The Newsletter for the Society for Medicines Research

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Highlights from the SMR Syposium Orphan G-protein Coupled Receptors

by Ian Morris and Robert Williams

In recent years research activity surrounding the G-protein coupled receptors (GPCRs) has accelerated greatly. For instance bibliometric analysis of hits for GPCRs on the database Pub Med shows that over four times as many publications on GPCRs appeared in 2001 compared to only five years earlier in 1997. This activity has arisen as a direct result of the phenomenal worldwide effort focused upon the sequencing of the human genome, a task now recently completed. Bioinformatic analysis of genome sequence information has led to the identification of numerous GPCRs, many of which have been termed 'orphan receptors', or receptors that do not possess a recognised ligand. Initial estimates suggested that there may be thousands of unpaired GPCRs, although more recently this figure has been revised downwards to fewer than 400.

It is perhaps no surprise that the pharmaceutical industry has invested heavily in this area in view of the established success of drugs acting as agonists or antagonists of GPCRs for catecholamines, histamine, 5-HT

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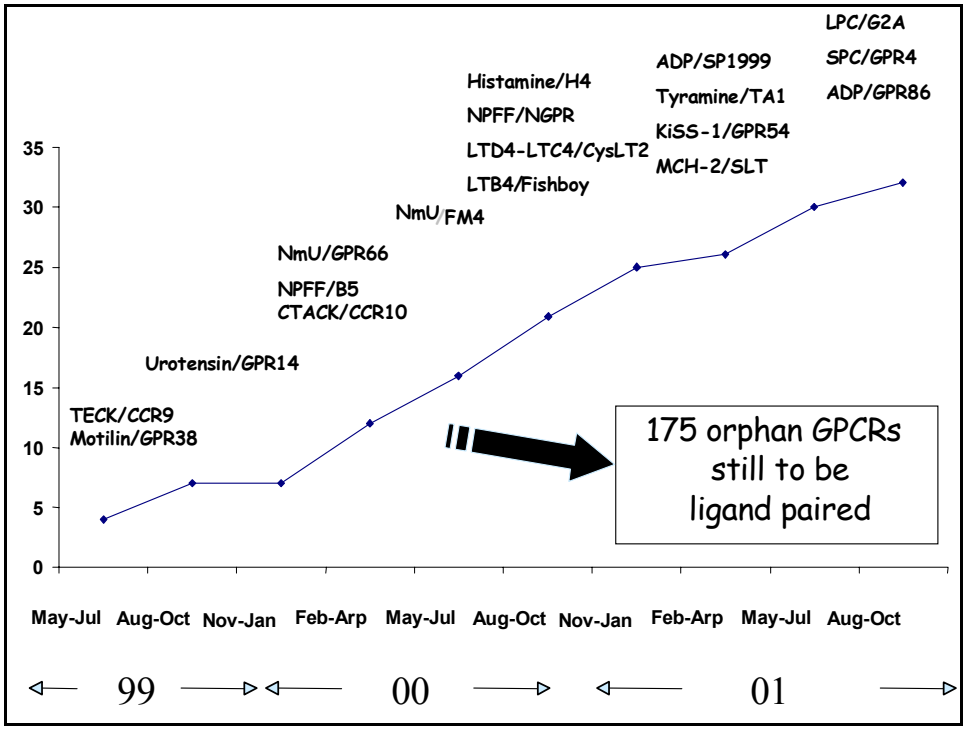

Figure 1 The trend and importance of orphan GPCR: ligand pairing. The number of ligands reported to have been paired to an orphan receptor has been plotted against the date of the report. With permission from Dr M Fidock

Call for New Logo for SMR

Everyone knows that logos are important for an organisation. The last SMR logo was designed by a committee and evolved via discussions in the 1970s. From hand-drawn mock-ups, the present logo signifies the interaction of a ligand with a receptor, in the cartoon style representation of the time. Thirty years on, we think the SMR needs a new logo.

