from AstraZeneca as a major employer in this sector in the UK. We intend to run this fund separately from the rest of the SMR's accounts in order that its accountability is guaranteed. Disbursements would be generated from investment income to the fund. The benefits will be long-lasting, stimulating many future years of student learning opportunities followed by many more years of productive contribution to the UK science base.

We are approaching some of the other major companies in the hope that more than one will support us. We hope very much that we will be able to report additional participants in a future issue of this newsletter. Details of how the scheme will work and how to apply will be circulated in the September mailing and on the website.•

(continued from page 1)

TNF-α, GRO-α and leukotriene B4.

Prospects for novel therapies for COPD are based on consideration of the cells, mediators and enzymes involved in pathogenesis (see Figure 1). Cigarette smoking brings with it a major burden of oxidants, including superoxide anion, hydrogen peroxide, hydroxyl radicals and peroxynitrite. This causes an inflammatory response that is characterised by an amplification or exaggeration of response when comparing subjects with COPD to healthy smokers. Promising therapies include phosphodiesterase (PDE) antagonists), leukotriene B_4 antagonists, chemokine receptor antagonists, TNF-α antagonists and elastase and matrix metallo-protease (MMP) inhibitors.

An increasing array of methods are available for the diagnosis and monitoring of COPD. Potential clinical investigations include spirometry (FEV_1/FVC), assessment of reversibility to inhaled β_2-agonist (salbutamol), a trial of oral steroid to document lack of response, plethysmography (lung volumes) and gas transfer evaluation (TLCO), imaging by chest X-ray and high-resolution computerised tomography scan (HRCT), arterial blood gas measurement and exercise testing.

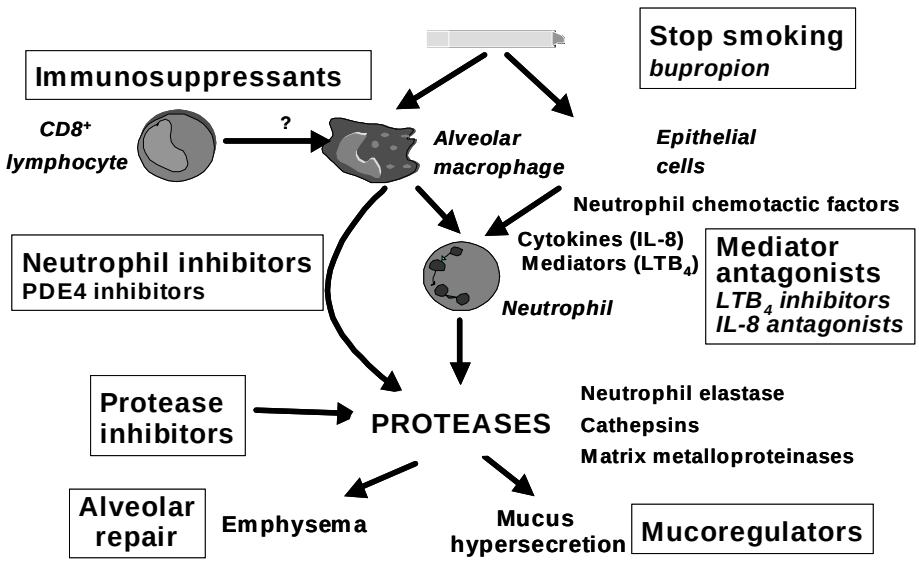
The cornerstone of management of a patient with COPD is to attempt smoking cessation or reduction. This should be backed by ensuring a healthy diet, adequate exercise, immunisation against influenza, broncho-dilator therapy (anti-cholinergic agents and short- and long-acting β_2-agonist; pulmonary rehabilitation, long-term oxygen therapy and volume reduction surgery should be considered in more severe cases. The World Health Organisation (WHO) in conjunction with the US National Heart, Lung and Blood Institute (NHLBI) has organised the Global Obstructive Lung Disease (GOLD) guidelines. These are analogous to the Global Initiative on Asthma (GINA) guidelines, and have been available on the National Institute of Health website since May 2001.

Recently licensed therapies that are proving effective in the management of COPD include the combination of ipratropium and salbutamol (Combivent, Boehringer Ingelheim) and long-acting β_2-agonists (formoterol and salmeterol). Promising therapies in Phase III clinical trials include the long-acting anti-cholinergic (M1/M3 antagonist) tiotropium bromide (Boehringer Ingelheim) (see Figure 2) that is employed in a single daily inhaled dose.

