Next generation therapeutics Looking to the horizon

Editorial overview

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Abbreviations

COX	cyclooxygenase
NO	nitric oxide
NOS	NO synthase
PDE	phosphodiesterase

This is the second issue of *Current Opinion in Chemical Biology* devoted to 'Next generation therapeutics' that seeks to identify chemistry and biology that is important to future drug discovery. Fifteen reviews describe methods, recent approaches and results that are likely to lead to new drug entities in the future; however, most of the research described here will not lead to additional drugs for some time. One of the important facets of drug discovery that is evident in this collection of reviews is the importance of identifying novel drug targets as the absolutely essential first step in the drug discovery process. Indeed, although modern methods to identify lead compounds (structural biology, combinatorial chemistry, high-throughput screening and so on) that ultimately produce the drug have improved dramatically in recent years, these methods must be used in conjunction with screening against some molecular target (receptor or enzyme) or biological response; without this functional endpoint that guides the screening process to produce the first 'hit' compound, all structural biology and chemical optimization must necessarily fail. Consequently, the selection of topics in this issue has begun to include a significant number of reviews of emerging biological areas that are likely to produce new therapeutics more towards the end of the next generation.

As in the first issue (*Curr Opin Chem Biol* 1997, vol 1, no 4), peptidomimetics, peptide antagonists and proteases continue to be major players in future drug discovery efforts. In the review on peptidomimetics by Ripka and Rich (pp 441–452), current developments are reviewed in the use of peptidomimetics to stabilize peptide-derived enzyme inhibitors. This area has produced many important clinically useful drugs in the past few years and new concepts that enhance the ability to systematically transform peptide-derived structures into nonpeptide structures, especially topological (type III) peptidomimetics, will prove especially useful.

Lin and Castro (pp 453–457) review the recent progress made in the development of inhibitors of very late antigen 4 that can be used as anti-inflammatory agents. Antibodies, as well as small molecules, have been disclosed that inhibit this system, and numerous potential therapeutics are likely to emerge from research in this area.

Shafer (pp 458–465) reviews the recent advances in anti-coagulant therapy. Warfarin, the anticoagulant discovered in Wisconsin in the 1940s, continues to be a major line of treatment for preventing deep vein thrombosis in spite of a severely narrow therapeutic window. This limitation drives research to develop novel, improved anticoagulants, especially small-molecule inhibitors of thrombin, a key serine protease in the coagulation cascade.

Johnson, Dyer and Hupe (pp 466–471) review recent work on defining the function of matrix metalloproteinases (MMPs) using genetic knockouts, and on assessing the clinical safety and efficacy of current inhibitors. They also suggest new disease targets and outline future directions in the design of improved inhibitors. The role of MMPs in tissue remodeling and in related pathologies due to inappropriate regulation of this complex family of enzymes remains a highly competitive field in both industry and academia.

Three other enzyme targets also harbor considerable future potential. The successful launch of Viagra (Sildenafil) for treatment of erectile dysfunction has received widespread publicity. This compound is an inhibitor of phosphodiesterase 5 (PDE5, one subclass of the many isoforms of PDEs; there have been 10 classes and 30 isozymes identified to date). Perry and Higgs (pp 472–481) review the potential roles these different classes of PDEs might play in the body and how inhibition of different isozymes might be used to generate additional, useful therapeutics. Selective inhibitors of many of these enzymes are needed to characterize their biological roles; for example, selective inhibitors of PDEs 1, 2 and 6–10 are all needed. In addition, it is possible that one side effect of Viagra results from unwanted inhibition of PDE6. It is clear that research in this field has much left to offer.

Two unusual heme-containing enzymes, cyclooxygenase 2 (COX-2) and nitric oxide (NO) synthase (NOS), also have considerable therapeutic potential if isoform selectivity

can be achieved. In the case of COX-2 the potential is close to reality. Marnett and Kalgutkar (pp 482–490) review the quest for selective COX-2 inhibitors that promise a new era in the medical application of non-steroidal anti-inflammatory drugs. Competition in this new drug class is fierce with the first market entries probably appearing in the next year. Although NO and NOSs have gained great celebrity in the past few years, the broad function of NO in multiple physiological pathways and the challenges of identifying isoform-selective inhibitors have had a sobering effect on developing a clear and unambiguous pharmaceutical vision for this target. Ramesh Babu and Griffith (pp 491–500) provide a lucid account of recent thinking in the field.

