Annual Review of Pharmacology and Toxicology, 2008. Arthur K. Cho *et al.* (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 48. 701 pp. Price not mentioned.

The volume under review presents a series of state-of-the-art articles ranging from cancer therapy to anti-AIDS drugs and signal transduction to the newly emerging concepts in metabolomics. Those wishing to keep pace with the recent advances in drug research, will find this volume a handy and useful resource.

Seven transmembrane domain G protein coupled receptors (GPCRs) comprise the largest family of cell surface signalling receptors encoded in the human genome with about 900 members. GPCRs are the targets of nearly half the drugs currently in use. It is therefore not surprising that there are six chapters exploring G-protein-related issues. In the chapter on 'Activation of G protein-coupled receptors: Beyond two-state models and tertiary conformational changes', the authors exemplify the structure of the light receptor rhodopsin as a prototype for explaining the transmembrane architecture of the GPCRs. Early biochemical, biophysical and pharmacological studies led to the conceptualization of receptor activation based on two-state equilibrium models and conformational changes in protein structure. However, the authors take us beyond these classical paradigms and bring in focus the phenomenon of the oligomerization of receptors. They explain how receptor activation occurs via an ensemble of different dynamic states of the proteins rather than a single state and how ligand binding modulates the activity of receptors by altering the distribution of dynamic states. Chemokine signalling is also mediated by the GPCRs. The chapter entitled 'Chemokines and their receptors: Drug targets in immunity and inflammation' takes the reader from the simple definition to highly complex phenomena, yet retaining the lucidity in style and interest in the content. The different aspects of chemokines, their diversity, classification, old and their equivalent new names, chemokine–receptor relationship and distribution of receptors on host cells have been addressed. With a series of easy-to-understand diagrams, the chemokine–receptor interaction unfolds, and paves the way to uncovering the different forms of G-proteins involved in multiple signal transduction. Information on how the chemokine system coordinates leucocyte migration in immunity and inflamation, and influences the pathogenesis of many human diseases is neatly presented.

Recent years have witnessed information on GPCRs blossom into clinical application. In the chapter on 'Targeting chemokine receptors in HIV: A status report', the authors furnish exciting information on HIV coreceptor inhibitors and their role in the prevention of HIV and control of disease in infected individuals. These drugs target a host-encoded, i.e. the coreceptor, rather than virus-encoded structure. The authors explain how the coreceptors play a crucial role in the fusion of the viral and host cell membranes and how the blockade of the coreceptor prevents the virus from infecting the target cell. Rapid strides in this area have led to the approval of the first coreceptor inhibitor, maraviroc, in the anti-HIV therapeutics. Over the next few years we can hope for more such coreceptor inhibitors to be added to our armory of anti-HIV drugs. In addition to these frontline topics, the lesser known aspect of GPCRs like processing and sorting, deactivation and recycling have been addressed in the chapter on 'G Protein-coupled receptor sorting to endosomes and lysomes'. The authors introduce the novel concept of receptor trafficking that is crucial for the spatial and temporal control of GPCR, and further suggest that physiological consequences of specific trafficking events may lead to new opportunities for drug development. The review entitled 'Caveolae as organizers of pharmacologically relevant signal transduction molecules' by Patel *et al.*, provides a general overview of caveolae and caveolins. Caveolae are flask-like invagination of the plasma membrane that contain caveolin proteins which facilitate interaction and organization of signalling molecules, inclusive of GPCRs, so as to bring about coordinated and efficient signal transduction.

There is an interesting article by Benedetti on 'Mechanisms of placebo and placebo-related effects across disease and treatments'. The placebo effect has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation. In recent years, placebo and placebo-related effects have been analysed with sophisticated biological tools that have uncovered specific mechanisms at both the biochemical and cellular level. Profusely citing examples like Parkinson's disease, depression, anxiety, addiction, cardiovascular system, immune and endocrine system, the authors demonstrate how the psychosocial-induced biochemical changes in the patient's brain and body in turn may affect the course of a disease and response to a therapy.

The review on 'Strategic approach to fit-for-purpose biomarkers in drug development' by John Wagner, is an attempt at exploring the biomarkers and their applications. The term 'biomarker' refers to any useful characteristic that can be measured and used as indicator of a normal biologic process, a pathogenic process or pharmacologic response to therapeutic agent. In a concise table, the author provides definitions for terms like surrogate end-point (a biomarker that is intended to substitute for a clinical end-point and expected to predict the clinical outcome), clinical end-point (a characteristic or variable that reflects how a patient feels, functions or survives), target engagement biomarker (a biomarker that occurs early in the pathophysiologic cascade and informs how the drug is working), disease-related biomarker (a biomarker that occurs late in the pathophysiologic cascade and is linked to clinical benefits of the drug) and proof of concept (. . . is achieved when it is established that a drug candidate works to improve a disease condition in a way predicted by the proposed mechanism of action).

Apoptosis not only plays an important role in physiological processes such as tissue and organ formation during embryogenesis, but also during adult life in processes like tissue renewal, regulation of the immune system and elimination of derailed or cancer cells. A decreased propensity for apoptosis contributes for tumour formation. Considerable efforts are underway in the development of new anticancer therapies, which are based on the induction of apoptosis. In the chapter on 'Apoptin: Therapeutic potential of an early carcinogenic transformation', the authors describe the chicken anaemia virus-derived protein apoptin, which induces apoptosis specifically in the tumour or transformed cells. The concept has enormous potential for novel anticancer therapy. The authors advance compelling evidence suggesting that apoptin senses relatively early stages during the multi-

stage process of oncogenic transformation. As these early changes are likely to determine the subsequent path of tumour progression, apoptin might target the Achilles heel of cancer cells.