Inhaled steroids have been studied in four long-term three-year studies in COPD (Euroscop, ISOLDE, Copenhagen, Lung Health 2), and although benefit can be demonstrated in terms of improvement in quality of life, the studies have been disappointing in that they have failed convincingly to alter the progressive fall in FEV_1 that occurs in COPD. Also, this expensive high-dose therapy carries a high risk of adverse events in this elderly smoking population.

Smoking cessation has proved remarkably difficult for most patients with COPD, despite the availability of nicotine replacement therapy and Zyban (GlaxoSmithKline), so that there remains a major need for new therapies for COPD. There is a requirement for specialised anti-inflammatory agents that act on neutrophils, macrophages, proteases, cytokines, chemokines and mediators. Since the small airways and alveoli need to be targets, oral therapy may have advantages over the inhaled route. The particular overriding need is to retard or even reverse the loss in lung function in COPD, thus providing genuine disease modification.

Figure 1 : Targets for COPD Therapy



Viozan

Viozan (AR-C68397AA) (see Figure 2) is a novel, dual D_2-dopamine receptor and β_2-adenoceptor agonist being developed to cause broncho-dilatation and limit breathlessness, coughing and mucous production. Alan Young of AstraZeneca (Charnwood) presented the rationale for dopamine agonism being to activate D2 receptors on sensory nerve endings, thus inhibiting reflex neuronal mechanisms that contribute to the symptoms of COPD. Viozan is a potent β_2-agonist in anaesthetised ventilated dogs. Furthermore, D_2-agonist activity can be studied in anaesthetised β-blocked dogs; where there is inhibition of histamine-induced discharge of rapidly adapting receptors, reflex-induced tachypnoea and ammonia-induced mucus production. In addition Viozan inhibits capsaicin-induced cough in conscious β-blocked dogs.

Three Phase II clinical studies of inhaled Viozan have now been completed in over 2,300 patients treated for 4–6 weeks. Study I involved a proof of principle and a pressurised metred dose inhaler (pMDI); study 2 a dose-ranging study from a pMDI; and study 3 a dose-ranging study from a Turbuhaler. These studies have demonstrated that Viozan brings superior control of symptoms when compared to salbutamol or ipratropium bromide given three times daily. Viozan at the high dose of 495µg t.i.d. was well tolerated, not causing nausea and vomiting, although a discernible taste was noted in 20% of subjects. Viozan represents a novel approach to the symptomatic treatment of COPD that is supported by pre-clinical and Phase II

clinical data. [Note added subsequent to meeting: Viozan was dropped from development in June 2001 due to insufficient efficacy in Phase III trials].

Cilomilast (Ariflo)

This novel oral phosphodiesterase type 4 (PDE4) inhibitor (see Figure 2) was presented by Chris Compton of Glaxo SmithKline (Harwood). Because of their ability to elevate cAMP content in key target cells, PDE4 inhibitors have anti-inflammatory, broncho-dilatory and neuro-modulatory activities. However, first-generation PDE4 inhibitors such as rolipram have the limiting side-effect of causing nausea, vomiting and increased gastric acid secretion. Second-generation PDE4 inhibitors have been selected using a strategy based on selection of antagonism of the low affinity binding confomer for rolipram that is located on inflammatory leukocytes, while minimising antagonism of the high affinity binding confomer for rolipram that is found on central nervous system and gastric parietal cells. This approach maximises anti-inflammatory activity, yet reduces the potential to cause nausea and vomiting. Indeed preclinical studies demonstrate the activity of cilomilast in inhibiting neutrophil recruitment, chemotaxis, activation and IL-8 production. In a six-week dose range finding study in COPD patients with a mean FEV_1 of 57% predicted, cilomilast 15mg b.i.d. caused a 10% improvement in trough FEV_1. Phase III studies have been performed in Europe and the US, and some results have been presented at the American Thoracic Society meeting in San Francisco in May 2001.

Modulating oxides

Dr Mark Currie (Sepracor, Marlborough, MA) presented his research on strategies against toxic oxidant species. Selective inhibition of the inducible form of nitric oxide synthase (or selective iNOS inhibitors) is an attractive therapeutic target in a variety of inflammatory diseases. The constitutive forms of NOS comprise endothelial eNOS that maintains blood pressure, inhibits platelet aggregation and hinders leukocyte adhesion; while the neuronal nNOS is a neuro-transmitter that promotes gastro-intestinal motility. Exhaled NO is elevated in the breath of asthmatics, epithelial iNOS is expressed and can be inhibited by steroids, and 3-nitrotyrosine immunoreactivity can be demonstrated. In a Lewis rat lipopolysaccharide (LPS) model the selective iNOS inhibitor SC 357 (see Figure 2) causes pronounced inhibition of plasma nitrite, reduction of exhaled NO and inhibition of tissue iNOS; but only causes elevation in blood pressure at higher doses.

