SMR The Society for Medicines Research

Volume 12 September 2004 Newsletter

SMR Committee News

The first half of 2004 has been a very busy time for the Officers and the Committee. Three key items have dominated our agendas.

New SMR Website

The new website has at last been finalised and is in operation in time for the next SMR meeting in September. Headed by the new SMR logo, the site has clear navigation buttons for our meetings, registration, joining and contacting the Society. Meeting reports, webcasts and newsletters can be found in the Archive section. An important change from the old site is that registration takes place through a secure Triangle Three webpage.

SMR Finances

As a registered charity and not-for-profit organisation, the SMR continues to run on a delicately balanced budget. Following a review of our situation, led by the Hon. Treasurer, the Committee endorsed increases in the registration fees for meetings to £60 for members and £110 for non-members. Fees for students and retired members remain unchanged at £35. These changes further highlight the advantages of membership of the SMR, with members now receiving a £50 discount at each meeting - excellent value as membership subscription is unchanged at £25. Although we remain committed to keeping our registration fees as low as possible, changes in venue costs for 2005 may lead to another review. However, even with these increases, the Committee believes the SMR meetings continue to offer the best quality, lowest cost meetings in the UK.

SMR Meetings

The Committee has now planned future meetings through to the end of 2005. As ever, the SMR will be holding one of its meetings outside London and in 2005, Organon have generously agreed to host a meeting at their site in Newhouse, Scotland. This will be the most Northerly meeting ever held by the SMR and represents an excellent opportunity for the Society to introduce its brand of meetings to a new audience.

Inside:

Page 4 - Highlights from our March Meeting: Chemokines and Drug Discovery

Page 7 - Highlights from our June Meeting: Type II Diabetes: Mechanisms and Emerging

Dates for your diary

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Membership news

New Members from January 2004

Name	Organisation
Dr A M Kardasz	The University of York, York
Dr K E Barnes	Elsevier, London
Ms H (W H) Mok	GlaxoSmithKline, Harlow
Mrs P K Copp	Novartis, London
Dr K Clark	Linton, Cambridge
Dr I A Pullar	Eli Lilly and Co. Ltd, Surrey
Dr M Paterson	Inpharmatica Ltd, London
Dr C Hazel	Covance Laboratories Ltd, Harrogate
Dr C J Long	Organon Laboratories, Lanarkshire
Dr T Fryatt	Didcot, Oxon
Mr K Rana	GlaxoSmithKline, Harlow
Dr E H Karran	Lilly Research Centre, Windlesham
Dr S C Young	Tularik Ltd, Stockport
Dr J W Myatt	GlaxoSmithKline, Harlow
Dr G Apic	Cambridge Cell Networks Ltd, Cambridge

Where are they now? We need your help.....

Below is a list of SMR members who we no longer have the correct address for. Please take a moment to read through and if you know where any of them are could you either contact the secretariat or ask them to, so we can update our membership list and include them in our mailings. *Thank you for your help*

Dr A R Ali
Dr DM Andrews
Mr M G Bird
Dr M G Bird
Dr M J Broadhurst
Dr H B Broughton
Dr M J Browne
Dr J B Buckton
Dr Christie
Miss J W Christie
Mr Y-K Chung
C J Clements
S M Cooper
Dr M Courtney
Prof. J Crossland
Dr B Domayne-Hayman
Dr T Eaves
Dr A C Flind
Dr C D Floyd
Dr J L Fraser
Dr M Garbarg
Dr NM Hamilton
Dr S L Hart
Dr H J Herdon
Dr S C Hirst
Dr S Howard
Dr P Huxley
Dr F Ince
Dr R C F Jones
Mr S J Jones
Dr H H Khodr
Dr L J S Knutsen
Dr N Lench
J G Maconochie
Dr B J Meakin
Dr J Mercer
Dr G Metcalfe
Miss M Miller
Dr Y Mohamed
Dr P K Moore
Dr D Neuhaus
Dr U M Ney
Dr R A O'Donnell
Dr Reynolds
Dr M Rowley
Dr F H Sansbury
Dr Scopes
Dr D Selwood
Dr C Southan
Dr P D Stonier
Mr J Turner
Dr M S Tute
Dr M B Tyers
Ms E Vernon-Wilson
Dr T Ward
Dr C J Wareing
Dr G J Warrellow
Dr A W Wheeler
Dr M Whittaker
Dr D Wu