Companies and organisations often use logo re-design in a wider corporate re-branding exercise. In 1999, the oil giant BP Amoco spent some US$100 million in an advertising campaign, replete with a new 'helios' logo on a green background and the 'Beyond Petroleum' slogan together with public acknowledgement that climate change is happening and that greenhouse gas emissions play a role in the process.

Members will be relieved to learn that the proposal to re-design the SMR logo is not likely to cost that much, nor is any publicity campaign envisaged. We recognise that one of the SMR's core assets is the creativity of its membership, and plan to tap into this resource for ideas as a first step.

We invite members with an artistic talent (however 'budding') to submit proposals for a new SMR logo, and as an incentive are offering travel vouchers to the value of £350 for the chosen winner. At

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SMR Committee

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etc. in a wide range of therapeutic areas. Mark Fidock (Pfizer UK) presented to the meeting an analysis of recent studies identifying ligands for novel GPCRs showing the speed of appearance of studies, which have deorphanised receptors (see Figure 1). Thus, the orphan GPCRs may be viewed as a Pandora's box with the promise of major drugs to be discovered providing fortune is on the side of the potential adoptive parent. The Society for Medicines Research convened a timely meeting on this dynamic and highly competitive field, which was held at the Novartis Research Centre, Horsham in April 2002. The meeting attracted a large and enthusiastic audience to hear about the research efforts of leading international research teams in this area whose immediate aim is to evolve these novel molecular targets into lead discovery programmes.

Overview: drug hunting among GPCRs

The scene was set with an overview by Dr Bob Coleman (Pharmagene, UK), who has spent over 35 years 'drug hunting' in the GPCR area. Many of these years were spent at Glaxo, a company with a rich history in the successful identification of GPCR modulating drugs, which have become the most fruitful class of molecular target for the pharmaceutical industry. In 1968 Allen & Hanbury launched AH3365 (salbutamol, Ventolin) as a bronchodilator for the control of asthma. This drug, a beta-2 GPC adrenoceptor agonist, transformed the company from an organisation known for manufacturing pastilles to a drug discovery company. Salbutamol was the first of Glaxo Group Research's raft of successful drugs modulating GPCRs, which include ranitidine (Zantac), labetolol (Trandate), sumatriptan (Imigran), ondansetron (Zofran) and salmeterol (Serevent). There were, however, frustrations among the success stories with unsuccessful efforts to develop drugs acting at prostanoid receptors. Even so in 2000, 26 of the world's 100 top-selling drugs target GPCRs, amassing annual sales in excess of US$20 billion.

Dr Coleman finished his overview by stressing the importance of examining human, rather than animal, tissue distribution of novel GPCRs when looking for clues to do with potential areas of future therapeutic utility. Using a bank of over 70 tissue-specific mRNAs and quantitative RT-PCR technology, Pharmagene has mapped the relative receptor concentrations of many GPCRs. The robustness of this technique was demonstrated with reference to prostanoid EP-3 and dopamine-D1 receptor mRNA distribution, which correlated well with established pharmacology.

GPCR application in searching genome sequences

Merck Research Laboratories' GPCR research strategy of searching genomic sequences, cloning novel open reading frames and expressing the mRNA in systems suited to the application of aequorin and aurora ß-lactamase screening technologies was described by Dr

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Jim Liu. This approach led to the identification of neuromedin U as a ligand for the novel GPCRs, FM3 and FM4. The neuropeptide NPVF was identified as a novel ligand for the receptors GPCRB5 and HG31 (also known as FF1/FF2). Once the ligands had been identified they were used in tissue-distribution studies to reveal discrete patterns of receptor expression in brain and spinal cord. NPVF, when administered intrathecally, was found to potentiate opiate-induced analgesia via activation of FF2 receptors. In contrast, administration of NPVF into the cerebral ventricles antagonised opiate-induced analgesia via an FF1-mediated mechanism. These receptors are currently a focus for efforts to derive novel, pain-modulating drugs. However, many neuropeptides play a role in multiple physiological pathways and the discovery that neuromedin U modulates food intake has provided the opportunity to pursue another goal to develop novel anti-obesity drugs.

