Newsletter

Society For Medicines Research

SMR

Volume 10 **October 2003**

2003 SMR Award for Drug Design & Delivery

INSIDE:

Included with this mailing

Multimedia CD-ROM

Featuring audio recordings and slides from our last two meetings:

Neuropathic Pain: Progress & Prospects

Trends in Early Drug Safety

See Page 15 for more details

The SMR Committee is pleased to announce that the 2003 SMR Award for Drug Design and Discovery has been awarded to the key scientists involved in the discovery and development of the anti-cancer drug, Glivec, from Novartis.

In the early 1990's, the research team in Basle identifed a series of substituted phenylaminopyridines as inhibitors of the tyrosine kinase BCR-ABL, a major target for the treatment of chronic myeloid leukaemia (CML). From this series of compounds, Glivec has been developed as a highly effective and safe therapy for CML, with unprecedented numbers of patients responding to treatment.

There are two clear reasons why the SMR Committee felt that Glivec met the criteria for an award winner.

1. Glivec represents the first successful approval of a kinase inhibitor and is therefore a landmark achievement in the drug industry for those involved in kinase research.

2. Glivec also provides an example of a rationally developed therapy leading to an effective, non-toxic cancer treatment.

We look forward to hearing the Award lecture at the Case Histories meeting in December, to be presented by Dr Juerg Zimmermann.

Notice to Members

We plan to use email more in the future to communicate with you. Please ensure that the secretariat has your correct email and contact details.

Email Lilian with your correct details

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SMR Treasurer

Dr Mark Giembycz, the Honorary SMR Treasurer for the past 4 years, has resigned from this position. He has accepted an academic appointment in Calgary, Canada, and whilst it would have been good to continue in this SMR Officer role, he felt it appropriate to hand over the reins to someone more local. Thus, please welcome Dr Peter Warne as your new SMR treasurer. Peter has served on the committee for a number of years and we are delighted that he has accepted this position.

NEW MEMBERS FROM MARCH 2003

NAME	ORGANISATION
Dr A L Rothaul	Arakis Ltd, Chesterford Research Centre
Dr R Hagan	BTG International Ltd, London
Mr M D Peacock	Novartis Institute for Medical Sciences, London
Dr C J Cribb	Lonza UK Ltd, Cheltenham, Glostershire
Dr P Bassin	University of Hertfordshire, Hatfield
Dr R Massingham	UCB Pharma, UCB S.A., Belgium
Mr T R Bosworth	GW Pharma Ltd, Ely, Cambridgshire
Dr F Kermani	Chiltern International, Slough
Dr D M Morgan	Morgan Consulting,Woking, Surrey
Professor C J Suckling	University of Strathclyde, Glasgow, Scotland
Ms D Panpher	Novartis Institute of Medical Sciences, London
Dr D M Andrews	GlaxoSmithKline, Stevenage
Mr D B Priestley	Millennium Pharmaceuticals R&D Ltd, Cambridge
Mr N H Nicholson	GlaxoSmithKline, Harlow, Essex
Dr R J Boffey	GlaxoMithKline Harlow, Essex
Mr A Huxley	GlaxoSmithKline, Harlow, Essex
Dr P M Cowley	Organon, Motherwell, Lanarkshire
Mr S Travers	Millennium Pharmaceuticals R&D Ltd, Cambridge
Mr R J Wilson	GlaxoSmithKline, Stevenage
Dr D J Hardick	Medivir UK Ltd, Cambridge
Professor S Ying	Beijing, China
Ms A A Somuyiwa	NHLI, Croydon, Surrey
Professor Y Chen	University of Illinois at Chicago, USA
Mrs P P K	Novartis Institute of Medical Science, London
Dr H Clay	Covance Laboratories Ltd, Harrogate
Mrs X F Cockcroft	Chemovation Ltd, Horsham, West Sussex
Dr Y Yu	Chengdu, China
Dr N Sawal	Behind Civil, Pathankot, Punjab, India
Dr I A Pullar	Eli Lilly and Co. Ltd, Windlesham, Surrey
Dr M Paterson	Genome Inpharmatica, London

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www.socmr.org

Is there a best strategy for drug discovery?
Dr Peter Warne & Prof Clive Page

Report from our March 2003 Meeting

When a conference programme starts with a Nobel Laureate and discoverer of two of the most significant drug classes of the 20th century, and ends with a presentation by the greatest drug generator of all time, it can be sure of a capacity audience.

When the intervening period of the day is filled with six other papers of significant content, you may be sure that, that audience went away with a feeling of a day well spent.

Sir James Black initiated proceedings with "reflections on the invention of new drugs - then, now and the future" and, in tune with his title, provided a potted history of the origins of drug discovery. From Perkins in the mid 19th century to Ehrlich with his toxic chromophores and on to the greatest drug discoverer of all time, Dr Paul Janssen and the concept of pharmacophores. In all that time, the fundamental requirements of the discovery scientist have not changed; they are concentration, commitment and creativity.

There is probably not one single best strategy but the principles of a good drug strategy are recognised. First and foremost, a vision of the required selectivity. Without this, the project is doomed from its inception and reduced to the level of wishful thinking. There must be a molecular template which in the past would have been generated from the structure of the physiological mediator. A bioassay is the third essential ingredient which underlies the discovery phase. Looking further, how will the drug activity be demonstrated in man and in what disease ? And finally, the funds must be available - one of the great unknowns in discovery is how long it will take - and someone must be committed (even passionate) to seeing the task completed.