Chemokine Receptors and Drug Discovery

Report from our March 2004 meeting
by Simon Hodgson, Steven Charlton and Peter Warne

Chemokines and Drug Discovery was a one day meeting organised by the Society of Medicines Research, held at the Novartis Horsham Research Centre on March 11th 2004. Over 100 scientists attended this meeting, mostly from industry. The meeting was opened by **Professor John Westwick** (Novartis, UK) who underscored the importance of chemokine research in the search for new therapies for numerous diseases.

Steve Kunkel (University of Michigan Medical School, USA) set the scene with an introduction to the field of chemokine biology and their importance in many immunological and physiological events. Their role in recruiting specific leukocyte populations from the vasculature to areas of inflammation has made them an important protein target class for the development of new anti-inflammatory therapeutics. Despite their initial classification as chemotactic proteins, however, a growing body of data supports their role in many other biological processes, including activating cytokine networks, altering the expression of adhesion molecules, increasing cell proliferation, regulating angiogenesis, promoting viral-target cell interactions, increasing haematopoiesis, stimulating mucus production, increasing the metastatic potential of tumour cells and activating the innate immune system. As such, these proteins and their receptors are likely to play an important role in the progression of chronic immune responses, leading to disease.

Gurdip Bhalay (Novartis, UK) described a library-based approach to discovering multiple CC-chemokine receptor antagonists. The hypothesis behind the design of this library came from analysis of the significant patent literature existing for CCR1, CCR2, CCR3 and CCR5 receptor antagonists, where it was found that many if not all shared a common pharmacophore. Common features revealed were: a hydrophobic region linked to a basic nitrogen atom which is separated by a carbon chain from a second hydrophobic region connected *via* an amide, sulfonamide, urea or an isostere thereof (Figure 1).

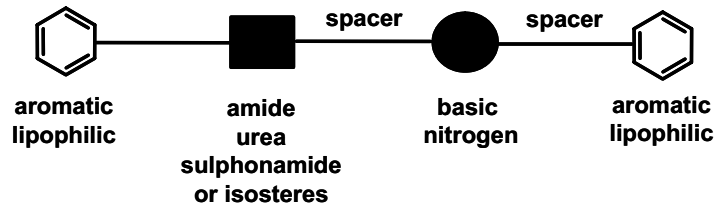


Figure 1 Putative pharmacophore model for CC-chemokine receptors

A library based on this pharmacophore was synthesised using fragments described in the patent literature, supplemented by commercially available building blocks. Compound activities at CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7 and CCR8 receptors were then tested and many potent (below 1 μM) compounds were discovered. Interestingly, many compounds showed activity and two or more receptors. In most cases, multiple receptors can be activated by a single chemokine, and it is anticipated that these multiple chemokine receptor antagonists may be more effective than compounds acting at a single receptor. In closing he suggested that at present it appears that combinations of CCR2-CCR3, CCR1-CCR3 and CCR3-CCR5 were the most feasible.

