Next generation therapeutics
Editorial overview

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Abbreviations

CNS	central nervous system
GPCR	G-protein-coupled receptor
iGluR	ionotropic glutamate receptor
PET	positron emission tomography

As we look towards drug discovery research in the new millennium, we face huge opportunities and challenges. The opportunities come from new technologies, our increasing understanding of the molecular basis of disease and from the new molecular targets and mechanisms arising from human genome research. The challenges are scientific (for example, to identify which out of the plethora of molecular targets are relevant to disease processes) and also economic (i.e. pharmaceutical research and development during the past two decades has become more expensive, takes longer from first synthesis until marketing, and yields less in terms of new chemical entities registered per year). Against this background, when considering which topics to include in this issue of *Current Opinion in Chemical Biology*, 'Next generation therapeutics', a variety of different approaches were considered. For example, capitalising on new techniques for exploiting high-speed chemistry and biology methods in order to identify candidate drugs has become a major emphasis across the pharmaceutical industry, and it was tempting to focus predominantly on the growing field of 'new technologies' for drug discovery. Alternatively, the theme could have followed traditional 'mechanistic' lines of emerging biological targets implicated in future drug R&D programmes. An even broader approach would be to overview selected therapeutic areas. The final result is a combination of these approaches.

There is a technology/technique bias in 'Pharmacokinetics and metabolism in early drug discovery' (Smith and van de Waterbeemd, pp 373–378), 'Chemoinformatics — a new name for an old problem?' (Hann and Green, pp 379–383), 'Recognizing molecules with drug-like properties' (Walters, Ajay and Murcko, pp 384–387) and 'Positron emission tomography neuroreceptor imaging as a tool for drug discovery, research and development' (Burns *et al.*, pp 388–394). This is followed by a mechanistic focus in the articles entitled 'Nonpeptidic ligands for peptide and protein receptors' (Freidinger, pp 395–406), 'Interfering with chemokine networks — the hope for new therapeutics' (Schwartz and Wells, pp 407–417), 'Cannabinoids, endogenous ligands and synthetic analogs' (Pop, pp 418–425), 'Muscarinic receptor ligands and their therapeutic potential' (Eglen *et al.* pp 426–432), 'Metabotropic G-protein-coupled glutamate receptors as therapeutic targets' and 'Ionotropic glutamate receptors' (Pellicciari and Costantino, pp 433–440; Bigge, pp 441–447), 'Pharmacology of voltage-gated and calcium-activated potassium channels' (Kaczorowski and Garcia, pp 448–458), 'The development and therapeutic potential of protein kinase inhibitors' (Cohen, pp 459–465) and 'Phosphodiesterase 4 inhibitors as novel anti-inflammatory agents' (Doherty, pp 466–473). Finally, there are therapeutically focused articles on 'Apoptosis: a potential target for discovering novel therapies for cardiovascular disease' (Yue, Olstein and Ruffolo JR, pp 474–480) 'Novel strategies for pharmacotherapy of depression' (Maubach *et al.*, pp 481–488), 'New targets for anti-inflammatory drugs' (Lewis and Manning, pp 489–494), 'Hormone replacement therapy' (Kooistra and Emeis, pp 495–499) and 'Novel anticancer drug discovery' (Buolamwini, pp 500–509). In all these therapeutic areas, novel molecular mechanisms and targets are rapidly emerging.

In drug discovery programmes, obtaining an adequate pharmacokinetic profile is often a greater challenge to the medicinal chemist than identifying molecules with the desired affinity for a particular receptor. Because the factors controlling metabolism and disposition of small molecules *in vivo* are becoming better understood, the optimisation of kinetic properties, using an emerging battery of medium- and high-throughput *in vitro* methods, is becoming a critically important component from the very earliest stages of the discovery process. Smith and van de Waterbeemd provide an overview of the state-of-the-art in this area, and outline the challenges still to be faced in correlating *in vitro* and *in vivo* data.

Maximising 'molecular diversity' has been the primary drive for design of combinatorial lead discovery libraries; as the activities associated with high throughput screening and combinatorial chemistry mature, however, it is becoming evident that success will not be achieved merely by increasing the number of compounds and data points. '*In silico*' techniques for analysing 'drug-likeness' of individual compounds, pioneered by Lipinski's 'rule of five' paradigm, are of considerable current interest and are reviewed by Murcko and colleagues. General rules are emerging that appear to predict the similarity of a virtual compound library to known drug molecules. These studies show that drugs, especially orally active ones, have a

definable 'envelope' of physicochemical attributes and are not actually 'diverse' in the broadest sense. This is not really surprising, since the molecular targets for drug action — proteins — although functionally promiscuous, are not chemically diverse, and there are large additional restrictions necessarily imposed to obtain metabolic and pharmacokinetic stability in drug molecules.