Bioinformatics has provided the foundation for many of the GPCR research programs although many scientists do often not appreciate the limitations of this approach. Professor Terri Attwood (Manchester University) set the scene for her presentation with the introductory slide 'which (witch) craft is best' supported by pictures of bubbling cauldrons. The presentation drew the audience's to attention the complexities of the in-silico world of bioinformatics and highlighted the need for caution when interpreting the output of database interrogation. The challenge of family analysis is to distinguish between highly divergent families with a single function or super-families with many diverse functions. Using the rhodopsin, opiate and muscarinic GPCRs as examples, Professor Attwood showed how a number of databases (for example, BLOCKS, PRINTS, PROSITE, PROFILE, PFAM and eMOTIF) could be accessed for 'motif-based' searching based upon the sequences of the transmembrane and loop domains. A particular problem commented on was the generation of false-negative data when using pattern matching based on single motifs, which can be over 20%.

The PRINTS program developed at Manchester University searches using multiple motif diagnostic 'fingerprinting' that characterises protein function. The overall message was clear. There are lots of databases and searching strategies need to be carefully formulated when trying to annotate sequences. Using a basic BLAST and PROSITE approach is likely to generate a significant amount of misleading information because of false negatives, false positives, annotation errors, etc. The user must also be cautious when using so-called 'expert systems', such as Genquiz, Magpie and Pedant which may rely heavily on BLAST and PROSITE. An integrated approach to find a consensus was likely to be the most successful although often more demanding in its execution. The reality check was that three-dimensional structures of proteins are still difficult to predict from DNA-sequence information and confirmation of biological activity will still require the witchcraft of *in-vivo* and *in-vitro* biological experimentation.

Work at GSK on novel ligand-orphan receptors

Dr Alan Wise (GSK, UK) addressed the use of functional genomics to identify novel ligand-orphan receptor pairings to family-A, non-sensory GPCRs. The multidisciplinary approach for effective target discovery was clear in this and other presentations from the impressive array of collaborators in bioinformatics, gene, cell and tissue biology as well as technologists well versed in high-throughput screening. The genealogy of this family shows interesting group homologies such as those shared by the leukotrienes and the PAF-like ligands or the adenosine and biogenic amine ligands and represents a wide variety of functions from olfaction to contraction of smooth muscle. Many of these receptors are not present in flies or worms, which may be indicative of a role in the mammalian central nervous or immune systems. After in-silico identification and selection of putative therapeutic targets GSK's typical orphan strategy focuses on receptor expression in mammalian (CHO, HEK293), yeast or Xenopus cells and screening against a panel of putative ligands. Functional readouts include yeast cell proliferation, calcium mobilisation, aequorin and pigment dispersion in melanophores. An advantage of

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using yeast as an experimental system is that work can be performed against a 'GPCR null' background. Yeast experiments identified GPR41 and GPR43 as receptors for short-chain fatty acids. GPR 41 is strongly expressed in adipose tissue and inhibits lipolysis but the role of GPR 43 is more difficult to define, as the tissue expression profile is more variable.

Identification of Axor35

Another interesting line of research was the identification of the GPCR Axor35, which phylogenetically was classified as an aminergic receptor closely related to the muscarinic GPCR and subsequently found to be a novel histamine receptor. When expressed in HEK293 cells the receptor was liganded by agonists (Imetit) and antagonists (thioperamide) previously thought to be H3-selective. However, expression profiling helped to identify Axor35 as a novel histamine receptor (H4) that was originally described pharmacologically in human oesinophils in 1994. Dr Wise concluded his presentation by illustrating the rapid advances in the field using the OGR1 GPCR and orthologues, which are activated by lipids such as sphingosylphosphorylcholine. Predicted future work would reveal many interesting opportunities in this very competitive field.

In a complementary presentation Professor Hans Bräuner-Osborne focused on the family-C GPCRs that are characterised by a large extracellular ligand-binding N-terminal domain. This family includes receptors for the neurotransmitters GABA and glutamine as well as for calcium. Novel receptors were sought using the sequence of GluR2 as a BLAST query that generated around 80 hits. Receptors identified using this strategy include GPRC5B, GPRC5C, GPRC5D and RAIG1, which were subsequently cloned for further investigation.