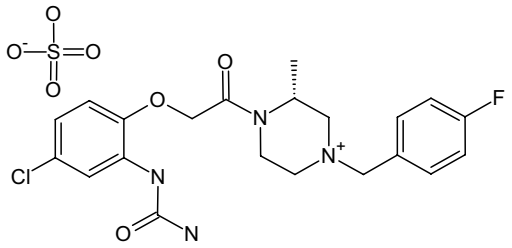
Ian Anderson (Cambridge Antibody Technology) offered a different approach to modulating chemokine function, namely the use of human monoclonal antibodies directed towards either the chemokines themselves or their cognate receptors. The important recent success of Xolair (anti-IgE antibody) in the treatment of asthma exemplifies the importance and value of the use of biological agents as drugs. Ian talked in detail about CAT-213, a high affinity (K_D 8.8 pM) anti-eotaxin1 IgG4 generated using phage display techniques. Eotaxin1 (also known as CCL11) is an important regulator of eosinophil and mast cell function, and is thought to play a role in the pathogenesis of asthma. CAT-213 is able to inhibit the biological function of eotaxin1 both *in vitro* and *in vivo*. It has a good safety profile and an elimination half-life of 8.5 days in man. Importantly, a randomised, double-blind clinical study showed that CAT-213 was able to inhibit eosinpohilia and mast cell numbers following intranasal allergen challenge in hayfever sufferers. These early successes suggest that CAT-213 may provide control of airway eosinophilia and therefore reduce exacerbation rate in patients with severe asthma.

The focus of the meeting then switched to work from several speakers who described results of small molecule chemokine antagonists that has progressed beyond the lead identification stage.

Richard Horuk (Berlex Biosciences, USA) described the potential importance of chemokines implicated in a variety of diseases, most notably autoimmune disease, and are commercially attractive in that they are GPCRs, a group which are the targets for more than 45% of all medicines. Since the first cloning of the CCR1 receptor and the subsequent maturation of cytokine biology, several CCR antagonists have been described in the patent literature.

Pfizer are developing a Phase II candidate for the treatment of rheumatoid arthritis (CP-481,715) and a CCR5 inhibitor for AIDS (see below), and there are CCR3 modulators targeted towards asthma.

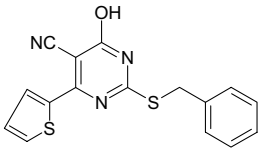
BX-471 (also known as ZK-811752) is a 2nM (Ki) inhibitor of the CCR1 receptor which is active in the EAE model of multiple sclerosis (MS) in the rat and shows promise in models of transplantation rejection. The product (see structure below) passed through Phase I trials during 2001 and 2002 and is currently in Phase II trials in MS patients which are scheduled to complete in July 2004.



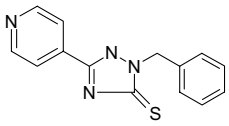
BX-471

Owing to a two orders difference in species specificity, BX-471 is considerably more active against the human CCR1 receptor than those of either the rat of the guinea pig. *In vitro*, low nM activity against the human receptor converts to Ki values in the region of 120 to more than 200 nM when tested against the corresponding rodent proteins. And high doses (5-50 mg/kg) have been necessary to show activity in the EAE model.
An interesting effect has been observed in a model of heart transplant rejection. Neither BX-471 nor cyclosporin alone is particularly active in this test (10mg/kg CysA required for activity) but together, BX-471 augments the effects of both low (2.5 mg/kg) and high (10 mg/kg) dose cyclosporin upon cumulative survival. Mechanistic studies suggest that BX-471 inhibits monocyte adhesion and subsequent infiltration of the heart from the systemic circulation. Similarly, In a model of kidney fibrosis in the rat (ligated ureter) treatment with BX-471 has been shown to reduce CD45 expression and fibroblast influx.

Roger Bonnert (Astrazeneca, UK) described their work on CXCR2 antagonists with interest in a range of immune and inflammatory diseases. In particular, the work focused on taking the output from an HTS and conducting hits to leads work and lead optimisation on three templates, pyrimidines, (1) triazoles (2) and pteridines (3).