Exciting recent developments on the mechanisms of transcriptional regulation are beginning to affect drug therapy and gene therapy. Gene expression by nuclear receptors suggests that a new generation of selective glucocorticoids, retinoids and estrogens with an improved safety profile lie on the horizon. The implications for improved cancer, anti-inflammatory and immuno-suppressive therapies are profound. Resche-Rigon and Gronemeyer (pp 501–507) review the current models for distinct transactivation and transrepression mechanisms of gene expression by the family of nuclear receptors and the emerging chemical prototypes for 'dissociated' glucocorticoids. Gustafsson (pp 508–511) expands further on this topic with a comprehensive discussion of current advances in the development of selective estrogen receptor modulators.

Our growing sophistication in understanding the mechanisms of small-molecule control of gene expression has been rapidly incorporated into the creative design of new gene therapy vectors. The tight control of target gene transcription on demand for the treatment of diseases is one of the great medical prospects of the next millennium. Harvey and Caskey (pp 512–518) review the pioneering advances in several approaches to gene regulation by small molecules and assess the prospects for gene therapy.

Other nucleic-acid-based therapies and genomics-based strategies are represented in two broadly diverse reviews. Agrawal and Zhao (pp 519–528) provide a comprehensive review of the current scope and limitations of antisense oligonucleotide therapy. The potential for exquisitely selective inhibition of specific gene expression by antisense oligonucleotides has remained so compelling that significant effort has been amounted to clear the formidable hurdles blocking the path to realized therapy.

On another front, the emergence of bacterial resistance to most antibiotics is a major health problem worldwide that promises a return to the pre-antibiotic era of the 1930s unless new agents are discovered. At the same time, DNA sequence technology has progressed to the point that sequencing of bacterial genomes has become routine, in part due to the small genomes (400–4000 proteins versus 100,000 proteins for the human genome). Schmid (pp 529–534) reviews genetic approaches to interpret the data contained in these genomes. The goal is to identify promising new targets, for example ways to counter resistance mechanisms, antagonize virulence factors, identify bacterial encoded targets not present in humans or obtain more selective antibacterials that spare useful bacteria. Such opportunities may actually exceed the emergence of resistance.

Future issues in this series could well be devoted to advances in neuropharmaceutical research. The richness of specific neurotransmitter receptor subtypes and their unique distribution in specific substructures of the brain predict a future wave of new drugs for the treatment of an array of neurological and psychiatric disorders. Faraci *et al.* (pp 535–540) review recent efforts in the design of potent and selective dopamine D4 receptor antagonists for the treatment of schizophrenia. They also discuss recent clinical data that have called this approach into question.

Therapies for alcohol and drug addiction are receiving renewed interest. Terenius (pp 541–547) reviews the developments in finding compounds that inhibit relapse in treatment for chemical addiction. The recognition that addiction is mediated by complex interactions between neurotransmitters in the central nervous system, including adrenergic, opiate, γ-aminobutyric acid, serotonin and dopamine, has led to trials to see if different agonists and antagonists might alter response to drugs of abuse, including alcohol, tobacco, heroin, cannabis and cocaine. Importantly, this work has led to identification of Acamprosate and Naloxone, two drugs recently registered for diminishing craving for alcohol and other substances of abuse, which can be used to suppress drug relapse. Most importantly, these developments suggest that additional compounds can be found that will prove useful in treating addictions.

Finally, technological advances in drug delivery are dramatically increasing the range of drug formulations available to address issues of bioavailability, pharmacokinetics and stability for both small-molecule and protein therapeutics. Putney (pp 548–552) presents a comprehensive review of protein encapsulation methods that may greatly simplify treatment regimens with human growth hormone, erythropoietin and nerve growth factor.

This second issue of 'Next generation therapeutics' is testimony to the remarkable scope of drug discovery programs. Many areas remain for future issues to explore, however, for, no matter how vigorously we pursue and chart the fields of drug discovery, new and enticing biomedical discoveries always lie just beyond our horizon.