The last ten years have seen remarkable changes in the pharmaceutical markets. There remains a great demand of course and they are international, but monopolies are being eroded by generic competition and fraud.
Costs have escalated and pressure has grown to increase R&D efficiency but with what impact upon the processes ?

The new technologies are centred upon combinatorial chemistry and high throughput screening. Systems in which the chosen candidates are predetermined and of limited structural complexity. In this system, there is no room for the iterative processes so successfully applied by Erhlich and Janssen.

There is a view that the easy targets have all been satisfied and what is left, demands a different approach. If this is true, the new technologies do not appear to provide the answer if the increased rate of attrition in the clinic is any guide. The fault may lie particularly in the fact that modern drugs target components rather than systems. Systems often operate in such a way that the mechanisms of their modulation are obscure; many messenger substances may be involved, there is conversant control with addition and even, synergistic effects. Inevitably in such systems there is biological redundancy so that modulation of a specific link in the chain may be by-passed as the system responds to nullify the targeted effect.

Sir James provided examples in the shape of the development of tolerance to antigastrin therapy where the receptors remained blocked after 7 days treatment but the phenotype of the tissue had changed so that the targeted pH changes were no longer achieved. Conversely, the effect of gemcitabine upon the proliferation of pancreatic tumour cells from nude mice, is minimal. Combine the treatment with an antibody to the growth factors and the effect is increased. Add in irradiation and the response is ablated. The individual targets have combined to provide therapeutic impact upon the system.

So what do the metrics of drug discovery suggest ? Dr Cyndy Lumley from the Centre for Medicines Research provided some of the answers in a broad appraisal of data which have been supplied in response to industry questionnaires.

The fundamental aim of a pharmaceutical company and the industry as a whole, is to remain profitable. This means balancing innovation with output. In the last 10 years, there have been notable increases in discovery technologies but no notable increases in the production of new molecular entities (NMEs). During the 1990s there were approximately 40 new compounds launched each year; since 2000, these numbers have declined. Pipeline numbers too are lower and development time is extending owing to increased internal development hurdles and regulatory risk aversion. Conversely, sales have increased and indexed growth has risen in parallel. However, it is difficult to imagine this being sustained if there are fewer new drugs. It is equally certain that companies will react to invest in other areas of their business if the technology does not soon start to show benefit.

In 1995, Jurgen Drews foresaw what he described as the "innovation gap" and suggested some ways of meeting the challenge. Top of the list was the acquisition of compounds through licensing opportunities and particularly, from biotech companies. Biotech companies, however, find themselves in a position much like most pharmaceutical companies and the few opportunities that are available, are keenly sought. His second suggestion was to question company structures and to understand critical mass. Some companies such as GSK have reacted to these ideas and created business units, smaller research teams created on the scale of biotech companies.

The industry watches with interest to see the success of these radical organisations. Thirdly, he turned attention upon the new technologies.

The metrics of R&D investment show a marked shift from ten years ago. While the clinical areas remain top of the poll with about 30% of total budget, discovery comes second with a 25% figure. This is a large skew upon earlier figures which is driven both by technology advances and the establishment of alliances. Non-clinical development now commands 17% of budget while Phase I units take a beggarly 6% and post-marketing surveillance 5%. No surprise that pharmaceutical management is looking very closely at discovery profitability.

Measurement of discovery success poses something of a conundrum. Numbers of new compounds as a criterion has little measure of quality and time savings in Phase I or Phase II measure development efficiency rather than discovery. The time taken from initiation of screen to first administration to man is about 4.4 years but the analyses suggest that speed (or lack of it) is not the issue. Quality, as judged by clinical success rates during the period 1994 - 2001, does not seem to have improved. In spite of improved selection criteria, 22% of clinical candidates fail because of insufficient efficacy and similar numbers fail through adverse effect profiles.

The current message is that increased spend has not, so far, equated to increased productivity. Lehman Brothers have estimated that pharmaceutical investment must be at least of the order of $100 million per year to compete in the post genomics era. New target generation from genomic technology is generating some 23% of new targets per annum with 28% of these proving novel. The trick is to identify the best targets for new drugs.

The current success of genomic-driven target generation was appraised by Dr Steven Foord from GSK. From a history in which new drugs have been targeted towards a few poorly understood proteins taking decades to investigate, genomic sciences certainly have the ability to identify large numbers of potential drug targets. The trick will be to reduce these numbers to manageable and useful proportions and produce clinically efficacious products. The classifications are already well in hand, clinical success will take longer to realise.

Although there are an estimated 30,000 potential drug targets in the human genome, current knowledge is limited to about 2000 and these are broadly divisible into 5 classes; 7 transmembrane receptors, nuclear receptors, ion channels, proteases and kinases. Of the 747 7TMs, 50% can be excluded from drug discovery on the basis of phylogeny and expression analysis. Subclassification into groups A, B and C and those with and without identified ligands, provides further criteria upon which to base a targeted approach. Each of these subdivisions is dependent upon genomic sciences. They also emphasise the depressingly large numbers of orphan receptors.

Genomic technology also brings the potential to clone and express human receptors for high throughput screening. Combined with high throughput functional assays, these techniques can expose unexpected pharmacological activity which, hitherto, had to await serendipitous clinical exposure. For example, the angiotensin II receptor antagonist, and antihypertensive drug, losartan also lowers serum uric acid levels through a mechanism not utilised by laboratory animals. Similarly, buprenorphine used in cases of narcotic addiction has a complex effect upon all opioid receptors but in human trials has been shown to stimulate the human ORL1 receptor which is likely to contribute to clinical efficacy. With genomic technology, screening systems can be widened appropriately to anticipate clinical responses of this type.