A role in cancer has been speculated about based on reports that a chromosomal locus containing RAIG1 and GPRC5D is deleted in a number of tumours and also that transcription of these receptors can be induced by retinoic acid, a treatment used for certain leukemias. However, the identification of the endogenous ligands was complicated by wide tissue expression, the small extracellular domain and the low sequence identity to the liganded family-C GPCRs. Even so it was possible using chimeric Ca and orhan GPCRs to delineate some of the intracellular signal-transduction pathways of the receptors. Screening of >1,000 putative ligands using a FLIPR (fluorescent-imaging plate reader)-based approach has failed to identify an activating ligand for these receptors. The deorphanisation of this group of GPCRs is likely to be challenging.

Global research in seven centres

Pfizer's global research into orphan GPCRs has been established in seven centres located throughout the world reflecting the intense competition in this area. Dr Mark Fidock (Pfizer, UK) described an orphan GPCR strategy not dissimilar to earlier speakers in the meeting, namely expression of receptors in a variety of host systems followed by screening of putative activating ligands. 'Reverse pharmacology', or identification of the receptor target before the generation of an agonist or antagonist is the modern paradigm for drug discovery being especially amenable to high-throughput screening.

The development of a robust screening platform was essential to efficiency of the program and aimed to ensure that the activation of all receptors resulted in the same measurable endpoint. To achieve this chimeric G proteins have been engineered to ensure signal transduction passes through the Pi pathway. The Aurora technology was a useful integrated method resulting in the activation of transcription of the beta-lactamase reporter gene that lies at the watershed of several transduction cascades.

Dr Fidock indicated that the strategic rationale for this was that the approach capitalised on efficiencies of scale, use of high-throughput technologies and synergies in medicinal chemistry. Even so the task and competition is so great that partnerships are essential for the rapid development of any drug discovery program and Pfizer's strategy has included associations with Celera, Incyte, Gennaisance, Deltagen, Inpharmatica, Lifespan, Genelogic and Affymetrix. The GPRC database built up by Lifespan is especially well developed and can provide data mining and curative services as

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well as tissue-specific and disease-associated information. The tie between bioinformatics and immunohistochemical localisation has proven to be especially useful. Deltagen's high-throughput knock-out (KO) mice technology can quickly generate analyses of phenotypic function of a particular gene. Dr Fidock presented data to show how use of KO animals in *in-vivo* screening for anti-psychotic drugs can greatly facilitate the discovery process. Dr Fidock rounded off his presentation by demonstrating the utility of the gene to drug target strategy using the GPCR orphans for histamine-H4 and NmU2R as potential drug targets in eosinophil function and appetite control, respectively.

GPCR applications in respiratory disease

GPCRs in respiratory inflammatory disease were established as a target with the advent of salbutamol, however, Dr Graeme Wilkinson (AstraZeneca) undertook to show that the beta adrenoceptor is not the only opportunity for intervention. Any disease process is the sum of pathological changes taking place in numerous cells involving, in this case, mast cells, eosinophils, dendritic cells and T cells. An understanding of the functions of these cells in asthma underpins the focus of the AstraZeneca programme. Cytokines play a key role in allergic diseases and GPCR mediated control of cytokine production in T-helper cell subsets (Th-0, Th-1 and Th-2 cell clones) is a key focus. A novel type-B GPCR was found to be differentially expressed in T-helper cells. In-silico data mining identified 16 GPCRs of interest some of which were highly expressed in eosinphils and other inflammatory cells. Using this information the group has discovered a novel neuropeptide-like ligand. Further evaluation of peptides, however, often requires the generation of antibodies as biological tools, which can delay research activities. Dr Wilkinson outlined the use of phage display, which offered a faster, more-controlled method for the generation of monoclonal reagents.

Using phage-generated antibodies, an unspecified orphan GPCR was localised to the cell membrane when expressed in HEK 293 cells. The orphan GPCR was also coupled to intracellular calcium in the FLIPR assay and could be activated by agonists identified in screening programs.