Superoxide dismutase (SOD) mimics are small molecules with catalytic activity similar to SOD, and include the manganese-containing M 40403 (see Figure 2). This molecule inhibits carageenan-induced changes in rodent paw volume, as well as lung and intestinal inflammatory models. SOD mimics also exert biochemical protection against norepinephrine breakdown during endotoxic shock

Peroxynitrite catalysts protect against cell death in the rodent paw model as judged by LDH release. These molecules scavenge peroxynitrite and convert it to nitrate, resulting in a reduction in the nitrite: nitrate ratio in rodent models. Vitamin B12a (hydroxo-cobalamin) represents a NO scavenger that prevents or reverses LPS-induced shock in rodents. Hydroxo-cobalamin is thought to trap NO and cause its distribution from the vascular compartment into the urine.

Protease inhibition

Matrix-degrading metallo-proteases (MMPs), serine proteases and cysteine proteases are expressed during specific periods of tissue development and repair. Professor Stephen Shapiro (Washington University School of Medicine) described how neutrophils produce neutrophil elastase, cathepsin G and proteinase 3 as well as MMPs 8 and 9. In contrast, macrophages have a complement of cathepsin S and L, MMPs 1, 3, 7, 9 and 12, as well as MT-MMP-1. Macrophage elastase has been demonstrated to be MMP-12 and is coded on human chromosome 11q. MMP-12 degrades a variety of substrates, including elastin, but not interstitial collagen.

Gene targeting has been useful in directly demonstrating roles for individual MMPs and elastases in tissue destruction. The macrophage metallo-elastase (MME) (MMP-12) double knockout (-/-) mouse has markedly diminished capacity of macrophages to degrade an extracellular matrix component, such as matrigel. These mice are protected from the development of cigarette smoke-induced pulmonary emphysema, and fail to recruit alveolar macrophages in response to cigarette smoke. However, these mice have compromised their host defence, with deficiencies against certain tumours and gram-positive bacterial infection.

Mice deficient in gelatinase B, MMP-9 double knockouts (-/-) are short due to a failure of primary angiogenesis in the metatarsal growth plate. MMP-9 may function physiologically in long bone development and contact hypersensitivity, while act pathologically in atherosclerosis, aortic aneurysms and bullous pemphigoid.

Mice knockouts for neutrophil elastase are 60% protected from cigarette smoke-induced emphysema. This suggests interaction between neutrophils and macrophages in the development of emphysema. Furthermore, neutrophil elastase is abundant in the neutrophil primary granules, and is important physiologically in host defence against gram-negative bacteria.

In considering therapies directed at inhibiting proteases for use in COPD, it is important to be aware of the potential to inhibit host defence against particular types of infection and tumours. It should also be considered that macrophage and neutrophil interactions could be fundamental to the pathogenesis of alveolar destruction that occurs in emphysema.

Neutrophil chemokine receptors

Dr Henry (Skip) Sarau of GSK Pharmaceuticals presented an overview on strategies directed against neutrophil chemokine receptors. The Chemo-attractant cytokines are small proteins of 70 to 80 amino acids. The molecular configuration of their four highly conserved cysteines permits classification into four groups : α (C-X-C), β (C-C), γ (C) and δ (C-X-X-X-C). Chemokine receptors have been ascribed to the following members: CCR 1–10, CR1, viral and Duffy

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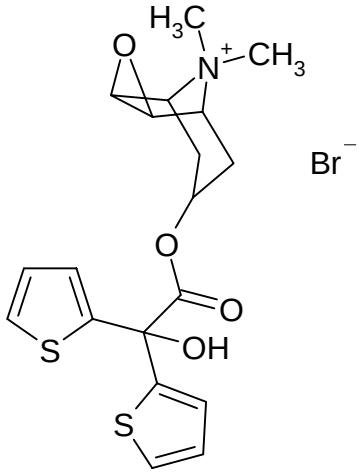
Tiotropium bromide