Animal model selection is being influenced by reciprocal blast technology, phylogenetic analysis and synteny. According to criteria generated by these systems, more than 95% of human drug targets have murine equivalents. Of course, the mere existence of a target does necessarily mean a similar function but, in practice, murine knockouts usually reflect human physiology. This is if one is able to ask the right question; H2 and 5HT1D receptor knockouts, for example, would not have suggested a route to the treatment of gastric ulcers and migraine. Conversely, H1 knockouts show signs of drowsiness and those without the gene for cysLT1 have improved lung responses. Elsewhere, there are successes and failures with genomic technologies; almost all 7TMs can be detected in Taqman analysis but the relevance of mRNA expression to protein synthesis is variable. Equally, array analyses are frequently limited by current knowledge.

And knowledge limitations ensure that 7TMs can be difficult to identify within biological systems. It is becoming increasingly difficult to fill in the gaps within systems and to pair ligands with receptors. It is true that for some classes, such as chemokines, clusters of ligands can be recognised and new drugs can be expected in the near future, but many remain outside simple classification. As an aid to target hunting, there have been attempts to look back through the evolutionary tree and look for functionality based upon the premise that if there is no receptor there will be no ligand. This technology is as applicable to the kinome as much as 7TM targets.

Inheritance, like the biological systems for which it codes, is not passed on through individual genes but as ill-defined blocks of information. This makes the association of individual genotypes with disease difficult to predict but this is increasingly the objective of genomic research in the areas of

pharmacogenetics and disease susceptibility.

Pharmacogenetics is the study of abnormal responses to drugs and was reviewed by Professor Rob Kerwin from Kings College, London. He differentiated his subject from pharmacogenomics which concerns the identification and characterisation of drug targets.

In the US alone, 2 million patients per year present with serious adverse effects to their therapy and these symptoms result in 100 deaths. The UK suffers a similar pro rata experience. Approximately 10% of schizophrenic patients commit suicide which is itself, a mark of treatment failure but when other markers are factored in, treatment failure rates in complex disease are between 20 and 30%. In psychotic patients generally, one in five can be said to have responded, in 30% there is no response and the rest experience adverse events.

While it is true that drugs are expensive, these costs pale when set against the costs of rehabilitation or patient containment. Pharmacogenetic profiling makes sound economic sense as a treatment goal.

Pharmacogenetics can affect drug activity in several ways. Kinetic variation of a number of products is known to be influenced by P450 enzyme variants which accelerate or slow their elimination giving rise to suboptimal therapy or toxic side effects respectively. In asthma, SNP variants of the ß receptor result in structural changes and altered susceptibility to bronchodilators. In cancer and Altzheimer's disease, several genes have been associated with disease development and a similar story is starting to emerge with psychotic patients.

In schizophrenia, remission rates are 0% and there is a high treatment failure rate. There are high costs to be borne through the social impact of the disease and so, drug price increases to fund pharmacogenetic profiling are economically sound. Equally, there are ethical points to consider; most notably, do we deny a patient their treatment on the basis that their profile suggests that, for them, the drug won't work ? This and other issues are complicating the subject which for many is predicting over optimistic gains.

Pharmacogenetic profiling in schizophrenia is currently targeting a profile of the most beneficial treatment. This will in turn, provide information for target validation and target hunting. The approach is to apply association methodology to clinical samples in a multi-gene testing paradigm.

Although there is opportunity for toxicogenetics and Cyp profiling, this has not proved useful in psychotic disease. Instead, the approach has been to investigate SNP variation of those genes which "light-up" during therapy. For example, the dopamine receptor has been a strong candidate for an association with the disease for many years. SNPs have identified in all subtypes from D1 to D5 but it is the D3 and D4 subtypes which present opportunities for novelty. The D3 gene has a positive association with the disease and the correlation of non-responders to clozapine therapy with SNPs validates D3 as a novel target. Similarly, serotonin has been a candidate mediator of schizophrenia for many years and SNP analysis of the 5HT2A gene is proving useful in the prediction of responders.

Currently, logistic/linear regression analysis of multiple genes provides an indication of likely responders to clozapine but the reverse is not always true. The combination of 5HT and H1 analysis for example seems to identify responders but is less predictive for non-responders. Conversely, SNP analysis of olanzapine sensitivity seems to be more predictive for non-responders. Always the complexity of these relationships demands more data before greater reliance can be placed upon the apparent conclusions.

So far, the studies have been retrospective and from the data, the prediction of clozapine responders appears to be about 80%. There are no data, as yet, from prospective studies but these are in hand as are the development of comparable tests for olanzapine, risperidone and haloperidol. These may not only be able to identify responders but also mark out those most susceptible to side effects such as agranulocytosis, tardive dyskinesia, weight gain and so on.

In parallel with inadequate clinical efficacy, preclinical toxicology combined with clinical safety are the other single largest reason for stopping projects in development. According to the CMR metrics, the attrition due to toxicity is 23% so that any measures that can be taken to filter out these candidates from the selection process is welcomed. Dr Mark Cronin from Liverpool (John Moores) University provided a summary of the potential and status of in silico systems for achieving just that.

E-screens for toxicity testing are attracting the attention of both the pharmaceutical industry and the regulators. For the industry, these systems are cheap and may provide direction for medicinal chemistry strategies. They can also cast a light upon mechanisms of action. Equally, there is increasing evaluation of these systems by the FDA who, in the future, are expected to prioritise, classify and assess risk by consideration of data currently being generated in toxicity databases.