American work on trace amine receptors

The final speaker of the meeting, Dr Tom Blackburn, crossed the Atlantic from Synaptic Pharmaceuticals (New Jersey) to give an evocative talk called 'Trace amine receptors — a new GPCR family, from a neoclassic pharmacological era'. Although the trace amines have a defined neurotransmitter role in invertebrates, the presence of ß-PEA, tryptamine, tyramine and octopamine in the mammalian nervous system was, until recently, something of a mystery.

Synaptic Pharmaceuticals identified 15 GPCRs for the trace amines and so established a new family and new functions for the trace amines in their own right. Dr Blackburn sought to convince the audience of the biological importance of trace amines by suggesting that among the pharmacologically active ingredients of chocolate, the trace amines, ß Phenylethylamine (ß-PEA), tyramine and tryptamine may account for the popularity of this confection. However, his description of the association of headache with tryptamine intake was perhaps more convincing, as this amine is present in high concentration in Chianti red wine!

Human and rodent receptor for biogenic amines

A human and rodent receptor for these biogenic amines, TA1, when expressed in Cos-7 cells binds tyramine with high affinity and specificity. There are, however, some interesting species differences. For instance, the Ki (nM) for the human compared to rat TA1 receptor is 8 cf 57 for ß-PEA, 57 cf 176 for amphetamine and 1084 cf 7 for tryptamine.

Perhaps disappointingly, an antagonist at the rat receptor was weakly active when tested against the human receptor. Expression of the mRNA is also species specific so while both rat, mouse and human stomach express TA1 mRNA, TA1 expression in the amgydala is only observed in the mouse. Interestingly, the genes for the GPCRs TA 2 to 5 are located within a susceptibility locus for schizophrenia on chromosome 6. ß-PEA, a TA-receptor agonist, increases monoamine oxidase release and has been found to be low in attention-deficiency disorder and depression and high

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Medicinal Chemistry at the University of Strathclyde

by Professor Roger Waigh

Research in medicinal chemistry at Strathclyde is conducted both in the School of Pharmacy and the Department of Pure and Applied Chemistry. Much effort has been invested over the last 10 years, primarily driven by the Strathclyde Institute for Drug Research (SIDR), to bring together scientists from a range of disciplines with common interests in new pharmaceutical molecules. The scope of this collaboration has recently been widened with the formation of the Synergy link with Glasgow University and particularly 'Pharmalinks', which brings together chemists, biochemists and biologists in the two institutions. This short article will concentrate on the activities at Strathclyde.

The best-known product from medicinal chemistry at Strathclyde is atracurium, which was developed under the direction of John Stenlake and Roger Waigh in the then Department of Pharmaceutical Chemistry, now subsumed into the Department of Pharmaceutical Sciences. Atracurium is a muscle relaxant which breaks down primarily by Hofmann elimination in the bloodstream and thus does not require the presence of enzymes which may vary, giving rise to unpredictable duration of muscle paralysis. The compound, first developed by Wellcome, has been very successful and made a major contribution to the university's finances over the last 20 years.

Atracurium was developed from bisbenzylisoquinolines related to tubocurarine, a natural product.

A focus on natural products

Subsequent work in many different fields has concentrated mainly on natural products as leads, assisted by a very prolific research programme conducted by Sandy Gray and others, which has resulted in the isolation and identification of over 400 new natural products from higher plants in the last 20 years. This effort has recently been strengthened by the part-time recruitment of Robert Nash, who specialises in natural glycosidase inhibitors; Robert is also research director of MolecularNature Ltd and has a research team at the Institute of Grassland and Environmental Research in Aberystwyth.

An example of the benefits of pursuing natural products as leads comes from the discovery that nitidine, a benzo[c]phenthridine, has potent antimalarial activity. This came from ethnopharmacological work with members of a Kenyan tribe, who use the plant *Toddalia asiatica* to treat fevers. Subsequent chemical development has improved its potency against chloroquine-resistant Falciparum malaria to low nanomolar concentrations *in vitro*.

