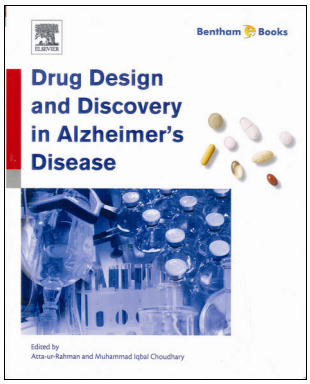


Drug Design and Discovery in Alzheimer's Disease. Atta-ur-Rahman and Muhammad Iqbal Choudhary (eds). Elsevier, Radarweg 29, P.O. Box 211, 1000 AE Amsterdam, The Netherlands. 2014. xviii + 766 pages. Price: US$ 130.

This book contains 16 chapters describing the key developments and innovative approaches in Alzheimer's disease (AD) drug discovery.

AD is the most common form of dementia affecting the elderly. It is a neurodegenerative disorder with characteristic pathological features, including the senile plaques (SP) and neurofibrillary tangles (NFT) primarily in the cortex and hippocampus coupled with compromised cholinergic transmission in the central nervous system. The causative factors appear to be (i) accumulation of 40–42 amino acid-long amyloid β (Aβ) peptide, derived from the sequential proteolytic cleavage of larger amyloid precursor protein by β-secretase (BACE-1) and γ-secretase, which forms the major constituent of SP; (ii) hyperphosphorylated Tau protein, increasing due to the imbalance between kinases and phosphatases, and forming paired helical filaments and NFT; (iii) increased acetylcholinesterase (AChE) activity resulting in decreased levels of acetylcholine at the synapse, thus reducing the cholinergic transmission.

Individuals affected with AD experience cognitive deficits which interfere with the quality of their day-to-day lives. Across the globe, in spite of several scientists aggressively pursuing research in the field of AD therapeutics, with increased momentum since the last three decades, complete cure is awaited to tackle this neurocognitive disorder.

In this context, the book provides descriptions on the key targets and offers leads to therapeutic approaches to AD. In the first chapter, Korabecny *et al.* set the stage for subsequent chapters by describing the current status on AD in terms of the available symptomatic treatments and about ten different possible therapeutic approaches in AD treatment. Subsequently, Rashid and Ansari offer an elaborate description on the rational drug design approach and study drug targets such as AChE, BACE-1 and Tau protein for treating AD. They further illustrate the complexity of the problem, such as crossing the blood–brain barrier (BBB) which needs to be overcome for successful targeting. Revadigar *et al.*, while restricting to inhibitors of cholinesterases and β- and γ-secretases, provide new information on α-secretase enhancers which are in the developmental stages. This assumes prominence since processing of amyloid precursor protein (APP) by α-secretase is postulated to be protective in the context of AD because the enzyme cleaves within the Aß sequence, thus precluding the formation of fibrillogenic Aβ.

Efforts by Aziz *et al.* in highlighting the disease modifying mechanisms shared by AD in common with Huntington's (HD) and Parkinson's disease (PD), all of which share some resemblance to accelerated ageing, albeit more closely linked to the central nervous system than true ageing, are noteworthy. In particular, for AD, this review offers the rationale and available validation data with commentary on physico-chemical properties of small molecules as the targets, and their advancement into pre-clinical and clinical studies. On similar lines, Joubert *et al.* move from 'one-drug-one-target approach' to that of multi-target-directed ligands and mention monoamine oxidase (MAO) and nitric oxide synthase (NOS) as potential targets for both AD and PD.

A radically new hypothesis that selective butyrylcholinesterase inhibition is of value in the therapy of AD was tested by Grieg and his colleagues. They developed novel agents such as cymserine and analogues, and this class of drugs is currently in preclinical development. In search of newer drugs which can be more effective than the currently available, FDA-approved drugs, Alcolea-Palafox *et al.* list a whole range of reversible and pseudo-irreversible inhibitors of AChE and other cholinesterases. Further, the potential of hybrid compounds with two or more complementary biological activities such as multipotent MAO and cholinesterase inhibitors for the potential treatment of AD is described.