In silico screens are generated according to similarity and here lies both their strength and their weakness. The strength is directly proportional to the stringency of the rule base, the weakness is knowing upon what to base similarity. Quantitative structure activity relationships (QSAR) have been

used to classify narcosis and formalised to generate expert systems. One of the better known systems, DEREK, is knowledge based and databases are also being generated by both the FDA and OECD. To date, the focus of activity has been upon mutagenicity, carcinogenicity and skin sensitivity but following several years of research and data manipulation, no system has emerged as reliable.

Understanding the poor performance of the current crop of systems is also proving problematical. It is probable that current knowledge is inadequate, a situation fuelled by the pharmaceutical industry's reluctance to release sensitive safety data. Equally, e-screens seek to analyse complex phenomena by as yet, simplistic comparator techniques.

The most obvious short-term advances are likely to be made by increasing the knowledge base. First and foremost, the area needs an influx of quality *in vivo* data and this is most likely to be sought from the pharmaceutical industry. Similarly, the collation of human tolerance data will prove a valuable resource if made available. However, the knowledge base could also advance through the generation (or acquisition) of *in vitro* data or that to be accessed through toxicogenomics and microarray technology.

Toxicogenomics, the study of differential gene expression following a toxic insult provides, in principle, the message by which to fingerprint toxic compounds. In turn, this can generate information upon mechanisms of toxicity and ultimately, may facilitate prediction of toxicity. These ideas are at present only goals. They are unlikely to be realised without the provision of more data and it is likely to depend upon the larger pharmaceutical companies to seize the initiative.

The chemical structures of drugs are also providing a basis for the mapping of the genome and the identification of the most suitable targets for their drug-like (druggability) properties. This is the thesis of Dr Andrew Hopkins (Pfizer) and his publishing colleague Dr Colin Groom now with Celltech.

According to current estimates, the genome contains approximately 30,000 targets (considerably fewer than first thought) but without further division, the industry is unlikely to make beneficial use of this information. It must recognise which of these targets will make a suitable drug target.

Given that Pfizer has been one of the leading exponents of what a molecule needs to make it a drug, they have been in a good position to assess druggability, an assessment of the tractability of a given drug target. Armed with this experience, the authors have sought sites suitable for the discovery of small molecule, orally available compounds and based their early classification upon the assumptions made by their colleague Lipinski when he described his "Rule of 5". However, they have gone further and superimposed consideration of ligand interaction parameters and the observation that most successful drugs are mimics of the endogenous mediator. Uncompetitive drugs binding at allosteric sites being rare. Applying these criteria to gene sequences and extrapolating the information to gene families (assuming that common sequences are indicative of a similar active site architecture), the number of druggable targets is not 30,000 but about 3,000. Although some 50% of proteins have yet to be discovered, it appears that all large protein families are accounted and it is unlikely that the number of targets will increase much above the current estimates.

Even so, the number of proteins against which one might want to target a drug is likely to be lower than 3,000 because only those linked with disease can be appropriate. By capturing proteins bound by a wide range of experimental drugs and eliminating those not modulated by compounds compliant with the "rule of 5", most of the chemical compounds, according to the above assumptions, do look like their endogenous ligand. The sequence data of the targets identified are representative of only 130 protein families and nearly half of the targets derive from a mere six; GPCRs, two classes of kinases, metallo-proteases, nuclear hormone receptors and phosphodiesterases.

Genomic sequence analyses of the types described have identified a relatively limited number of protein classes which satisfy the industry predilection for orally administered medication. The predictive power of the techniques remains to be demonstrated but, as of today, they represent a plausible method of directing medicinal chemistry towards tractable targets. This may not only provide a practical means of exploiting the enormous potential of the human genome but may also improve the quality of NMEs and reduce attrition which is not, to date, demonstrably better than it was ten years ago.

The opening sequence of slides from Dr David Brown (previously head of Discovery at Roche and currently CEO of Cellzome) described project attrition data derived from studies at Roche which he believes to be representative of the industry as a whole. According to these data, one in 57 novel compounds is progressed to the market. The figure is slightly better for MeToos where the chances are 1 in 25.

In discovery, 37% are lost through a failure to validate the target and 62% because either a lead cannot be found or optimised. In development, attrition is due to poor portfolio decisions, preclinical toxicity and poor efficacy in Phase II trials.

Conversely, the chances of success are enhanced by selection of an appropriate target type and early clinical input. For all the

years of pharmaceutical research, 4 target classes have proved most susceptible to modulation by chemicals; GPCRs, enzymes, ion channels and nuclear receptors. Selection of targets in these classes is still expected to pay dividends. Equally the existence of surrogate clinical markers and/or clear disease endpoints greatly improve the chances of success. Where there are no surrogates or clear disease endpoints, the prospects for success are very low.

Timing is also of the essence. Like all growth curves, the introduction of new technology follows a sigmoid curve with lag, exponential and maximal phases. How early to invest may be a key decision; striking a balance between maintaining a competitive position while curbing expenditure. There may be advantage to a late intervention with the opportunity to leap-frog others and buy state-of the-art equipment at the outset. Alternatively, late investment may be a deterrent to potential investors.

So what really helps ? Knowing what the competition is doing is important both with respect to technology platforms and processes. Target identification technologies, including both bio and chemo informatics, may prove positive as will (and always has) chemical tractability. The technology to support rapid chemical assessment and multi-dimensional optimisation has, according to the metrics, yet to prove its worth. The figures superficially suggest that high throughput ADME technologies have reduced attrition attributed to inappropriate pharmacokinetics. However, it appears that the early data were skewed by large numbers of poorly absorbed antibiotics so that even this apparent success, may require further investigation. Toxicity databases are making little progress because the industry is reluctant to share its data.

