OVERVIEW OF CNS NEUROPHARMACEUTICALS

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1 INTRODUCTION

The advances in the molecular neurosciences during "the decade of the brain" in conjunction with new genomic and proteomic sciences have radically changed the paradigm of central nervous system (CNS) drug design and development. The classical, chemistry-based small-molecule drug discovery has been broadened by the twenty-first century biology-driven paradigm of large-molecule neuropharmaceuticals: peptides, recombinant proteins, monoclonal antibodies, antisense oligonucleotides, and gene therapy [1].

An interdisciplinary approach focusing on the chemistry–biology interface would facilitate a more rapid and efficient discovery process of novel lead compounds for CNS diseases. Moreover, combinatorial chemistry and high-throughput screening techniques, combined with structure-based or ligand-based de novo design algorithms, have resulted in libraries containing hundreds of thousands of drug candidates with diverse chemical bases and have consequently enormously increased the possibility of finding new lead structures. Synthetic chemistry platforms paralleled by high-throughput screening (HTS) serve as decision aids in planning neuropharmaceutical development projects. A computational prediction strategy that classifies the compounds by their high-affinity to the target and adequate biopharmaceutical properties must be incorporated early in the discovery process because it would enable rapid selection of promising new chemical entities and also would save both costs and time. [2, 3].

Despite the progress in the field of neuroproteomics and rational drug design strategies, there is still a high failure rate of the candidates in later stages of projects (over 98% of novel compounds do not cross the blood–brain barrier) and consequently an unsatisfied demand for novel neurotherapeutic and neurodiagnostic medicines. Therefore, CNS drug discovery and CNS drug targeting must be merged early in the CNS drug development process in order to obtain neuropharmaceuticals active in the brain following systemic administration [1, 4].

2 NEUROPROTECTION AND CNS DISORDERS

The enormous social and economic impact of CNS disorders is highlighted by the incidence of 80 million cases in the United States and the annual cost exceeding $90 billion per year [1]. For example, the financial cost to society of Alzheimer's disease (AD) is estimated at $20–$40 billion per year in the United States [5].

Amyotrophic lateral sclerosis (Lou Gehrig's disease, ALS) is a prototypic age-related neurodegenerative disease, characterized by the progressive and specific loss of motor neurons in the brain and spinal cord, which begins in midadult life (the average age at onset is 55 years), life expectancy after the clinical onset varying between 3 and 5 years [5, 7, 8]. Two clinically indistinguishable forms of ALS have been identified: the sporadic form accounting for 90% of cases and the

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