

sequenced are that of several archaea, many bacteria, unicellular eukaryotes like *Saccharomyces cerevisiae*, multicellular organisms like *Caenorhabditis elegans*, *Drosophila melanogaster*, *Arabidopsis thaliana*, *Oryza sativa*, *Homo sapiens*, etc. Genomic studies of these organisms are important from the point of evolution, development, adaptation to extreme environments, health and food production. This chapter describes the emergence of new biology to study the whole genome, known as genomics, transcriptomics and proteomics. An important description in relation to evolution of different organisms is given as follows: 'once evolution solves a particular problem – for example, designing an enzyme to catalyze a particular biochemical reaction – it tends to stick with that solution. This kind of evolutionary inertia is responsible for the centrality of RNA in cellular processes: life started in an "RNA world", and the legacy remains with us to this day. And the inertia extends to the biochemical details: 43% worm proteins, 61% fruit fly proteins, 75% of fugu proteins have marked sequence similarities to human proteins. Some 90% of the domains that have been identified in human proteins are also present in fruit fly and worm proteins. In effect, therefore, even a protein unique to humans is likely nothing more than a reshuffled version of one found in *Drosophila*' (p. 218). Here the authors give an interesting explanation between gene number and intelligence in humans.

The ninth chapter describes human evolution. Though there is no written record of our evolution, we all carry the history written in our DNA as mentioned: 'Prehistory by definition refers to the period prior to written records, and yet we find written in every individual's DNA sequences a record of our ancestors' respective journey' (p. 252). This chapter describes by analysing the Y chromosome as well as mitochondrial DNA from different human populations; the patrilineal and matrilineal origin of human population respectively, is being traced in Africa. Denaturation and renaturation studies of DNA molecules revealed that the chimpanzee is the closest organism to humans and that the human genome is different from that of the chimpanzee by only 1%. In fact, the chimpanzee is closer to humans than to gorillas. The authors describe 'humans are, I suspect, simply great apes with a few unique – and special – genetic switches' (p. 266). The tenth chapter de-

scribes the contribution of DNA fingerprinting in forensic science today, to identify criminals and sort out paternity disputes. Many incidents have been cited in this chapter that were solved by DNA fingerprinting, which signifies the importance of this technology. The eleventh chapter introduces different genetic diseases of humans that are inherited by simple or complex traits. The authors describe the difficulties that lie in cloning human genes and successful stories of cloning genes for several diseases like Huntington's disease, Duchene's muscular dystrophy, cystic fibrosis and breast cancer.

The twelfth chapter describes methodologies used to detect genetic disorders by prenatal diagnosis and the ethics involved. This chapter also introduces gene therapy technology and several incidences where this has been used. The thirteenth chapter describes the importance of nature (gene) and nurture (environment) in the development of human behaviour. This chapter also describes Lysenko and his pseudoscience, Lysenkoism. The last chapter is correlated with the first chapter in that both nature and nurture have to be given importance in studying human behaviour. In conclusion, the authors emphasize that great potential lies with DNA-based technology, which should be used judiciously for making our future safe and healthy. There are several sentences in the book written in an amusing manner, e.g. describing Pauling's wrong model of DNA: 'the world's best known, if not best, chemist had gotten his chemistry wrong. In effect "Pauling had knocked the A off of DNA"' (p. 50). Each chapter of the book also contains several anecdotes, which keep the reader engrossed.

Overall this a wonderful book!

SUVENDRA KUMAR RAY

*Department of Molecular Biology and Biotechnology,
Tezpur University,
Tezpur 784 028, India
e-mail: suven@tezu.ernet.in*

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This is a compilation of seventeen reviews which are categorized under the following subjects for ease of discussion: Drug

metabolism, Signalling, Receptors and Proteases. Chapters written by experts are educative for those who are new to pharmacology, while experts in the area are likely to appreciate the grand scope of the volume.