So what hope for the future? This was a subject addressed by one of the scientists most fitted to do so. The one person responsible for more novel drugs than any other (by a long way). Dr Paul Janssen chose to address the issue by reading from a presentation he had made some 25 years ago and it was a stark message to all that not very much had changed.

What do we mean by a better drug ? A substance that treats a disease better than another and when two drugs are equiefficacious, the adverse event profile may provide the differentiation. Only patients can decide and they may base their decision upon wholly parochial parameters such as the ease of compliance and even the colour of the tablet.

How to find them ? Surely no accident that Dr Janssen returned to a message earlier given by Sir James Black; drug hunting requires persistence. But here there was a humanitarian slant that persistence will only be found in a creative, free-thinking world. It cannot operate in a selfish world loaded with bureaucracy, regulations, old prejudices and habits of mind.

The air is filed with scepticism that the pharmaceutical industry is seen as a professional exploitation of disease. The birth rate of new drugs is low and declining and was highlighted by the failure to develop antiprotozoal drugs. All this was 25 years ago. He left us to discuss amongst ourselves just how much had changed. If there was a single message, it may have been that the golden age of drug discovery - an age in the late 1980s and early 1990s that could benefit from a vast knowledge base - was over; at least until the knowledge base takes another leap forward. The day's presentations had provided considerable grounds for optimism that the new generation of knowledge development is under way.

Highlights from our June 2003 Meeting

Pharmacotherapy for Neuropathic Pain: Progress and Prospects by Sandy Pullar and Alan M. Palmer

On June 26, 2003, we held a very successful and well attended symposium at the Eli Lilly Research centre at Erl Wood Manor, Windlesham. The meeting focused on the progress that has been made in the discovery and development of new drugs for the treatment of neuropathic pain and looked forward to assess the prospects for the emergence of new medicines for this chronic debilitating disorder. The meeting was organized by Sandy Pullar (Eli Lilly, UK) and Alan M. Palmer (Pharmidex, UK), who, together with Ian Regan (Eli Lilly, UK), chaired the proceedings.

Now let's set the scene: Imagine a pain so excruciating that words fail to describe it and doctors can't explain it. A pain that may in fact worsen over time. Tragically, some people don't have to imagine such pain, they experience it and it makes their life unbearable.

Neuropathic pain, as it is called, can be described as a malfunction in the nervous system that usually follows injury to the nerve or to certain regions of the spinal cord or brain. It is the most severe form of pain and the only one that leads patients to commit suicide. It is triggered by conditions such as diabetic neuropathy, AIDS-related neuropathy, postherpetic neuralgia, chronic degenerative spinal disease, sympathetic dystrophies, post-amputation stump (phantom) limb pain, trigeminal neuralgia and multiple sclerosis. Multiple changes in the processing of pain signals from peripheral nerves to the cerebral cortex do occur following nerve injury and the relative clinical significance of these is still being determined. However, neurones that are normally concerned with the processing of innocuous sensation (eg touch) sprout into areas of the dorsal horn that normally mediate nociceptive

processing. Thus there is a "rewiring" of the dorsal horn so that innocuous tactile stimuli are interpreted by the brain as painful (as in allodynia or trigeminal neuralgia).

Estimates of the potential market for neuropathic pain range from 400,000 to 900,000 patients annually in the United States alone, where the market is valued at $450 million. The market for pain drugs is considered to be in the early stages of development, with potential for significant and rapid growth. Neuropathic pain (unlike acute pain) is not adequately managed with available medications and so represents a substantial unmet medical need. There currently are very few truly effective, well-tolerated therapies for this neuropathic pain. Opiates (which work well for acute pain) are not particularly effective. Tricyclic antidperessants (which act by blocking the uptake of the neurotransmitters noradrenaline or serotonin or both) have been used 'off label' and claimed to be effective, but they suffer from undesirable side-effects. Also, some of the more recently introduced antiepileptic agents have been claimed to be effective, eg lamotrigine and gabapentin; the latter compound has now been approved for the treatment of neuropathic pain. Other approaches to therapy include NMDA receptor antagonism, sodium channel blockade (1) and cannabinoid receptor agonists. Such approaches to therapy will be considered today alongside a description of the challenges facing neuropathic pain drug discovery at both the research phase (e.g. how do we predict efficacy) and development phase (e.g. what type of neuropathic pain should we target first and what are the best outcome measures).

Sympomatology

Neuropathic pain is not a single entity, but rather includes a range of heterogeneous conditions that differ in aetiology, location and initiating cause. The clinical picture was clearly and graphically described by John Wedley (Guy's and Thomas' Hospital, London). Clinic diagnosis is made on the basis of emergent characteristics - the description from patients is not reliable and often made in emotional terms. It may be accompanied by characteristic sensory changes such as allodynia and hyperpathia.

The physical findings reflect the aetiology and will be greater where there is peripheral nerve injury (e.g. Complex Regional Pain Syndromes-CRPS) and least where the cause is entirely central (e.g. thalamic pain). Most patients present with a mixed picture. Even where the original tissue injury is entirely peripheral there will be central changes. An understanding of these changes both facilitate drug discovery and provide a framework for rational drug therapy.