Inhibiting the generation of Aβ from the amyloid precursor protein by modulating BACE-1 activity is yet another strategy for the development of therapeutic compounds aimed at treating AD. However, caution needs to be exercised since complete knockout of BACE-1 in mice resulted in hypomyelination and neurological adverse effects. This suggests that partial inhibition of BACE-1/modulation of the enzyme activity by other cellular components, in particular lipids, proteins that interact with BACE-1, and ubiquitination might be a safer alternative. These aspects with the current knowledge and the molecular and physiological challenges associated with BACE-1 inhibition are presented in the following reviews. Further, the agents in clinical development with emphasis on metal chelators, human trials with peptidomimetics and anti-BACE-1 antibodies are discussed.

In addition to AChE and BACE-1, a number of other targets are also being screened for AD drug discovery. Sandoval *et al.* exploit the fact that the somatostatin subtype-4 receptor (sst4) is expressed in key regions of the brain impacted by AD. It is pertinent to mention here that somatostatin regulates neuronal neprilysin activity, a key enzyme involved in Aβ catabolism. In this chapter, the viability of non-peptide sst4 agonists within the context of AD therapy, in conjunction with strategies for design, synthesis and recognition at the macromolecular level is discussed. Pope and Cascio continue on targeting Aβ catabolism by evaluating the specific interactions underlying neprilysin-mediated Aβ degradation. The abundance of information on neprilysin structure, binding and proteolytic activity towards Aβ providing a basis for utilizing the neprilysin–Aβ interaction in development of a potential AD therapy is well brought out.

As opposed to neurodegeneration in AD, it is known that some specific regions of the brain contain neural stem cells (NSC) capable of becoming neurons in adulthood. Wnt/β-catenin signalling is a key pathway in modulating the balance between NSC proliferation and differentiation. Wnt signalling is regulated by glycogen synthase kinase 3 (GSK3) that is constitutively active in the cells. A connection exists between

deficient neurogenesis in AD patients and a possible role of GSK3 in this deficit. Zeidan-Chulia and Moreira review the Wnt/β-catenin signalling and critically analyse the validity of inhibiting GSK3β in the disease.

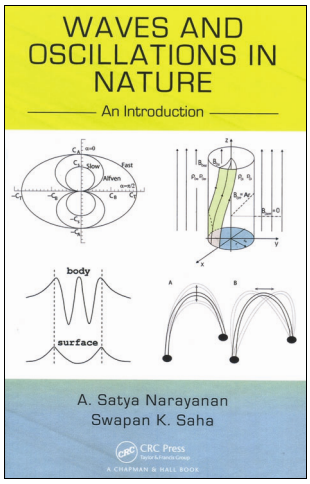
The importance of Tau as a dynamic regulator of microtubules in maintaining neuronal shape and functionality is well established. Alternative splicing of Tau and the uncontrolled post-translational modifications (hyper-phosphorylation, glycosylation, prolylamide bond isomerization, oxidation, etc.) lead to tauopathies, including AD. The most prospective therapeutic avenues targeted against these pathologically driven steps are presented and critically discussed by Seneci. Each target is presented together with its known small-molecule modulators.

Despite the progress in research in drug discovery, the effective pharmacotherapy in AD remains restricted due to the presence of physiological barriers like BBB, blood–cerebrospinal fluid barrier and p-glycoproteins. In this regard, Ahmad *et al.* aptly describe the emergence of nanotechnology-based drug delivery, targeting and localized delivery by means of nanomedicines. Further, they illustrate the AChE drug-loaded nanomedicines for management of AD, the clinical relevance and the challenges associated with their bioavailable brain delivery.