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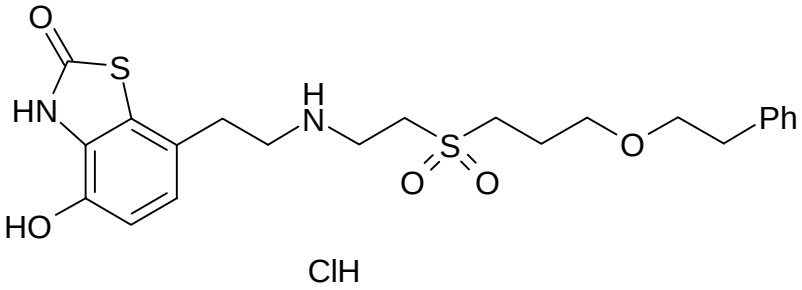
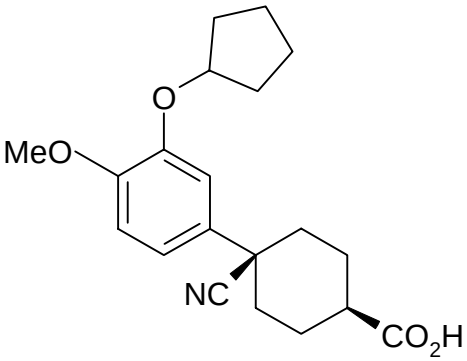


Cilomilast (Ariflo) SB 207499



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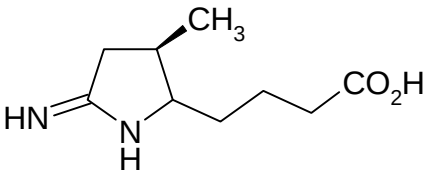

Figure 2. Chemical structures

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receptors, CXCR 1–5 and CX3CR1.

The presentation centred on the neutrophil CXCR receptors, which are members of the superfamily of G protein-coupled, seven transmembrane spanning receptors. CXCR1 binds IL-8 and GCP-2, while CXCR2 binds IL-8, GRO-α, β, γ, NAP-2, ENA-78 and GCP-2. CXCR2 appears to be responsible for IL-8-induced chemotaxis of human neutrophils and T cells, while CXCR1 is responsible for neutrophil degranulation.

SB 332235 (N-3-aminosulfonyl 4-chloro-2-hydroxy N'- (2,3 dichlorophenyl urea, (see Figure 2) is a selective CXCR2 antagonist, with an IC50 for CXCR1 of 9.6μM and an IC50 for CXR2 of 9.3nM. This molecule potently inhibits IL-8 and GROα-induced chemotaxis of human neutrophils, T cells and dendritic cells. This molecule has been studied in an LPS-induced rabbit airways neutrophilia model, an acute arthritis model in New Zealand White rabbits, and in a phorbol ester (PMA)-induced cutaneous inflammatory model in the rabbit. Interestingly, several recent reports have shown increased amounts of IL-8 in sputum supernatants from patients with COPD. SB 332235 is a promising potential therapy for pulmonary disease (COPD and more severe asthma), rheumatoid arthritis, psoriasis and inflammatory bowel disease.

Monoclonal antibodies

Dr Ted Torphy (newly of Centocor Inc) began by describing the development of a range of types of therapeutic monoclonal antibody (mAb) that have progressed from being of murine to human origin. The murine anti-CD3 Orthoclone was launched in 1986, the anti-TNFα chimeric mAb Remicade has been licensed for rheumatoid arthritis and Crohn's disease, the anti-HER-2 humanised mAb Herceptin employed in cancer therapy, and the fully human anti-TNFα mAb D2E7 is currently in Phase III clinical studies.

MAbs have several attractive features compared with traditional small molecular weight drugs. First, mAbs have a high degree of selectivity for their molecular targets, resulting in predictable biological effects. Second, mAbs have fewer side-effects since they do not effect hepatic cytochrome P450 drug metabolism pathways, and have reduced potential for drug interactions. Third, there are predictable and prolonged pharmaco-kinetics. Finally,

(continued on page 9)

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with advanced technical development, R&D cycle times are considerably reduced.

The technology to develop mAb has advanced considerably in the past decade; moving from hybridoma and chimaeric methods to transgenic mice, while bacteriophage display offers the chance to select from an extended library of specificities. In addition, some of the hurdles in development of mAb therapies have been overcome. New delivery technologies are being evaluated to minimise the inconvenience and lack of patient acceptability for injections. New manufacturing technologies based on transgenic animals and plants may reduce production costs by 25-fold. The immunogenicity of mAbs has been reduced by production of humanised or fully human forms.