The treatment of Neuropathic pain falls into three categories, psychotherapy, drug treatment and nerve ligation/stimulation. In the rare condition, CRPS type I, which is caused by soft tissue damage, patients should be encouraged to use the affected limb as this can lead to improvements. It is probably for this reason than psychotherapy is effective in this condition. In the more common CRPS Type II, which results from nerve damage after such things as a prolapsed intercerebral disc, herpes zoster infection, spinal cord injury, amputation (phantom limb pain), nerve ligation is effective but only for a short time. It may lead to a long term exacerbation of the pain. Anticonvulsants such as carbamazepine seem to work but there usefulness is limited by side-effects.

Atypical facial pain, tooth pain that persists that even after removal of the tooth, tricyclic antidepressants such as amitriptyline are effective as are high doses of SSRIs.

- Increasing awareness of the plasticity of the nervous system and replacement of the 'hard wired' model with that of a matrix has enhanced the movement away from neurodestructive techniques to neurom odulatory treatments such as transcutaneous nerve stimulation (TNS) and spinal cord stimulation (SCS) although neurodestructive procedures may still have a place in the treatment of cancer pain. Neuropathic pain remains the most difficult form of pain to treat. Pain may be reduced but is very rarely eliminated.

Multidisciplinary cognitively behaviourally based Pain Management Programmes optimise the patient's quality of life. As someone who sees patients suffering from neuropathic pain on a regular basis, Dr Wedley pointed to three key additional tools to add to analgesic armamentarium. These are:

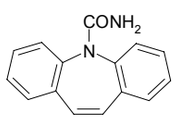
- A better ketamine
- A long acting local anaesthetic
- Drugs with multiple actions

Biological basis

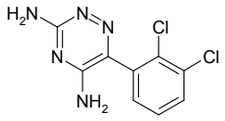
A key prerequisite for meeting the need for better treatment is a clear understanding of the biological basis of neuropathic pain. This topic was well covered by Tony Dickenson, (Dept. Pharmacology, University College, London). This approach to therapy was largely stimulated by The Gate theory of pain (1965), which predicted that pain could be modulated. Damage to a nerve should only lead to sensory loss, but the incidence of spontaneous pain (allodynia and hyperalgesia) indicate marked changes in the nervous system that are possible compensations for the loss of normal function.

Neuropathic pain arises from initiating changes in the damaged nerve which then alter function in the spinal cord and the brain and leads to plasticity in areas adjacent to those directly influenced by the neuropathy. The peripheral changes drive central compensations so that the mechanisms involved are multiple and located at a number of sites.

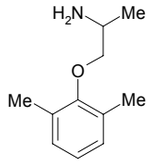
Nerve damage increases the excitability of both the damaged and undamaged nerve fibres, neuromas and the cell bodies in the dorsal root ganglion. These peripheral changes are substrates for the ongoing pain and the efficacy of excitability blockers such as carbamazepine, lamotrigine and mexilitine.



Carbamazepine



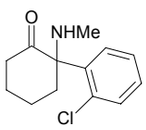
Lamotrigine



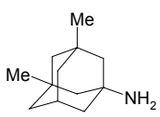
Mexilitene

A better understanding of ion channels at the sites of injury has shown important roles of particular sodium, potassium and calcium channels in the genesis of neuropathic pain.

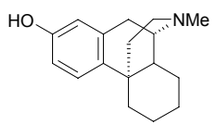
Receptors for excitatory amino acids, especially the N-methyl-D-aspartate (NMDA) receptor, are also thought to play a key role in neuropathic pain. NMDA receptors, for example, trigger wind-up and central hyperexcitability. Examples of NMDA receptor blockers include ketamine (a dissociative anaestheitic), memantine (a new medicine to treat Alzheimer's disease) and dextrorphan (an analgesic).



Ketamine



Memantine



Dextrorphan

It can be said that at present our understanding is that neuropathic pain is associated with:

- Peripheral changes in sodium and potassium channels
- Ectopic activity, ephaptic, sympathetic…
- Increased NT release from intact fibers
- Increased central NMDA and N-type calcium channel activity
- Possible changes in opioid, NA and 5-HT systems

A better understanding of the multiple mechanisms of neuropathic pain should lead to a more effective use of existing drugs and provide a basis for the development of potential new therapies.

Experimental models

To establish that potential drug candidates are likely to be efficacious in the clinic, it is essential to have predictive experimental models of neuropathic pain. Alyson Fox (Novartis Institute for Medical Sciences, London) reviewed this topic. Until recently little was known of the mechanisms underlying the various neuropathic pain conditions, making the directed development of novel therapies almost impossible. However, the advent of a number of animal models of neuropathy has led to a huge increase in research activity into neuropathic pain. The animal models are divided largely into those due to peripheral nerve injury and those mimicking a particular disease condition. The most widely used are the nerve injury models, principally the partial sciatic ligation model (2), the chronic constriction injury (CCI) model (3) and the spinal nerve ligation (SNL) model (4). All these models show behavioural signs characteristic of clinical neuropathic pain conditions including mechanical and thermal hyperalgesia, tactile allodynia and cold allodynia.

