Drug Designing: Open Access
ISSN: 2169-0138

Haque et al., Drug Des 2013, 2:2
DOI: 10.4172/2169-0138.1000e120

Editorial Open Access

Global Current Trends in Drug Designing for Management of Type-2 Diabetes and Neurodegenerative Disorders

Haque A, Alam Q, Alam MZ and Kamal MA*

Fundamental and Applied Biology Group, King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia

Abstract

Neurodegenerative diseases (NDs) and Type 2 diabetes (T2D) are progressive disorder often advances with age. T2D is characterized by hyperglycaemia, insulin resistance or relative lack of insulin uptake whereas NDs are characterized by the decline in cognitive function, diffuse deposition of amyloid plaques and neurofibrillary tangles in AD and degeneration of dopaminergic neurons in substantia nigra, leading to a reduction of striatal dopamine (DA) levels in PD. Since conventional drugs fail to surpass the natural CNS protective barriers, therefore, in order to overcome these hurdles, targeted drug delivery is of foremost significance for the treatment of AD and PD. New generation of drugs has discovered through innovative nanotechnology approaches such as polymeric nanoparticles are promising candidates in the investigation of AD because nanoparticles are capable of opening the tight junctions, crossing the BBB. Thus, there is a need to adopt current trend and newer strategies such as nanotechnological, computational and gene therapy approaches for drug design and delivery.

Keywords: Alzheimer disease; Type-2 diabetes; Insulin; Amyloid; Nanotechnology; Nanodiagnostics; Nanomedicine; Neurodegenerative disorders; Drug design

List of Abbreviations: AD: Alzheimer Disease; PD: Parkinson's Disease; T2D: Type-2 Diabetes; CNS: Central Nervous System; BBB: Blood Brain Barrier; NDs: Neurodegenerative Diseases; APP: Amyloid Precursor Protein

Introduction

Type 2 diabetes (T2D) and neurodegenerative diseases (NDs) are commonly associated with growing age. They have drawn significant attention due to their rise at an alarming rate [1]. The increasing occurrence of both these diseases has lead to a great socioeconomic burden as well as major public health concerns worldwide [2]. NDs include a range of disorders, which involves dysfunction of the central nervous system (CNS), due to degeneration of neurons and associated pathological processes. These diseases include Lewy body dementia, vascular dementia, Huntington's disease, Parkinson's (PD), and Alzheimer's diseases (AD) [3]. Interestingly, in spite of different pathophysiology of these neurodegenerative diseases, there are some common similarities between these neurodegenerative disorders namely atypical protein assemblies as well as induced cell death [4]. Hence, most of the neurodegenerative disorders are characterized by the inappropriate aggregation of amyloidic proteins, such as Aβ peptides derived from Amyloid precursor protein (APP) and paired helical filament (PHF) aggregates of microtubule-associated protein (MAP), tau, which are known respectively as senile plaques and neurofibrillary tangles in the context of AD [5]. Other pathological examples of abnormal protein aggregates include PHF tau in tauopathies and frontotemporal dementias, huntingtin proteins in HD, α-synuclein in PD, and filamentous prion proteins in Creutzfeldt–Jakob disease (CJD) [6]. T2D is characterized by hyperglycaemia, insulin resistance or relative lack of insulin insulin is secreted by β-cells but in T2D it fails to stimulate glucose uptake by the cells and hence it is called insulin independent diabetes [7].

AD is a major health concern worldwide affecting nearly every society. The disease is an irreversible, progressive and age-related neurodegenerative disorder. It is characterized by declined cognitive function, diffuse deposition of amyloid plaques and neurofibrillary tangles. Various multi-disciplinary studies (epidemiologic and clinical) were carried out in an effort to identifying the etiology, pathogenesis and risk factors linked with AD. These studies revealed strong evidence that AD is related with T2D and that both these diseases share the same patho-physiology hypothesizing that AD might be type-3 diabetes [8]. Emerging evidences disclosed many similarities between both the diseases, such as protein conformational disorders, insulin resistance, inflammation and endoplasmic reticulum stress, en-route initiation and/or stage aggravation [9]. So far, evidence suggests that patients with hyperinsulinemia, insulin resistance and T2D are at an increased risk of memory impairment and getting AD supporting the hypothesis that T2D is linked with an increased risk of AD and thus controlling diabetes could have a positive impact in the prevention of the AD disease [10]. At present, several drugs are used for the treatment of both these diseases but none of them offers complete remission of the disease except, symptomatic relief [11]. Moreover, these drugs lack efficacy due to their various limitations, such as conventional drug delivery systems beyond the blood brain barrier (BBB), lack of target specificity and diminished potency. In this perspective, the emerging field of nanotechnology has offered new techniques and tools to overcome these challenges [12]. Similarly, Parkinson's disease (PD) is also a chronic progressive neurodegenerative disorder and it is the second most common neurodegenerative disorder after AD. Patients exhibit a range of clinical symptoms, with the most common affecting; motor function includes resting tremor, rigidity, akinesia, bradykinesia and postural instability and non-motor symptoms like