Collaboration between scientists in pharmacy and chemistry (Colin Suckling and Roger Waigh), stimulated by SIDR, has resulted in a long-running programme of synthesis of DNA minor-groove binding agents. This work started with substantial industrial funding but latterly has received synergy support. Unlike some of the previous work in the US, this project has focused from the outset on retaining deliverability of the end products as potential medication; physicochemical properties and particularly molecular weight have to be considered if this very tempting route to new pharmaceuticals is to give clinically useful results. Application of some novel ideas has given compounds with much improved affinity and sequence selectivity, the subject of a very recent patent application. John Parkinson has recently joined the Department of Pure and Applied Chemistry and brings a portfolio of abilities, including a high level of expertise in NMR studies of ligand-DNA interactions.

Expertise in the wider areas of synthetic organic chemistry, closely allied to medicinal chemistry, is represented by John Murphy, William Kerr and Colin Gibson. Ewen Smith and John Reglinski are primarily interested in biological inorganic chemistry, for example the biological effects of gold and selenium, while Peter Halling, Mark Dufton and Andrew Pitt represent different aspects of bio-organic chemistry, with interests in, for example, biological catalysts and proteinaceous toxins. All eight of these are in pure and applied chemistry, while Iain Hunter, who specialises in bio-transformation of lead compounds and bio-combinatorial chemistry, is in pharmaceutical sciences and has

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strong links with the Department of Bioscience. Overall the picture is one of cross-discipline collaboration, a feature which has been enhanced by the formation of the Strathclyde Institute for Biomedical Sciences (SIBS). The latter comprises the departments of Bioscience, Immunology Pharmaceutical Sciences and Physiology-and-Phamacology, which submitted jointly to two pharmaceutical-related subject groups, in the recent research assessment exercise. Both submissions gained a '5' rating in the research assement exercise of the UK unversities.

Analysing compound structure

Most medicinal chemists have to be analysts, at the least to be able to determine the structure of the compounds that they make, and it would be inappropriate to leave out of this account those such as Graham Skellern, David Watson and Justice Tettey, who are all analysts in pharmaceutical sciences, specialising in areas such as drug metabolism and impurity profiling. Their expertise in LCMS and capillary electrophoresis, for example, makes a major difference in studies of DNA binding. Last but not least, Simon Mackay is a specialist computer modeller of ligand-protein and ligand-DNA interactions, with his own interests in the medicinal chemistry of heterocycles such as the benzophenanthridines. His work is aided by the university's recent acquisition of a silicon graphics supercomputer.

In our view, it is essential that scientists in an intrinsically cross-disciplinary subject such as medicinal chemistry should be prepared to collaborate with those who have expertise in biochemistry, molecular biology, immunology and so on. One of the major advantages of a School of Pharmacy is that many of these disciplines are represented and work together. Additionally, there is also close contact with those who work in drug delivery, where such matters as solubility and bioavailability are constantly to the fore.

At the interface between the disciplines, one collaboration brings together the medicinal chemists and Ijeoma Uchegbu's group, who specialise in novel polymers for DNA delivery. Such molecular design is closely related to drug design, involving synthetic chemistry, computer modelling and NMR studies.

In Strathclyde this already wide circle of expertise has been increased substantially by the formation and activities of SIDR and SIBS. We look forward to increasing involvement with Glasgow University through synergy and pharmalinks. The two universities have declared themselves to be 'preferred research partners', which has produced one of the largest groupings of pharmaceutically-related researchers in the UK.

More information is available at http://www.strath.ac.uk/Departments/.•

The home of research in medicinal chemistry at Strathclyde

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in paranoid schizophrenia. ß-PEA has also been proposed as an endogenous amphetamine linked to the antidepressive effects of exercise. These and other data suggest that the TA family have potential roles in food intake, depression, anxiety, gastrointestinal function, electrolyte balance and hypertension. Concluding, Dr Blackburn alluded to the fact that the TA1 knock-out mice are phenotypically normal but display an 'interesting pharmacology' on administration of trace amines — a story for another day!