(1)



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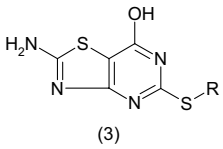
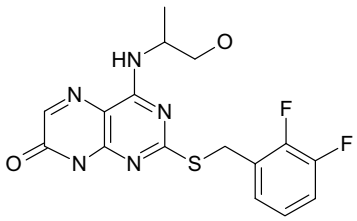


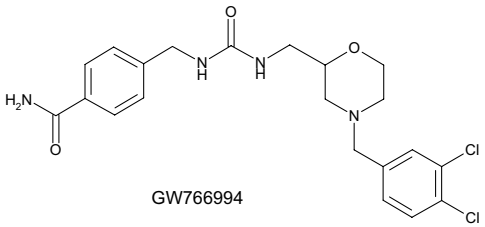
(3)



(4)

The target was PIC50 =8, pA2 in whole blood of 6 and other features of developability (selectivity, P450, solubility etc). A 20x80 matrix array of the pteridine template gave an example (4) with high potency, pIC50 =9, and 40% oral bioavailability in the rat.

Simon Hodgson (GlaxoSmithKline, UK) described their work on CCR3 antagonists for asthma and allergy. Based on pharmacophore generation and array work, an animomethylmorpholine series was identified. Lead optimisation gave a series of acetamides, an example of which had good PK properties in rat, guinea-pig and dog. However, some P450 inhibition and extensive metabolites were seen. A series on ureas was optimised, giving GW766994. This profile of this compound was described and had good selectivity, PK in rat and dog, no significant P450 inhibition, and the compound had now entered clinical development. GW766994, and its profile was the first CCR3 antagonist to be described in clinical development. The GSK series showed an interesting set of anti-inflammatory effects on eosinophils in rat and guinea-pig, and on clinical outcomes and mast cell degranulation in a mouse model of allergic conjunctivitis.

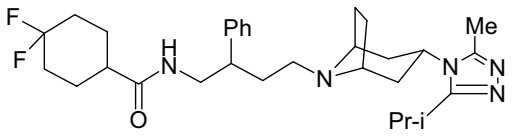


GW766994

David Price (Pfizer Global Research, UK) completed the meeting with the possible application of CCR5 antagonists to address AIDS. In spite of significant progress made in the treatment of AIDS in recent decades, there remains a need for improved therapy. Resistance to existing therapy is greater than 10% and there are toxicity and tolerance limitations so that more than 50% of all patients are forced to change their treatment.

The involvement of CCR5 in the transmission of AIDS is derived from a small population of patients in whom there is a 32 base pair deletion in their CCR5 expression. This group are immune to HIV even though they continue with high risk sexual behaviour. Similarly, heterozygotes display a delayed progression of the disease compared with homozygous wild types. These findings have now been reconciled by the demonstration that CCR5 activation is essential for the interaction of the lymphocyte CD4 receptor with the gp120 viral protein.

The Pfizer scientists had a clear vision for their product; a potent and durable antagonist of CCR5 suitable for once daily dosing and devoid of P450 inhibition (an issue pertinent to the use of several of the current products). Starting from a known compound in the company collection (UK-107543) and analogues, an early breakthrough in the demonstration of antiviral activity was complemented by modification to remove P450 2D6 inhibitory activity. UK-382,055, however, inhibited the hERG channel and required structural modification to increase its cardiac safety profile. This was achieved in the shape of UK-395,859 but although initially exciting, this product suffered from poor cell permeability. Other modifications increased cell permeability but introduced metabolic instability and it needed a change of chemical scaffold before UK-427,857 could emerge.



UK-427,857

UK-427,857 has IC90 antiviral activity of 2.1nM and while the product is still poorly orally bioavailable, this potency coupled with a sound safety profile is regarded as acceptable for project progression at a dose of 100mg bid. Key to the product's efficacy are its slow offset binding kinetics which contribute to potency and reduce the impact of apparently adverse pharmacokinetics. The product is currently undergoing Phase II trials.