Today, drug discovery utilises vastly greater numbers of compounds and associated data than ever before. This has been driven by the opportunities presented by the emergence of high speed, parallel and combinatorial synthesis, and at this time the major drug companies have databases comprising several million compounds. The need to register and utilise information effectively is vital and has led to the birth of 'chemoinformatics', another 'new technology' whose origins can in fact be traced back over 50 years. But, as explained by Hann and Green, chemoinformatics has been rediscovered by a wider audience recently, partly as a result of the vastly increased data, computer power and the drive to accelerate the discovery and optimisation of new chemical leads.

Positron emission tomography (PET) has the potential to make expensive and time-consuming clinical trials more efficient. PET is a noninvasive imaging technique, described in the article by Burns *et al.* in the context of designing dosage levels and regimens for clinical trials of new drugs for the central nervous system (CNS). One of the best known examples of the use of PET involved ^{11}C-labelled anti-schizophrenic drugs, which were used to show how the percentage occupancy of dopamine D_2 receptors relates to efficacy and side-effect profile in humans. More generally, PET can be used to measure the relationship between the dose of a test drug and receptor occupancy for a specific target binding site in the CNS, hence providing a means for selecting the dose required to assure valid testing of a clinical hypothesis. One of the main impediments limiting the take-up of PET is the additional research work that is required to develop and profile the radiotracer ligand, although recent activities with small animal PET cameras may facilitate its use in the preclinical setting.

The search for peptidomimetics acting at G-protein-coupled receptors (GPCRs) has been an active area of drug discovery research for over a decade. Initially, this was considered a highly challenging area but today nearly all the peptide-responsive GPCRs have yielded to the medicinal chemists' attack. This research continues apace and is supported with therapeutically useful drugs such as the AII receptor antagonists. Freidinger reviews the latest developments, and illustrates how a judicious combination of rational design, high-throughput screening and combinatorial chemistry can uncover nonpeptide agonists, as well as antagonists. These programmes have led to recent clinical trials with orally active antagonists of substance P, bradykinin and endothelin.

The chemokine receptors are the latest family of peptide agonist GPCRs to have received attention as drug discovery targets. The complexity of this area of multiple agonists and receptors is unravelled by Schwartz and Wells, who describe therapeutic potential for chemokine receptor antagonists in several areas, including inflammation, immunology and virology. The association of the CXCR4 and CCR5 receptors with HIV-1 cellular entry has stimulated considerable drug discovery efforts and, like other peptide agonist GPCRs, nonpeptidic ligands have recently been identified. Because the chemokine molecules themselves act on several different receptors, it is anticipated that new selective 'drug-like' ligands will help to assess the roles of the chemokine system in disease.

Plant extracts containing mixtures of compounds that we now term 'cannabinoids' have been used for their therapeutic and recreational properties for several millennia. After traditional research involving natural product chemistry and the identification of endogenous receptors, the field of cannabinoid research is now experiencing a substantial resurgence of interest within drug discovery laboratories; this is partly as a result of the discovery of endogenous ligands, the discovery of two cannabinoid GPCR subtypes and signs of changing government regulations in some countries. For this reason, the account of the structures of endogenous and synthetic cannabinoid ligands provided by Pop is germane and many scientists will follow future developments in this area to see whether the application of modern research techniques will provide the holy grail of a nonaddictive analgesic or novel psychiatric therapy.

R&D projects targeting classical neurotransmitter receptors may seem a far cry from the fashionable new technologies but they continue to deliver blockbuster drugs. The area of muscarinic receptor agonists and antagonists is reviewed by Eglen *et al.*, and this area is of sufficient maturity to have yielded ligands with differing degrees of receptor subtype selectivity and efficacy. Several agonists and antagonists have been evaluated in clinical trials for activity in the CNS (cognition, analgesia, schizophrenia) and for peripheral indications (urinary incontinence, irritable bowel syndrome) and the rationale for use of selective M1 agonists for treatment of cognitive deficits in Alzheimer's disease remains strong. Side effect issues have been a major problem but this may be overcome if medicinal chemists are able to crack the tricky problem of designing compounds with much improved receptor subtype selectivity and pharmacokinetic/pharmacodynamic properties. Future agents may even require mixed actions at multiple muscarinic receptors.

The ionotropic glutamate receptors (iGluRs) have been important CNS targets for the past decade and here Bigge concentrates on new developments in the biology and pharmacology of this field. The recent characterisation of receptor subtypes, together with emerging information on the agonist-binding site from X-ray crystallography, are

major advances, which are likely to stimulate this mature field. Drug discovery efforts in this area have proven frustrating, with few compounds in development, largely because of side effects and poor physical properties of antagonists. The therapeutic perspective is very wide, encompassing acute neuroprotection following strokes, as well as a variety of psychiatric disorders, and new molecular information on the receptors should help to motivate interest in finding subtype-specific agents.