Preclinical studies using these models have confirmed the antihyperalgesic and antiallodynic profile of gabapentin and the increased potency of pregabalin. In addition to providing a predictor of clinical efficacy, these models have contributed (or have the potential to contribute) in three other areas. They provide an opportunity to explore their mechanism of action. The hope is that with the increasing knowledge of neuropathy gained using these models we may be able to arrive at a more mechanistic classification of neuropathic pain conditions in the clinic, rather than one based solely on aetiology. In the first instance this may allow a targeted patient selection process for clinical trials in an area notorious for its high placebo effect and number of failed trials. They may lead to a more accurate drug selection tailored for each patient, thereby avoiding the 'polyphamacy' approach and the greater risk of adverse effects. They can assist in the identification of a surrogate marker of neuropathic pain. This would be extremely helpful in clinical trials, but no such marker exists at present

NMDA receptor antagonists

Chris G. Parsons (Merz Pharmaceuticals, Frankfurt, Germany) provided a detailed presentation of the role of NMDA receptor antagonists in neuropathic pain. He indicated that

glutamate is the major fast excitatory neurotransmitter in the CNS and that it has been implicated in a wide variety of neurological diseases. Ionotropic glutamate receptors are classified into three major subclasses AMPA, kainate and NMDA. Preclinical evidence indicates that hyperalgesia and allodynia following peripheral tissue or nerve injury depends on NMDA receptor-mediated central changes in synaptic excitability. Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site (competitive), strychnine-insensitive glycine site (glycineB), polyamine site (NR2B) and the uncompetitive channel site. Uncompetitive NMDA receptor antagonists act in "use-dependent" manner, meaning that they only block the channel when it is in the open state.

Antagonists that completely block NMDA receptors cause numerous side effects such as memory impairment, psychotomimetic effects, ataxia and motor incoordination because they also impair normal synaptic transmission - a two edged sword. The challenge has therefore been to develop NMDA receptor antagonists that prevent the pathological activation of NMDA receptors but allow their physiological activation. Uncompetitive NMDA receptor antagonists with rapid unblocking kinetics but somewhat less pronounced voltage-dependency than Mg2+ seem to be able to antagonise the pathological effects of the sustained, but relatively small, increases in extracellular glutamate concentration but, like Mg2+, leave the channel as a result of strong depolarisation following physiological synaptic activation. Thus, uncompetitive NMDA receptor antagonists with moderate, rather than high, affinity may be desirable.

Another promising target for NMDA receptor antagonism is the glycineB modulatory site. Recent data indicate that systemically-active glycineB antagonists have good therapeutic indices following systemic administration, as analgesics in models of hyperalgesia, as neuroprotective agents in models of focal ischaemia and trauma, as anxiolytics, and as anti-epileptics. In contrast to high affinity uncompetitive antagonists, glycineB antagonists do not have psychotomimetic effects, have minor negative effects on learning, and even very high doses do not cause any neurodegenerative changes in the cingulate/retrosplenial cortex of rats. Several glycineB antagonists are presently under development.

NR2B selective agents have also been reported to be effective in suppressing hyperalgesia in animal models of chronic pain at doses devoid of negative side effects on motor co-ordination or behaviour (including in man) indicating that NR2B selective antagonists may also have clinical utility for the treatment of neuropathic and other pain conditions in man with a reduced side-effect profile. These therapeutically-safe NMDA receptor antagonists are also able to slow or prevent the development of opioid tolerance, indicating the synergistic utility of their combination with opiates in the treatment of chronic pain, both in terms of symptomatic analgesic effects and prevention of the development of chronic pain states.

NA and 5-HT uptake inhibitors

David G. S. Perahia (Lilly, Windlsham, UK) considered the use of NA and 5-HT uptake inhibitors in the treatment of neuropathic pain. NA and 5-HT uptake inhibitors have been successfully utilised in the treatment of depression since the introduction of tricyclic antidepressants (TCAs) such as imipramine in the late 1950's.

In addition to their well-established efficacy in depression, TCAs have long been known for their efficacy in chronic, especially neuropathic, pain. Their analgesic effects are likely mediated by dual 5-HT and NA reuptake inhibition. This is based on preclinical evidence comparing dual vs. single NA and 5-HT uptake inhibition. In one such study (using the formalin paw test), a combination of paroxetine (a SSRI) and thionisoxetine (a noradrenaline reuptake inhibitor) had greater efficacy than either alone. Clear efficacy was also demonstrated in this model with the dual serotonin, noradrenaline reuptake inhibitor duloxetine which was also shown to be efficacious in the Chung model of neuropathic pain and to reverse capsaicin -induced mechanical allodynia.

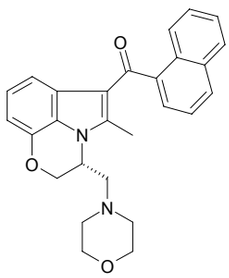
There have been numerous double-blind, placebo-controlled studies of TCAs in the literature, together with a multitude of case reports and reviews showing consistent evidence of efficacy of imipramine and amitriptyline in neuropathic pain. These trials provide evidence that the dose, and the choice of the TCA itself, in terms of relative effects on 5HT/NA, are factors influencing efficacy. An analysis of the clinical effectiveness of TCAs and SSRIs indicates that they are more effective when given in combination.

Since the introduction of SSRIs, novel agents (e.g venlafaxine) have been developed which recreate the dual 5-HT & NA reuptake inhibition of some TCAs but with less of the safety and tolerability limitations of the older antidepressants. Venlafaxine has shown clear efficacy for Diabetic neuropathic pain and a number of studies suggest efficacy infibromyalgia, neuropathic pain following breast cancer treatment, tension headache and chronic headache

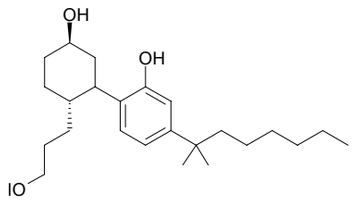
Cannabinoid receptor agonists

Stuart Bevan (Novartis Institute for Medical Sciences, 5 Gower Place, London) reviewed the use of cannabinoid receptor agonists for neuropathic pain. This is supported by considerable preclinical and clinical evidenceand there are anecdotal reports to suggest that smoking cannabis may relieve

the pain and spasticity in multiple sclerosis sufferers. It is now known that the effects of cannabinoids are mediated via an interaction with CB1 and CB2 receptors. Both these G-protein coupled receptors have markedly differing distributions, with CB1 receptors having a widespread distribution in the central and peripheral nervous systems, and CB2 receptors restricted largely to cells of the immune system. In animals, cannabinoids have long been known to be analgesic in models of acute pain, an effect which is now known to be mediated through spinal and brain CB1 receptors. More recently, it has been shown that synthetic cannabinoids such as WIN55,212-2 and CP55,940 as well as the endogenous CB agonist anandamide are effective in models of chronic neuropathic and inflammatory pain, reversing established mechanical or thermal hyperalgesia and tactile allodynia.