Simon Hodgson, Steven Charlton and Peter Warne, SMR Committee

Type II Diabetes: Mechanisms and Emerging Therapeutic Targets

Report from ourJune 2004 meeting
by Robert Williams and Ian Morris

The SMR Symposium 'Type II Diabetes: Mechanisms and Emerging Therapeutic Targets' was held on 17th June 2004 at the National Heart and Lung Institute, Imperial College, London. The conference programme brought together an international program of speakers representing academia, small biotech and large pharma to review approaches aimed at increasing our understanding of the aetiology of the disease and advances in the development of novel therapeutics. Type II Diabetes is a major, worldwide healthcare problem and the incidence of this disease is rising. In the USA alone 13.3 million people were diagnosed with diabetes in 2002, an increase of 5.8 million in a decade following an alarming trend beginning in the eighties. People who have diabetes are at an increased risk of developing serious life threatening complications, notably cardiovascular disease as well as experiencing morbidity, which severely impairs their quality of life. This trend will pose an increasing burden on governmental healthcare budgets.

It is not often that the start of a meeting confronts the audience with a cryptic clue of what was coming next but that is what the first speaker did. **Victor Zammit** from the Hannah Research Institute in Scotland presented his first slide which said 'What if Minowski had been aguesic?' to the bewilderment of some of the audience. It however soon became obvious that the audience was being focused on the essential role of fatty acid metabolism in the aetiology of Type II Diabetes initially by drawing attention to the article published in Science by John McGarry in 1992. Diabetes has long been considered a disease of glucose metabolism but it has become clear in recent years that it is also a disease of deranged lipid metabolism. Metabolic Syndrome, first defined in 1989, is a condition that predisposes to the development of Type II Diabetes and is a collection of health risks including abdominal obesity, high serum triglycerides, low HDL-cholesterol, high blood pressure and elevated blood glucose. This condition has also been referred to as Insulin Resistance Syndrome as decreased efficacy of insulin is an important characteristic. Fatty acids affect glucose metabolism, insulin-signalling and insulin-secretion at multiple levels. For instance, a key finding has been that malonyl-CoA, a product of glucose metabolism, inhibits fatty acid oxidation via inhibition of carnitine palmitoyltransferase (CPT1). This leads to increased synthesis of di- and tri-glycerides, which in turn inhibit insulin mediated glycogen synthesis and glucose uptake. Elevated malonyl-CoA levels have also been implicated in dysregulation of satiety signalling. Zammit also was able to link pancreatic beta cell dysfunction in the pre-diabetic state to FFA exposure through down regulation of the PPAR gamma receptor. The emergence of insulin resistance and beta cell dysfunction occurs in parallel in spite of having a different mechanistic origin. Thus the multiple effects of FFAs and glucose synergize in the aetiology of Type II Diabetes so offering the prospect of a diversity of therapeutic targets.

Following on from Victor Zammit's introductory tour around the biochemistry of glucose/fatty acid interactions in the development of insulin resistance, **Andreas Kopke** from Devgen (www devgen.com) in Belgium spoke about the utility of an invertebrate model in the search for new drugs modulating this axis. Devgen have capitalised on the extensive literature on *C. elegans* as a model organism for an enormous number of biological processes. These nematode worms are 1 mm in size, comprised of approximately 1,000 cells and are amenable to liquid handling in micro plate format. Molecular pathways are orthologous to the 70% of the human pathways represented in the worm genome. Devgen have deployed a variety of knock in/knock out technologies to interrogate effects on a range of phenotypes in high-throughput experiments. Interestingly these approaches have produced worms with impaired insulin signalling and accumulation of fat droplets, representing a model of obesity, which may involve DAF2, the worm equivalent of the IGF-1 receptor. Devgen's proprietary approach in this area is a novel approach to RNA interference technology by genetically engineering the RNAi into *E. coli*, which are eaten by the worms. Subsequently, digestion of the plasmid releases the active RNAi within the worm. A number of druggable targets have been identified by this approach and further validated in mammalian systems. These include two kinase targets with a role in diabetes and obesity. 'Kinase 1' has subsequently been knocked out in mice and confers protection against high fat diet induced glucose intolerance. In addition to biological target validation, Devgen have a library of nearly 100,000 compounds, which are used in lead generation against validated targets. A druggable lead against kinase 1 with an affinity of 400nM has been identified.