Drug metabolism: Five complementary review articles deal with drug metabolizing enzymes and multi-drug transporters. The cytochrome P450 (CYP) enzymes have been well characterized for their efficacy in the breakdown and clearance of drugs. They also generate carcinogens from otherwise harmless chemicals. Altered levels and activity of these enzymes due to mutation or polymorphism lead to drug resistance in diseases. As a consequence, there is either a decrease in the bioavailability of drugs or drug-induced xenotoxicity. Activity of the enzymes and their isotype distribution are important criteria in the pharmacokinetic administration of the drug. Although some cancers can be cured with current-day drugs, the major impediments towards a complete cure are innate or acquired drug resistance, toxicity and relapse. These aspects are reviewed in the context of childhood leukaemia by Cheok *et al.* Treatment regime has to take into account the genetic background and associated polymorphism. To recapitulate these and to overcome the often disparate results obtained using animal models, generation of humanized animal models appears to be mandatory. The article by Gonzales and Yu covers current status of such humanized mouse models for CYP and xenobiotic receptor humanized mice. Tying neatly with these articles is the related topic on the role of drug-metabolizing enzymes in inflammation (Regulation of drug metabolizing enzymes and transporters in inflammation). The chapter focuses on regulation of CYP, the major enzyme involved in this process with brief notes on flavin monooxygenase (FMO), phase II enzymes and hepatic transporters. Apart from chronic inflammatory cases, due to the role of inflammation in sepsis and cancer, this article will have a wider impact. Cashman and Zhang cover basic aspects of FMO, the lesser studied of the detoxifying enzymes. Isoform distribution and tissue-specific expression are particularly well covered. These authors predict further expansion of knowledge about these enzymes. The focus would be to distribute the drug load between CYPs and FMOs, and the design of pro drugs that can be metabolized specifically by the FMOs into their clinically potent active forms.

Currently, there is a flurry of research activities on stem cells. There is growing opinion that these progenitor cells may dictate cancer development. The article on the ABCG2/BCRP transporter (Role of ABCG2/BCRP in biology and medicine), which is predominantly expressed in stem cells is a must read (although the functional significance of these transporters in stem cells is not yet clear). Further reading of Gottesman *et al.* (*Nature Rev.*, 2002, **2**, 48–58) on Multidrug resistance in cancer: Role of ATP-dependent transporters, is rewarding.

Signalling: Three individual articles cover the current status of small molecule signalling: nitric oxide (NO), carbon monoxide (CO) and reactive oxygen species (ROS) respectively. These molecules are small in size, highly reactive and their effect is pluripotent. Therefore, understanding specificity in signalling mediated by these molecules and identifying suitable molecular/pathway targets for therapeutic intervention is a challenging task. Although NO is transiently produced and CO is a more stable entity, signalling achieved through them is both overlapping and distinct. The chapter by Dudzinski *et al.* describes current understanding of regulation of endothelial nitric oxide synthase. Kim *et al.* deal with CO. Understanding the crosstalk between NO and CO pathways is predicted to be the future research goal. (Further reading: On carbon monoxide biology see Ryter, S. W. and Otterbein, L. E., *BioEssays*, 2004, **26**, 270–280. For those keen on structure and mechanism of NO synthase see Alderton *et al.*, *Biochem. J.*, 2001, **357**, 593–615.)

Hansen *et al.* show how ROS-mediated signalling is rendered specific through their reaction with thiols, their prime targets. A clear account of various redox couples involved in ROS-mediated signalling is presented. This article highlights the recent advances in technology that will allow investigators to monitor the specificity of thiol modification and their inter-compartmental differences. For those interested in oxidative damage-induced molecular mechanism in ageing, cancer, and neurodegeneration, this article is an excellent starting point for novel ways of thinking and the design of experiments towards more conclusive results.