The role of neuropeptides in the cell–cell communication in brain/endocrine system is well studied. Neuropeptides are synthesized from protein precursors (termed proneuropeptides or prohormones) that require proteolytic processing primarily within secretory vesicles that store and secrete the mature neuropoeptide to regulate control target cellular or organ systems. In the chapter on 'Proteases for processing proneuropeptides into peptide neurotransmitters and hormones', Hook *et al.* describe the interdisciplinary strategies that have elucidated two primary protease pathways for prohormone processing consisting of cysteine protease and subtilisin-like proprotein convertase pathway that together support neuropeptide biosynthesis. Furthermore, this review discusses important areas of current and future interest, like the biomedical neuropeptide research with respect to biological regulation, inhibitors, structural features of proneuropeptide and protease interactions, and peptidomics combined with proteomics for systems biological approaches.

Metabolomics is the study of metabolism at the global level. This rapidly developing new discipline has important implications for pharmacological sciences. A critical metabolomics concept is that a biomarker that predicts disease or helps monitor drug therapy is most often not a single molecule, but rather a pattern of several molecules. The metabolomic studies take into consideration all the biochemical reactions taking place in a cell, tissue or organ or biological fluid followed by the application of informatic techniques to define metabolomic signatures. These can lead to enhanced understanding of disease mechanisms and to diagnostic markers as well as advanced understanding of mechanisms for drug effect and increased ability to predict individual variations in drug response. Initial metabolomic signatures have already been reported for several disease states, including motor neuron disease, depression, schizophrenia, Alzheimer's disease, cardiovascular and coronary artery disease, hypertension, diabetes, liver cancer and Huntington's disease. These signatures are made of tens of metabolites that are deregulated with concentrations that are modified in the disease state or after drug exposure. Analysis of these signatures can provide information on the pathophysiology of the disease. Metabolic signatures that change following drug treatments have also been identified.

I found the book particularly useful for briefly introducing the reader to the recent vocabulary added to the science of pharmacology. In some chapters, the authors have focused on the 'Future issues', wherein we get a glimpse of what the future might hold. Most of the chapters contain excellent coloured illustrations with imaginative and novel efforts to get across to the reader, and 'Biomarkers of acute kidney injury' is a case in point. The reference work is as recent as it can get. Occasional brief and refreshingly apt comments in the margin are a great value-addition. Such comments in the references, highlighting the major contribution of a paper, create interest in what is otherwise a mundane reading. I strongly recommend the book for its depth and range.

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Annual Review of Biochemistry, 2007. Kornberg *et al.* (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. vol. 76. 864 pp. Price not mentioned.

Biochemistry earns the distinction of being the most interfacial of all sciences, and the volume under review once again provides a firm basis for this fact. The review presents articles on a wide range of contemporary topics to rejuvenate the excitement of discovery. A number of articles discuss the molecular mechanisms of some of the key processes directly involving nucleic acids. The opening article, for example, reviews the understanding of the role and the molecular mechanism of somatic gene diversification processes in the production of vertebrate antibodies. Somatic hypermutational studies have provided evidences for programmed changes in the DNA coding information through targetted base modification. The biochemistry and the mechanism of nonsense-mediates mRNA decay (NMD) is reviewed by Chang *et al.* NMD is an evolutionarily conserved housekeeping mechanism that selectively degrades mRNAs containing nonsense codons. Translation of such mRNAs and thus production of truncated proteins could produce deleterious gain-of-function activities. The authors discuss the current understanding of the constituent proteins, the NMD assembly, and the molecular interactions that define nonsense codons. Housekeeping is also performed by the tmRNA system by degrading proteins in the regulation of transcriptional circuits. In addition, tmRNA rescues stalled ribosomes that can neither terminate nor continue with translation. This field is visited by Moore and Sauer.

Establishing the relationship between structure and mechanism of biological molecules and molecular assemblies is central to designing molecules and ligands, and to achieve control over molecular functions. The advent of powerful molecular modelling methods and a variety of structural tools has greatly facilitated structure–mechanism studies. The volume promotes several articles based on this. The chapter on 'Structure and mechanism of helicases and nucleic acid translocases' by Singleton *et al.* and the discussion of 'Structure and mechanism of 6-deoxyerythronolide B synthase' by Khosla *et al.* exemplify these articles. An interesting related area is the role of mass spectrometry in structure elucidation of protein complexes. This area is reviewed by Sharon and Robinson. The authors have also included a concise introductory section on the methodological aspects of mass spectrometry for readers who are not quite familiar with the subject. The authors then discuss structural studies of protein assemblies.

A relatively new research area is single-molecule and single-event studies that have been augmented by emerging spectroscopic, and electrophysiology and imaging techniques. There are several advantages to such studies. For example, measurement of macroscopic behaviour reports only on the average, and this average behaviour is not associated with any of the members of the population. Also, interpretations of the results of macroscopic measurement cannot be unambiguous. Single molecule studies re-