Overall, the book describes the current molecular understanding of AD condition, existing drugs, and recent advances in the field of AD therapeutics. However, the flip side is the repetitiveness of information on inhibitors of AChE and BACE-1 in a good number of chapters. Nevertheless, with the comprehensive coverage, this book would be useful as a reliable source of review of the literature for experimental neuroscientists and clinicians in the field of drug discovery for AD. Other neuroscientists who wish to have a quick summary on the current status of anti-AD drug design would find this compilation useful.

SARADA SUBRAMANIAN

Department of Neurochemistry,
National Institute of Mental Health and Neurosciences,
Bengaluru 560 029, India
e-mail: sarada@nimhans.ac.in



Waves and Oscillations in Nature: An Introduction. A. Satya Narayanan and Swapan K. Saha. CRC Press, Taylor & Francis Group, 6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742, USA. 2015. xxix + 521 pages. Price: £ 65.99.

Natural phenomena are dominated by the occurrence of oscillations and waves, whether it is light propagation, water wave disturbance, magneto hydrodynamics or plasma oscillations. There are many common features encompassing wave propagation and oscillatory behaviours in these diverse systems. Any attempt to consider these common features comprehensively, as has been done in this book, is a welcome contribution to physics literature. In addition, these waves and oscillations can behave linearly or nonlinearly, covering quite different aspects. This book covers these aspects essentially in the linear regime in electromagnetic and optical wave propagation, uniform and nonuniform media, hydrodynamics, magneto hydrodynamics and plasmas, though the nonlinear aspects are touched upon occasionally in a cursory manner. Overall, the book encompasses a wide variety of wave and oscillatory phenomena in diverse areas of physics, though there are a few shortcomings (which can always be addressed in a subsequent edition) which I will point out towards the end.

The book consists of 10 chapters. To start with, a comprehensive discussion on the basic notions of waves and various aspects of electromagnetic waves (including phase velocity, group velocity, dispersion relations and classifications, and spectrum, interference and diffraction phenomena) is given in chapter 1. In particular, the diffraction phenomenon is discussed exhaustively and the notion of resolving power of a telescope is clearly spelt out. Chapter 2 contains a nice discussion on the physical and mathematical aspects of electrostatics, magnetostatics, time-varying fields and Maxwell's equations in free space, which any student of physics will enjoy. This is followed by a rather careful analysis of wave propagation generated from a source through an antenna and its ramifications, including radio astronomy. The chapter ends with a short but penetrating analysis of waves through the ionosphere and determination of time through appropriate measurements on Earth, for example, by the National Physical Laboratory, New Delhi.

Chapter 3 contains a brief discussion on the general aspects of linear waves in uniform media, followed by a short discussion on nonlinear waves, namely solitary waves and soliton solutions of the Korteweg–de Vries (KdV) equation. Simple harmonic motion, damped and resonant motions and linearly coupled oscillators are discussed as well as propagation of waves in systems modelled by linear wave equation and Helmholtz equation, and longitudinal wave propagation, though the motivation for all these discussions is not made clear. Finally, the KdV equation is introduced (but again the purpose is not spelt out clearly) and the idea behind the introduction of the linear eigenvalue problem (3.159) is hazy (that is, there is no mention of the associated linear time-evolution equation and how by the requirement of compatibility condition for the KdV is deduced). Similarly, the discussions on nonlinear Schrödinger (NLS) equation and two-soliton solution of KdV (Sec. 3.11.2) are rather incomplete. There are many latest books available on these aspects, including those by Indian authors, and they could have been referred here.

Hydrodynamic waves (that is, waves in fluids, both liquids and gases) are investigated in chapter 4. The chapter mostly concentrates on waves in incompressible fluids, including small-amplitude waves, linear capillary and gravity waves, and surface waves. The notion of shallow water waves (that is, the depth of the water layer being smaller than the wavelength) is analysed in some length, including nonlinear effects. Some examples in geophysical fluids (like Poincaré, Kelvin and inertial waves), and Rayleigh, Lamb and Rossby waves in hydrodynamics are also discussed. This chapter also includes useful