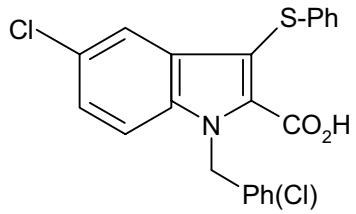
Philippe Froguel, Head of the Hammersmith Genome Centre in London delivered the final presentation of the morning. Professor Froguel reviewed the contribution of genomics and genetics to target identification in Type II Diabetes. One of the driving forces behind this approach is the recognition that current therapies are unable to prevent deterioration of the pancreatic beta cell and progression of the disease. Monogenic forms of Type II

Diabetes (5 % of all cases) have aided our understanding of molecular determinants of glucose homeostasis. Glucokinase was identified in 1992 by a familial gene linkage analysis. Inactivating mutations in this enzyme, which acts as a glucose sensor in pancreatic β cells and hepatocytes, leads to the development of maturity onset diabetes. Activators of this enzyme have been identified and show major potential as new drugs for Type II Diabetes. Diabetes however is largely a polygenic disease arising from the interplay between genetic and environmental risk factors. Professor Froquel described some of his work examining whether current diabetes treatments target susceptibility genes. Findings have revealed that variants of the β-cell K_{ATP} channel Kir 6.2 and the sulphonyl urea receptor are associated with diabetes in humans. In contrast a pro12ala mutation in the PPARγ transcription factor increases insulin sensitivity and is a protective variant. Several single nucleotide polymorphisms in the adiponectin gene have been show to modulate production and polymerisation of this 'adipokine', which promotes insulin sensitivity and inhibits hepatic lipid output. Pima Indians in the USA have a high incidence of Type II Diabetes and it has been reported that the most predictive protective factor in this population is adiponectin levels. Professor Froquel stressed that a focus on translational research and alliances between academia and industry would be required to make significant breakthroughs in the treatment of Type II Diabetes leading in the future to rational, individualised prescribing.

Matthew Coghlan from the Diabetes and Drug Discovery Team of Astra Zeneca, UK also described Glucokinase as a target of interest. Glucokinase (GK) is a variant hexokinase the expression of which is restricted to the pancreas, liver, brain and gut. It is physiologically important as GK is the rate limiting step for glucose uptake into cells. As the kinetics of this enzyme are sigmoidal its allosteric activity is highly sensitive to glucose concentrations and insulin secretion is triggered in the beta cell at 25% of the Vmax of GK. Activators of this enzyme therefore have the potential to promote glucose uptake and insulin secretion leading to better control of blood glucose. In addition to evidence from human genetics, this approach has also been validated in transgenic mice carrying an activating mutation of GK. The threshold for glucose stimulated insulin secretion is reduced in these animals. High throughput screens subsequently identified and 2 [6-[(3-isobutoxy-5-isopropoxybenzoyl)amino]nicotinic acid and 5-([3-isopropoxy-5-[2-(3-thienyl)ethoxy]benzoyl]amino)-1,3,4-thiadiazole-2-carboxylic acid as competitive inhibitors of the closed inactive conformation of GK that increase overall activity. Studies of the mode of action of these compounds indicate that they bind to the enzyme at some distance from the catalytic site and in some respects may reflect changes similar to the activating mutations studies in the transgenic mice. *In vivo* the compounds promote glycogen synthesis in rat hepatocytes and improved the results from glucose tolerance tests. Future studies in man will determine whether these compounds live up to their therapeutic expectations.