The range of cells and mediators that have been implicated in the pathogenesis of COPD include TNFα, IL-6, IL-8 and EGF; and therapeutic mAbs have already been generated against these targets. Following the two-year ATTRACT study, Remicade (anti-TNFα, Centocor) has recently been licensed by the FDA as an agent that inhibits the progression of joint damage in rheumatoid arthritis. This offers the insight that COPD, despite being a chronic progressive lung disease, could be amenable to disease modification through mAb therapy.

Retinoids

In the final talk of the day, Dr Paula Belloni of Roche Bioscience (Palo Alto, CA) presented a comprehensive update on the development of retinoic acid receptor agonists, or vitamin A analogues, for COPD. Retinoids have been employed clinically to treat a variety of inflammatory skin disorders, especially to promote the repair of UV-induced skin damage. Retinoic acid receptor (RAR) agonists have potential for use as anabolic therapy to retard or even reverse the loss of lung function that occurs in COPD.

Retinoids, natural and synthetic, as a class are structurally related to vitamin A (retinol). As a class they are pleiotrophic regulatory compounds that modulate structure and function of cells at various times during and after tissue development. Retinol is primarily stored in the liver as retinyl esters, it is carried in the plasma bound to retinol-binding protein (RBP), and is converted within the cell cytoplasm of target tissues to the active hormone all-trans retinoic acid (ATRA). Retinoids are inactive while bound to the cytoplasmic receptors (CRBP and CRABP) and exert biological activity via the nuclear retinoic acid receptors (RAR). These receptors are ligand-inducible transcription factors belonging to the steroid nuclear hormone receptor superfamily. ATRA bound heterodimers of RAR/RXR bind to RA response elements (RARE) to promote and/or suppress gene expression. ATRA has roles in modulating lung structure and function; branching morphogenesis of the embryonic lung, peptide growth factor receptor expression, matrix protein metabolism, and mucocilliary function. However, the major role in relation to COPD therapy is alveolar type II epithelial cell and myofibroblast proliferation, differentiation, and elastin synthesis, resulting in alveolar septation. Retinoids and RARs are temporally and spatially regulated during lung development and drive branching through regulation of homeobox genes. The last phase of branching, alveolar septation, is regulated by RARγ and increased local concentrations of ATRA within and interstitial myofibroblast. Broncho-pulmonary dysplasia (BPD) of infancy is associated with a retinol deficiency, delayed alveolar septation and impaired lung function. Retinol deficiency is also associated with patients and preclinical studies suggest that a key carcinogen in cigarette smoke, benzpyrene, induces local vitamin A deficiency in the lung. Since retinoids can inhibit matrix metallo-proteases transcription through activator protein-1 (AP-1), deficiency in ATRA may contribute to the protease/ antiprotease imbalance associated with COPD.

In an important series of experiments published in 1997, Don and Gloria Massaro have described the role of ATRA in promoting alveolar septation in the rat, noting that RARβ impairs septation (2000). Recently, McGowan et al. have noted that in RARγ (-/-) knockout mice there is reduced lung elastin and alveolar septation. Ro 44-4753 is a selective RARγ agonist that drives tropo-elastin gene expression and alveolar repair and/ or alveolarisation in adult rats. Ro 44-4753 has been shown to induce alveolar repair in two rodent models, pancreatic elastase-induced emphysema in rats, and cigarette smoke-induced emhysema in mice. Lung function assessed by PaO2 is also improved after treatment with ATRA or Ro 44-4753 in elastase injured rats. Tepper et al. (2000) have also shown that ATRA partially reverses lung function in elastase damaged rats, enabling increased lung volume and compliance and a decrease in carbon monoxide diffusion capacity (DLCO).

The critical question is whether the adult human lung is capable of alveolar repair, since that organ may not have the capacity to regenerate alveoli.

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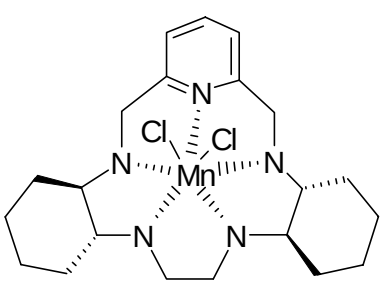

SB 332235

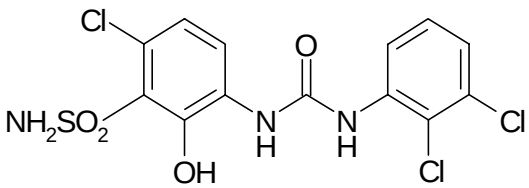

Figure 3 Chemical structures

Medicinal Chemistry at Bath

by Professor Barry VL Potter

The Department of Pharmacy and Pharmacology of the University of Bath has a long and distinguished history and can trace its origins back to the Bath and West of England College of Chemistry and Pharmacy, established in Bath in 1907. In 1929 the college was taken over by the Merchant Venturers of Bristol and became the School of Pharmacy of the Merchant Venturer's Technical College. This college successively developed into a College of Technology (1949), and a College of Advanced Technology (1962) and, in 1966, became the newly established University of Bath. In 1974 the name of the school was changed to Pharmacy and Pharmacology and, in 1997, following the adoption of a faculty structure, the school became a department within the faculty of science.