WIN 55,212-2

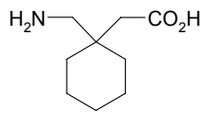


CP 55,940

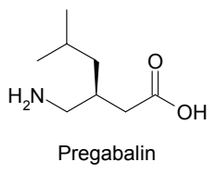
In behavioural studies, injection of WIN55,212-2 or anandamide directly into the ipsilateral but not contralateral paw has been shown to inhibit hyperalgesia in models of neuropathic and inflammatory pain. Importantly, this effect of locally administered WIN55,212-2 in the model of neuropathic pain was inhibited by systemic but not intrathecal administration of a CB1 antagonist, SR141716A, implying a peripheral mode of action. These studies in animals show that CB receptor agonists have considerable potential utility in the treatment of neuropathic pain. However, it is clear that if they are to be used routinely in the clinic then they must have analgesic efficacy without the CNS side. Whilst one approach would be to develop CB2 agonists, a potentially more promising mechanism offering greater efficacy and broader use would be the development of peripherally restricted CB1 receptor agonists.

Gabapentin and Pregabalin

Dic Williams (Pfizer Global Research & Development, Sandwich, UK) reviewed the gabapentin story.



Gabapentin



Pregabalin

As the first approved treatment for neuropathic pain, it has made a major impact on the lives of thousands of patients suffering from this condition. Gabapentin is now widely recognized as a treatment of choice for neuropathic pain although there still exists a need to develop more potent, easier to use products which are supported by strong clinical evidence. Pregabalin was specifically designed to be an advance in the treatment of neuropathic pain and is supported by the largest group of controlled clinical trials in neuropathic pain of any agent, including gabapentin. The studies have demonstrated that pregabalin is a potent, efficacious and well tolerated compound with linear absorption kinetics. A large body of evidence, which has emerged over several years, indicates that these agents act through a novel mechanism that is involved with the peripheral and central changes in pain processing associated with neuropathic pain.

Pregabalin and gabapentin bind to a single high affinity binding site, widely distributed in the central nervous system. This has been identified as the alpha-2-delta accessory protein of voltage-gated calcium channels. The binding protein is up-regulated in primary afferents in animal models of neuropathic pain. There is evidence that these alpha-2-delta ligands may act at both central and peripheral sites. Whilst electrophysiological studies on neurons in normal spinal cord slice preparations have shown a complex pattern of action, it seems clear that the relevant mechanisms may only be revealed in preparations derived from animal models showing hyperalgesia and allodynia.

Taken together, the evidence summarized above supports a role of alpha-2-delta in the development and maintenance of hypersensitive states such as those seen in neuropathic pain, and that this protein constitutes the primary mechanism through which gabapentin and pregabalin exert their therapeutic actions. The central effects of pregabalin extend beyond its antiallodynic and antihyperalgesic actions, since they also include anxiolysis and improved sleep quality. Neural modulation via the alpha-2-delta ??protein may involve a number of integrative processes in the CNS and that pregabalin may correct the dysfunction associated with neuropathic pain via actions at multiple sites in the neuraxis.

Clinical trials in neuropathic pain

The final presentation of the day was from Andrew Rice (Imperial College, London) and focussed on key issues relating to clinical trials in neuropathic pain. The first issue is that the likelihood of success in the clinic is directly proportional to the predictive value of the experimental models used. There are clear limitations associated with the current animal models of neuropathic pain in that:-

- They are designed to yield a high incidence of pain-related outcomes following peripheral nerve injury.
- Outcome measures reflect evoked reflex response to sensory stimuli rather than integrated behavioural response to ongoing pain.
- They usually share similar methods of inducing partial nerve injury which have limited relevance to human disease.
- There is strain/genetic/dietary variability of rodent responses to injury and analgesics.

Two common types of neuropathic pain used in clinical trials are Psot Herpetic Neuralgia (PHN) and painful diabetic neuropathy. Gabapentin (Pfizer), the first neuropathic pain agent to acquire widespread regulatory approval, has shown efficacy in both of the above models, as well as in mixed neuropathy (6; 7; 8).

A practical issue of clinical trials is whether it is possible to compare a test compound with placebo or whether the comparison has to be made against a comparator compound. The Declaration of Helsinki, 2000 (www.wma.net) states that 'the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods' This does not exclude the use of placebo, where no proven prophylactic, diagnostic or therapeutic method exists, but clearly with therapies (such as Gabapentiin) reaching the market, it provides a standard that has to be improved upon.

Conclusion

Considerable progress has been made in understanding the anatomical, cellular and molecular basis of neuropathic pain and this forms a solid foundation for the emergence of new therapies for the effective treatment of this debilitating disorder. Although, at present, Gabapentin is the clear forerunner in this process promising research holds out the possibility of alternative future treatments.

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