Joel Berger, Merck Research Laboratories USA, presented a look into the future of research arising form the discovery of PPAR receptor activation by the thiazolidinediones (TZDs) and fibrates. TZDs are agonists of the gamma receptor subtype of PPARs, which are ligand regulated transcription factors. PPARγ is highly expressed in adipocytes. TZDs possess anti-lipaemic and anit-glycaemic properties and have proven to be efficacious in the treatment of Type II Diabetes for a number of years. However, significant side effects including weight gain and cardiovascular changes have emerged which are restricting more widespread application of these agents. Merck have discovered a unique class of non-TZD partial agonists of PPARγ that have been shown to be less adipogenic than full agonists based on *in vitro* assays and to induce a unique gene signature profile. These compounds are as effective as full agonists in terms of anti-glycaemic activity in mice, but do not cause cardiac hypertrophy. This class of compound may prove to display a more favourable therapeutic window in man compared to full agonists.

nTZDpa



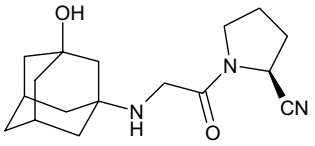
A further interesting target highlighted by PPAR research is 11-β hydroxysteroid dehydrogenase-1 (11β-HSD-1). This enzyme is highly expressed in insulin responsive tissues where it converts the adrenal hormone corticosterone to the more potent cortisol. Over expression of 11β-HSD-1 in animals causes insulin resistance whilst PPAR agonists inhibit expression of the 11β-HSD-1 gene. The drug discovery team at Merck have taken this observation to the next step and have identified novel inhibitors of 11β-HSD-1 that display anti-lipaemic, anti-glycaemic and insulin sensitising activity in animals. Further gene microarray studies have led to the discovery of compounds possessing both PPARα and γ

activity and favourable effects on the expression of multiple genes known to control lipid metabolism.

Phosphatases as a target for the treatment of diabetes have only recently emerged although **Agnes Bombrun** from the Serono Pharmaceutical Research Institute, Switzerland, recalled in her talk that clues have been around for many years. Vanadium, a phosphatase inhibitor, was first used for the treatment of diabetes in 1899. Protein tyrosine phosphatases (PTPs), in particular PTP-1B, are a well described component of the negative regulation of insulin receptor signalling and are the focus of a research programme at Serono. In mice, disruption of this gene enhances insulin sensitivity and improves glucose tolerance and obesity. In order to be active phosphatase inhibitors, of which there are a substantial number available for experimental studies, must mimic a dianionic phosphotyrosine. However once this activity is established the translation from the test tube to *in vivo* treatment raises many hurdles, not least of which is how to deliver such a drug to an intracellular target. The molecular polar surface area versus molecular weight relationships allowed some selection from many of the compounds described in the literature. Using this information Serono developed novel compounds for further study although *in vitro* potency was not always carried with drug like properties such as selectivity or solubility. Using this approach a number of chemical series were selected (oxindoles hydrazides, pyrrazolidinediones and substituted methylene amides) and carried forward into further testing. Although the structures were not disclosed several inhibitors were tested in an interesting *in vivo* model of diabetes, the db/db mouse which has a spontaneous mutation in the leptin receptor. These mice are obese, hyperglycaemic, hyperinsulinaemic and have impaired insulin sensitivity, which lends itself to being an effective screen for PTP-1B inhibitors. PTP-1B inhibitors with good pharmacokinetics and pharmacodynamics have now been identified and are in the process of more extensive preclinical testing.