The aim of the Department of Pharmacy and Pharmacology is to provide a challenging and stimulating education to enable and inspire the student to pursue a professional career in the pharmaceutical sciences or in pharmacology. The department is recognised as being one of the premier British centres of teaching and research in the pharmaceutical sciences with a QAE grading of 'excellent' for its teaching and an RAE grading of 5A for research. The department runs two four-year degree programmes, an MPharm leading to a professional qualification in pharmacy after a pre-registration year, and an MPharmacol that produces pharmacologists who enter a range of scientific professions.

Two major building projects have helped to shape the department in recent years. The first, in 1994, was the building of an extension funded substantially by Glaxo Group Research providing a clean room and aseptic suite for pharmaceutical technology and clinical pharmacy. More recently, the department has benefited from the building of a major new extension, completed in 1998, (see photo) providing some 1,800m^2 of new research space. This multidisciplinary environment has enabled research particularly in the key areas of inflammation and cellular signalling to be consolidated and enhanced under one roof and we have recently also strongly enhanced our international profile in cardiovascular pharmacology. This has provided added value to the well-established multi-disciplinary theme of cell signalling research by adding new electro-physiological and imaging expertise to established broad molecular and chemical research in the area.

The department currently consists of some 40 academic staff within eight research clusters across four formal groupings: Medicinal Chemistry (headed by Professor BVL Potter), Pharmacology, Pharmaceutics and Clinical Pharmacy and Pharmacy Practice, with professorial leadership in all areas. Together, these groupings provide a dynamic and flexible structure that supports research across all aspects of the pharmaceutical sciences 'from concept to clinic', with a current research grant portfolio of about £7million from diverse charitable, research council and industrial sources.

The Medicinal Chemistry Group within the department has always had a strong synthetic element. In the mid-1970s, Professor Bob Parfitt was appointed as the first Professor of Medicinal Chemistry and he then recruited Dr Alan Casy in 1979, who traced his inspiration for the study of the importance of drug stereochemistry to biological activity back to Arnold Beckett at Chelsea in the early 1950s. Together, they worked in the area of synthetic opioids and published *Opioid Analgesics* in 1986, giving Medicinal Chemistry at Bath a particular reputation in that field. They also brought the first NMR facility into the group. This enabled Dr Casy to carry on his pioneering work of exploiting NMR spectroscopy to probe the conformation of drugs in solution and to relate this to their biological activity. He published widely in this field and his second book, *The Steric Factor in Medicinal Chemistry* (1993), still represents the most complete review of that field up to 1990. His collaborations in opiates included international pharmaceutical companies and the Stanford Research Institute with funding from the NIH and NIDA.

This group declined seriously in the late 1980s until the university made a major general commitment to the life sciences across the board that included, with the appointment of Professor Potter and other staff, the reinvigoration of Medicinal Chemistry, side by side with an established Organic Chemistry Group in the Chemistry Department at Bath that also had medicinal interests under Professor Malcolm Campbell. Despite serious discussions about merging the two activities, the Medicinal Chemistry

(continued from page 10)
Group kept its uniqueness and augmented its activities while, alongside, the Organic Chemistry Group changed its focus gradually towards more traditional synthetic methodology, catalysis, etc.

The university, therefore, now possesses a particularly strong organic chemical focus with medicinal chemistry firmly established as the biological/pharmacological arm. Research activity in the opioid area has also now recently been revitalised by the move of John Lewis's group, led by Steve Husbands from the University of Bristol to Medicinal Chemistry in Bath. This is the only non-US medicinal chemistry group directly funded by NIDA. The main theme of its research programme is the discovery of new pharmaco-therapies for drug abuse following the introduction of buprenorphine, discovered and developed by John Lewis as an alternative to methadone. Through these studies significant insight into the molecular basis of drug/receptor interactions has been attained. Major collaborations are with the University of Michigan and the Stanford Research Institute. Opioid chemistry at Bath has thus now come full circle and Bath is well placed to continue as a leading centre in this now rare speciality area.