As well as the iGluRs, glutamate acts as an agonist on a family of metabotropic GPCRs (mGluRs), reviewed here by Pellicciari and Costantino; these have also become important targets in the CNS. Unlike the peptidic GPCRs, where nonpeptidic ligands abound, it has proven difficult to find 'nonamino acid' ligands for the mGluRs, although receptor models based on mutagenesis, and information from the related γ-aminobutyric acid B receptor, are aiding drug design. Despite apparently poor physical properties, the existing subtype-specific ligands have proven useful in defining potential utility in schizophrenia and ischaemia. Whether potential side effects may be as much of a liability as in the iGluR area is as yet uncertain.

The voltage-gated potassium (K_v) and calcium channels are two large families of ion channels with considerable potential as drug discovery targets. Although structural information of channel architecture is emerging, this area has proven particularly challenging for design of small molecule ligands. Kaczorowski and Garcia review the pharmacology of these targets and describe some recently identified inhibitors, including correolide, a natural product inhibitor of the $K_v1.3$ channel with potential immunosuppressive properties.

Protein kinase inhibitors have broad therapeutic potential in cancer, inflammation and immunology. Cohen reviews progress in this field, where several compounds have entered clinical trials and where the burgeoning new findings on cell signalling pathways continue to provide many attractive targets for drug seeking. Structural information shows that most existing compounds are predominantly competitive, binding to the ATP recognition site, but it is clear that specificity can nevertheless be achieved, making the protein kinase family highly attractive as 'drugable' targets.

Several inhibitors of phosphodiesterase 4 (PDE 4) are now in the clinic for indications including asthma, chronic obstructive pulmonary disease and atopic dermatitis. Doherty reviews the properties of existing compounds, and possible clinical utility, which is impressively wide. Current PDE 4 inhibitors are not subtype-selective and are likely to possess side effects such as emesis, but show very promising therapeutic potential. Demonstration of freedom from side effects at the clinically effective doses seems to be needed for useful drugs to emerge from this area.

Depression is now recognised as a disease that affects almost 1% of the population in the developed economies of the West. First-generation drug therapy utilised monoamine oxidase inhibitors and the so-called 'tricyclic' antidepressants. More recently, the selective serotonin reuptake inhibitors have found widespread use in clinical practice, making Prozac the world's biggest selling CNS drug. Subsequent variations on this theme include adding other monoamine-modulating activities to the pharmacological mechanism in order to improve efficacy or reduce the side-effect profile in patients. Hill and colleagues cover the major ongoing R&D programmes, and, in keeping with current trends, the emphasis is on the newer 'non-monoaminergic' approaches including the clinical testing of substance P and corticotrophin-releasing factor antagonists.

Kooistra and Emeis provide an account of clinical and preclinical drug discovery research aimed at using hormone replacement therapy to alleviate (post) menopausal symptoms such as osteoporosis and cardiovascular disease. The HERS and RUTH clinical trials are discussed, together with new opportunities for improving clinical selectivity and efficacy offered by the selective estrogen receptor modulators and ERα-/ERβ-selective ligands. The ageing human population, our increasing understanding of this family of intracellular hormonal receptors and a growing awareness of gender-specific therapy are likely to act as a driving force for further developments in estrogen-linked drug discovery research.

The biological mechanisms leading to apoptosis are being actively researched and hold promise to provide new targets for the future in many therapeutic areas. Ruffolo Jr and co-workers review the current state of knowledge of apoptosis in cardiovascular disease, with particular emphasis on mechanisms that may be potential targets for pharmacological intervention. The review describes what is known, what is not known and where current speculation is heading.

Our understanding of the molecular basis of inflammatory and autoimmune diseases is advancing rapidly and there are significant opportunities emerging for new approaches to treatment of asthma, rheumatoid arthritis and psoriasis. Lewis and Manning review the impact that the new protein targets involved in intracellular signalling are now having in this area. The prospects for replacing old drugs such as steroids and nonsteroidal anti-inflammatory drugs with more specific and selective agents appear promising, with novel targets identified including the cytokines, transcription factors and their regulators, the mitogen-activated protein kinase pathways and NF-κB.

There is still a massive scientific challenge to identify 'cancer-specific' molecular targets for drug discovery, and hence research into tumour cell proliferation, angiogenesis and metastasis continues apace. New approaches towards selective anticancer drugs that do not possess the cytotoxic effects of current agents are reviewed by Buolamwini, including growth factor receptor tyrosine kinases, cell

cycle targets, apoptosis-related targets, extracellular matrix targets and cell life span targets.

Finally we wish to thank the authors of the reviews for their valuable contributions. They have succeeded in highlighting the key discoveries and opportunities, from both chemical and biological perspectives, across a broad range of current topics in drug discovery. The emphasis in all of the articles in this issue is on the 'tried-and tested' discovery and development of small molecules as therapeutic agents, which admittedly reflects Editorial bias. Although approaches to gene and protein therapies are beginning to show promise, the drive to deliver cheap, efficacious and orally-active drugs shows few signs of diminishing. With the rapidly advancing new technologies for target and lead discovery currently being widely exploited, the challenge to discover selective 'drug-like' ligands for the vast numbers of newly found molecular targets is expected to remain a major objective for the next generation of therapeutic agents.