Dr James Foley from the Global Clinical Development and Medical Affairs group of Novartis, USA outlined the company's philosophy towards research in the diabetes area moving on to describe advances in their dipeptidyl-peptidase-4 (DPP-4) programme. In the 1990's Novartis switched focus from trying to stimulate glucose uptake into muscle to focus on dysregulated insulin secretion and impaired suppression of glucagon as key events. Novartis scientists focussed in on the therapeutic potential of incretin hormones released from the gut and the multiple mechanisms of GLP-1. GLP-1 infusion reduces fasting glucose and improves insulin sensitivity and β-cell function in man. Animal studies have also revealed a role for GLP-1 in stimulating β-cell neogenesis and decreasing apoptosis. A fundamental problem when looking at GLP-1, a protein, as a potential therapeutic is its short half-life (1-2 minutes). Novartis decided to adopt a strategy of searching for inhibitors of the enzyme DPP-4, responsible for degrading GLP-1. The approach was validated when the DPP-4 inhibitor valine-pyrrolidide was shown to improve glucose tolerance in rodents and monkeys. Novartis' combichem effort identified the lead molecule in this area, LAF237, which binds specifically to the catalytic site of DDP-4 and improves the half-life of GLP-1 to about 130 minutes. This compound is a potent (k_d = 5 nM) and reversible inhibitor of DPP-4 that displays good oral bioavailability (~ 80 %) and does not significantly inhibit p450 enzymes. Phase 2 evaluation yielded highly promising results and LAF237 is currently in phase III trials. Clinically, LAF237 shows a durable effect in lowering HbA1c levels in combination with metformin. LAF237 is also effective as a monotherapy and does not promote weight gain. Interestingly there are other DDP-4 inhibitors of different chemical classes in development by other pharmaceutical companies which may be a good sign of the utility of these compounds

GLP-1 has also provided the foundation for the discovery



LAF237

of a new promising protein therapeutic being developed by Novonordisk, Denmark, their program being presented by **Lotte Bjerre Knudsen**. GLP-1 has been validated clinically as a potential treatment for Type II Diabetes. Infusions of GLP-1 to patients with Type II Diabetes have been shown to be beneficial in controlling both blood glucose and body weight. Acylation of GLP-1 increases the binding of the peptide to serum albumin and prolongs its bioavailability by protecting the peptide from degradation by DPP-4. Further development of this chemical strategy also demonstrated that extensive acylation as well as modification of the N terminus of the peptide reduced the potency showing that the opportunities for the discovery of a therapeutically useful compound were limited. Liraglutide, Arg(34)Lys(26)-(N-epsilon -(gamma-Glu(N-alpha-hexadecanoyl))-GLP-1(7-37), a peptide with a long chain fatty acid (palmitoyl) modification was finally chosen as the lead compound with a good pharmacokinetic profile for a once a day administration. Liraglutide has a bioavailability of 55 %, T_{max} =9-12 hours, $T_{1/2}$ =11-15 hours and steady state

concentrations were reached after 3 doses. Liraglutide is currently in phase 2 trials. No serious adverse effects have been recorded although the dose limiting factor is nausea. In patients with mild Type II Diabetes Liraglutide decreases fasting and food related blood glucose, which was associated with an increased insulin secretion. In obese patients liraglutide prevented weight gain. Interestingly in rats liraglutide inhibited food intake, improved food preferences and decreased body weight, data that support the suggestion that these compounds may also play a role in the control of satiety and food intake, a beneficial activity in the treatment of Type II Diabetes.

It is pertinent to close this review of this meeting of the Society for Medicines Research with the observation that there is clearly an unmet need in the pharmacological treatment of Type II Diabetes, The UKPDS study shows that after about two years of treatment the current modalities gradually loose effectiveness. We hope that the current research effort so effectively demonstrated by the speakers at this conference will reverse this trend.

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Dates for your diary

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Trends in Medicinal Chemistry
2nd December 2004
National Heart & Lung Institute, London

Chemical genetics and genomics
10th March 2005
National Heart & Lung Institute, London

The therapeutic potential of tissue engineering and regeneration
15th June 2005
National Heart & Lung Institute, London

Cardiovascular disease
8th September 2005
Organon Laboratories Ltd, Lanarkshire

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