Current medicinal chemistry research encompasses the activities of nine staff and is spread broadly into two clusters: medicinal chemistry of receptors and signal transduction which focuses upon the design of ligands acting at extracellular and intracellular receptors, and medicinal chemistry of neoplastic disease where novel antiproliferative agents are explored.

Two compounds synthesised recently at Bath, one for hormone replacement therapy, and the other an anti-cancer agent, are currently in clinical trials with a major pharmaceutical company and the CRC, respectively. The synthesis of novel molecules to intervene in cellular signal transduction pathways, funded primarily by a five-year Wellcome Trust Programme Grant to Potter (around £1 million) has resulted in two papers in *Nature* in the last two years with potential for the design of novel immunomodulatory 'signal transduction therapy' drugs.

The design of novel anti-cancer drugs, originally supported by the CRC, is now carried out in association with the spin-out company Sterix Ltd, which is located within the Department. Sterix Ltd was formed in 1998 with Imperial College London, to capitalise upon discoveries made in the Medicinal Chemistry Group in novel therapy for hormone-dependent breast cancer and other indications. The company was capitalised initially using patent licence income from an agreement with a major multinational pharmaceutical company and has substantial R&D contracts placed in Bath, London and elsewhere. This development has been crucial for the expansion and continuing vigour of the Medicinal Chemistry Group, that now has a refurbished laboratory dedicated to Sterix work housing up to 12 researchers. Sterix is close to finalising major venture capital funding to consolidate and expand its position. It aims to be, uniquely in the current climate, a spin-out company with a strong medicinal chemistry focus.

Currently, our experience in analytical chemistry is being enhanced and extended, with a new focus towards drug metabolism to include our natural product interests, the development of synthetic CNS-related projects, aimed at dopamine, GABA, Glu, nicotine/acetylcholine pathways, cellular signalling pathways involving inositol phosphates, and the emerging new nucleotide-based intracellular calcium-releasing second messengers cADP ribose and NAADP, novel ligands for steroid, opioid and imidazoline receptors and associated enzymes (kinases, phosphatases, sulfatases, cyclases, polymerases), developing new dynamic combinatorial methods for inhibitor design, hypoxia-activated prodrugs and discovering new chemical leads for intervention in ischaemia reperfusion injury and drug and gene delivery systems. Many of these areas are underpinned by a new joint biophysical NMR centre to add modern structural biology elements to the research programmes.

We were fortunate to raise major Wellcome Trust support (about £700,000) and recruit a leading NMR specialist from North America to head a new 600MHz biophysical NMR unit. Members of the department were also successful, jointly with other departments, in securing major JREI funding for new instrumentation, an X-ray diffractometer with CCD area detector and a UV Raman spectrometer. Most of the staff in medicinal chemistry have collaborative links, for example, with the universities of Oxford, Cambridge, Hamburg and Southern California. Since undergraduate student numbers in the Department are rising until at least 2002/2003, a significant number of new academic appointments will be available to us over the next two or three years. We plan to exploit this unique opportunity with a proactive recruitment programme, targeting selected areas of expertise in order to build on our current strengths *and* consolidate research links between the existing research clusters. Medicinal chemistry activities will benefit from this.

We plan to lay a strong foundation to enable the department to play a leading role in the new growth area of chemical biology, particularly with respect to small molecules that have potential as drugs. Enhancing our potential in drug design is also a key aspiration, which demands a high level of expertise, currently lacking, in the relevant aspects of computer modelling and molecular enzymology. The search for small molecules with selective activity will also be accelerated by recruiting appropriate expertise elsewhere in the department in post-genomic analytical techniques and physical pharmacy.

To integrate new compounds of potential therapeutic interest to the pharmacological and clinical pharmacy expertise in the department, we aim to appoint in the areas of molecular drug metabolism and pharmaco-kinetics. We also plan to nurture clinically linked positions over the next 2–3 years, to exploit advances in drug design and development at the level of clinical pharmacy.

This, in combination with a major Department of Biology and Biochemistry (RAE Grade 5A) and Departments of Chemical Engineering and Materials Science, means that medicinal chemistry and the university as a whole are excellently placed to meet the new interdisciplinary challenges of the 21st century.•

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However, it is encouraging that recovery from adult respiratory distress syndrome (ARDS) can occur. In COPD there has been found to be an inverse relationship between plasma retinol status and the degree of airway obstruction, while a small study has demonstrated that therapy with retinyl palmitate improves FEV_1 in COPD. It has been hypothesised that high levels of retinoic acid receptor (RAR) activity may be associated with chronic repair and the mucous hyperplasia of chronic bronchitis, while low levels of RAR activity may be associated with inadequate repair of damaged elastin resulting in emphysema.