Two additional reviews cover macromolecular signalling. One of them deals with GTPases, and their accessory proteins by Sato *et al.* These accessory proteins, particularly noted for their non receptor-induced signal enhancement, are

recent additions to the signalling cascade. Summary on both receptor and non receptor-induced signal enhancement, and the informative long table listing the currently known human accessory proteins along with their biological effect are hallmarks of this review. The article is thorough in describing the advances, scope and application of this novel signalling mechanism with a vast therapeutic potential. (One may also read *Receptors and Channels*, 2003, **9**, 195–204 by Blumer, J. B. and Lanier, S. M. for a more mechanistic understanding of signal enhancement.) Emerging role of phospholipase C and its regulation through RAS GTPases, including a perspective on structure, isoform types, and regulation is succinctly summarized by Harden and Sondek.

Receptors: The chapter on the mechanism of seven transmembrane (7 TM) receptor activation by Shwartz *et al.* may seem a little out of place in this particular edition. Nevertheless, it is an excellent summary of the challenges faced by the biochemist, biophysicist and modelling experts to provide new insights into the mechanism of action of a receptor in the absence of any structural data on the active form. The all-familiar rhodopsin belongs to this class of receptors. For the first time by developing new strategies, the authors have mapped the structural changes in the extracellular domain of the 7 TM receptor. They propose a novel model, called the global toggle switch, wherein upon ligand binding, select transmembrane domains move in opposite directions across a hinge. Their results help bridge the gap in knowledge between inactive and active states of such receptors. This model forms a platform that can help in the design of pharmacologically relevant agonists and antagonists, which had remained elusive till now. The authors have published their experimental results in a recent article (Elling, C. E. *et al.*, *J. Biol. Chem.*, 2006, **281**, 17337–17346).

Articles on the role of PPR α , β and (δ) γ in atherosclerosis by Li and Palinski and those of the retinoic acid receptors in mouse embryogenesis by Mark *et al.* are particularly noteworthy because of the reviewers attempts to reconcile with the enormous data available from *in vitro* and animal-model studies. Such studies are prone to controversial results due to multiple roles of these receptors and their tissue and cell type-specific regulation. Even carefully designed genetic studies are not sufficient enough, dampening the hope of arriving at a consensus. That is

precisely why the two articles, especially the one on retinoic acid receptor, spear-headed by none other than Chambon, are lucid in dealing with such information in a clearly perceptible manner. Reviews on P2 and cannabinoid receptors as possible therapeutic agents are other useful articles in this category.

Proteases: There are two reviews on proteases with specific emphasis on the potential for pharmacological intervention. Sloane *et al.* summarize the advantages of developing three- and four-dimensional (spheroid) model systems and live mice carrying the engineered proteases to overcome recurring frustrations where purely mechanistic, structural and functional understanding of the protease have failed to lead to the development of clinically successful drugs. In stark contrast to the failed results in extrapolating the *in vitro* data to human diseases, is the success story of one of the active-site inhibitors of the proteasomes, bortezomib, employed now in various clinical trials in the treatment of cancer. Proteasomes are ATP-dependent proteases and are the key players in the maintenance of normal cellular homeostasis. Their primary job is to degrade proteins into small peptides in a regulated manner. We are still in the process of understanding the full spectrum of activity, tissue specificity and the role of proteasomes in normal and abnormal circumstances in the human context and yet the inhibitor is clinically useful. This review by Voorhees and Orłowski is particularly informative for the compilation of the possible molecular consequences of inhibition, the prospect of combination therapy and identification of novel therapeutic targets under conditions where proteasome function is inhibited.

Overall, the 2006 review is a remarkable blend of contributions dealing with small and macromolecular signalling, molecular basis of diseases and signalling during development, technological and conceptual advances that can pave the way for new research trends. The benefits and pitfalls of currently used drugs, the mechanism of drug action and prospects for novel drug design and identification of new targets are the focus of such research befitting the journal's requirement.

PRASANNA VENKATRAMAN

KS 137, Sector 22,
Kharghar,
Navi Mumbai 410 208, India
e-mail: vprasanna@actrec.gov.in