Thanks to Novartis

The meeting was closed by the Society for Medicines Research chairman Dr Malcolm Duckworth who expressed thanks to Novartis for their generosity in hosting the symposium. The speakers had shown impressively that orphan GPCRs are an important and exciting target for drug discovery.

Dr Duckworth spoke for many in the audience in expressing the view that progress in pairing new ligands to the orphan GPCRs and discovery of synthetic agonist and antagonists seemed to be disappointingly slow.

Perhaps the groundwork has been laid and fervent in-house activities are currently shielded from public view. The next time that novel, genomically derived GPCRs are visited as a SMR conference topic, we may see that the line-up of speakers could include a band of medicinal chemists reviewing the success of their lead identification programmes. •

COMING ATTRACTIONS...

The next issue of the newsletter will contain Alan Palmer's meeting report of the SMR meeting of 27 June on New Horizons in Drug Metabolism, Pharmacokinetics and Drug Discovery at tthe National Heart and Lung Institute in London.•

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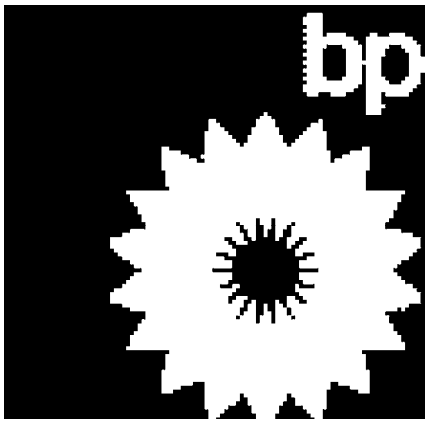
current estimates, this amount should cover a good proportion of a weekend trip for two in Paris in Spring 2003, but there is no restriction on destination or time of travel. Nor is there a restriction on type of hotel, although we expect that the winner will probably need to top up the vouchers to cover three nights in the Plaza Athenee and return first-class airfare. It is likely that the final design will be polished up by a professional designer, so there is no need for a photo-lithograph to be produced — the choice will be made by the SMR committee based on the concept rather than the delivery.

The competition is open to all SMR members and their colleagues or relations, but for reasons of transparency closed to members of the SMR committee. Entries, which can be in letter or electronic form, (but not by fax) should be submitted by Friday 13 September to the SMR Secretartiat — a lucky date for someone.•



The new BP logo: embarking on a green future?

SMR Notes

Future meetings (contact secretariat for more information. The e-mail address is secretariat@ socmr.org):

19 September 2002. SMR meeting on Proteomics: New Developments in Target Discovery. Joint meeting with BMCS section of the RSC (Scientific Societies Lecture Theatre in London).

1–5 September 2002. XVIIth International Symposium on Medicinal Chemistry. Website: URL: http:// www.uex.es/17ismc. (Barcelona, Spain).

22–26 September 2002. The Society for Biomolecular Screening, Eighth Annual Conference and Exhibition (Netherlands Conference Centre, The Hague, The Netherlands).

NEW MEMBERS

Argenta Discovery: Dr AG Roach; *GlaxoSmithKline:* Dr G Bruton, Mr JM Fleming, Dr H Lyons, Mr SQJ Rice; *Gold Partners, Doylestown, USA:* Ms MJ Mowry; *Interpharma Consultants, Seoul, Korea:* Mr SC Lee; *Medivir UK:* Dr C Clissold, Dr S Miah; *Millennium Pharmaceuticals:* Dr SP Langston; *Novartis Horsham Research Centre:* Dr P Finan, Ms E Willmott; *Novartis Institute for Medical Sciences:* Dr A Groarke; *Organon Laboratories:* Dr B Henry; *Oxagen:* Dr N Lench; *Pfizer:* Dr MD Fidock; *Pharmagene Laboratories:* Dr RA Coleman; *University of Cambridge:* Dr AP Davenport; *Woodford Green:* Dr PJ Warne; *no affiliation given:* Dr A Alanine, Dr J Rasmussen, Dr N Saghir.

NEWSLETTER PRODUCTION

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