ATRA, Roaccutane 13-cis RA, and 9-cis RA are RAR pan-agonists that have a narrow therapeutic window; due mainly to teratogenicity and hepatotoxicity. Teratogenicity is believed to be a factor for all retinoids by virtue of their role in pattern formation via homeobox gene activity. Other adverse events include psychiatric disorders, hypertension, high blood lipids, hyperostosis and mucous hypersecretion.

Selective RARγ agonists, such as Ro 44-4753, have a range of advantages over ATRA; in particular lacking hepatotoxicity because the liver does not have RARγ receptors. There are no apparent effects on triglyceride levels (experimental therapeutic window of ≥3000). In addition, mucous hypersecretion does not occur. However, the problem of teratogenicity remains, albeit less of an issue in elderly females, and mucocutaneous effects of dry skin and chapped lips may occur.

A group of investigators from Los Angeles have undertaken a proof-of-concept study with ATRA in COPD (Mao, ATS, 2000). Twenty COPD patients were enrolled in a six-month two-way cross-over study, administering ATRA 25mg/m^2 for three months. ATRA was generally well tolerated, with the anticipated side-effects noted. No significant changes in lung function occurred, however, preliminary assessment of high-resolution computerised tomography (HRCT) images suggest improvement in a subset of structural measures, and eight of the 20 patients reported positive subjective responses.

The National Institute of Health FORTE study has also undertaken a study in COPD with retinoids. In a multi-centre study, 300 COPD patients will be randomised into one of four treatment arms: placebo, 13-cis RA, low-dose ATRA and high-dose ATRA.

Treatment outcome measures include HRCT to assess lung structure, lung function testing, quality of life and broncho-scopy to explore potential surrogate markers associated with retinoid-induced repair.

A number of issues remain to be resolved for the therapeutic use of RAR-selective agonists in COPD. The relative merits of pan-agonists compared with selective agonists need to be considered, the route of delivery (oral or inhaled) needs to be defined and proof-of-concept clinical studies need to be performed. Clinical studies may need to be performed in current and former cigarette smokers, both early and late in the progression of COPD.

Conclusion

This meeting ended on a note of cautious optimism, in that progress is certainly being made with the various therapeutic strategies covered in the course of the meeting. Tiotropium is likely to be licensed in the near future and will offer symptomatic benefits to COPD patients, while the results of large-scale studies of Ariflo on lung function are awaited with great interest. Therapies to combat reactive oxidant species, neutrophils and proteases are entering early clinical studies, while retinoids offer perhaps the greatest potential for lung repair and regeneration. However, there remains the requirement to improve our knowledge of the molecular pathogenesis of COPD, to develop non-invasive techniques for the classification and monitoring of this disease, and to develop reliable clinical trial methodology. The inspiration to these efforts is the lack of effective therapy for this disease of growing magnitude in our society.

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SMR Notes

Future SMR meetings (contact secretariat for more information: secretariat@socmr.org):

27 September 2001. Sodium Channels in Disease (National Heart and Lung Institute, London).

6 December 2001. Case Histories in Drug Discovery, including SMR Award (National Heart and Lung Institute, London).

14 March 2002. Orphan Receptors (Novartis, Horsham).

27 June 2002. Drug Metabolism, Pharmacokinetics and Drug Discovery (National Heart and Lung Institute, London).

19 September 2002. Proteomics (Joint meeting with BMCS section of RSC) (Scientific Societies Lecture Theatre, London).

NEW MEMBERS

AstraZeneca, Charnwood: Dr KM Thong; *GlaxoSmithkline:* Dr M Woodrow, Dr GS Leonard; *Kingston University:* Dr S Gegbe; *Madhav Baug (Mumbai India):* Dr PA Thakurdesai; *Medivir UK Ltd:* Dr T Johnson; *University of Missouri:* Dr S Dakshnamurthy; *Nature Publishing Group:* Dr P N Kirkpatrick; *Novartis Pharmaceuticals:* Dr S Collingwood, Dr I Bruce; *Novartis Horsham Research Centre:* Dr A Li, Dr H Sahri; *Pfizer:* Dr M Miller; *UCB Pharma:* Dr M Peck.

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