***Corresponding author:** Kamal MA, Fundamental and Applied Biology Group, King Fahd Medical Research Center, King Abdulaziz University, P.O. Box 80216, Jeddah 21589, Saudi Arabia, E-mail: meu.fabg@hotmail.com

Received September 04, 2013; **Accepted** September 05, 2013; **Published** September 10, 2013

Citation: Haque A, Alam Q, Alam MZ, Kamal MA (2013) Global Current Trends in Drug Designing for Management of Type-2 Diabetes and Neurodegenerative Disorders. Drug Des 2: e120. doi:10.4172/2169-0138.1000e120

dementia, depression, visual hallucination and autonomic dysfunction [13]. The main neurochemical abnormality in PD is degeneration of dopaminergic neurons in substantia nigra, leading to a reduction of striatal dopamine (DA) levels .The clinical decline parallels that of the progressive degeneration of the remaining dopaminergic neurons [14]. Currently, use of Levodopa (L-dopa) as dopamine-replacement therapy is the chief treatment of motor symptoms in PD [15-18]. However, this drug is suffered with a major limitation by developing dyskinesias if the L-dopa treatment is prolonged [19]. The pathophysiological mechanisms of L-dopa-induced dyskinesia are poorly understood, though non-physiological release of synaptic dopamine is likely to play a major role in its development [20]. Recently, it has been suggested, based on studies in rodents, that L-dopa induced dyskinesia may be associated with a disrupted BBB and that this may in turn contribute to its pathophysiology, by further exacerbating dyskinesia [21].

Regardless of all above facts, scientists throughout the world have been continuously trying to discover novel drugs that can be used for the prevention and treatment of such debilitating diseases [22]. In this endeavor, approximately, 554 drug candidates, including 504 small molecules, 40 recombinant proteins and 10 monoclonal antibodies, were approved in USA between 1980 to 2001 [23]. Although, there is a steady increase in the development of drugs in the last century, as evident from our current data, approximately 1,200 new therapeutic agents have been approved since 1950 by Food and Drug Administration (FDA) [24]. In spite of the constant increase in the total money spent on pharmaceutical research and development (R&D) over the past decade, the number of new drug approvals has declined in recent years. Such a drastic decrease in the generation of new drugs has led researchers to adopt new trends in innovative drug discovery and design. Innovative drug discovery is not only based on technical component, but also rely on new ideas or strategies. The advent of modern molecular techniques and tools along with new technologies has had a strong impact on drug development and research over the couple of decades [24]. Moreover, in the beginning of 21st century, there has been further increase in the development of biochemical techniques and cutting-edge technologies that has made available of new approaches in drug design and invention. The utilization of biochemical assays [25], employment of biomarkers [26], exploitation of mathematical models [27], microarray gene-expression technologies [28], operation of molecular imaging, pharmaceutical crystal engineering [29], application of high speed synthesis technologies [30], computational drug design including computational methodologies firmly rooted in statistical thermodynamics [31], as well as the adoption of genotoxicity testing [32] have greatly facilitated the selection and optimization of lead compounds.

Current Trends in drug designing

Evidences accumulated so far has support the hypothesis that T2D is associated with an increased risk of AD [33] and that controlling diabetes could have a major impact in the prevention of the AD. The management of AD patients is heavily dependent on the currently available treatments, which usually offers only symptomatic benefit. In such a situation, there is a need to evolve a better strategy that can lead to disease modifying therapeutics [34]. In this perspective, robust diagnosis tools are prerequisite for an early stage detection of AD. Further, it is crucial in clinical trial setting to evaluate drug efficacy and for implementing finest patient management strategies. Currently, there are five FDA-approved Alzheimer's drugs that can provide symptomatic relief among 50% of the patients by temporarily helping in memory retention and enhancing thinking ability [35]. Thus, it seems that the treatment strategies for AD are limited and can only provide temporally relief from these drugs that modulate neurotransmitter disturbances. Of the five drugs approved to treat symptoms of AD, two are derived from plant alkaloids: galantamine, originally from *Galanthus woronowii,* and rivastigmine, which is based on the chemical structure of physostigmine from *Physostigma venenosum* [36]. These drugs inhibit acetylcholinesterase to improve cholinergic neuronal dysfunction and the associated cognitive symptoms that occur in AD, the most common form of dementia. Many other alkaloids and their derivatives have been investigated for their ability to modulate cholinergic functions in AD and other dementias [36,37]. But these medications do not treat the underlying causes of Alzheimer's. In contrast, many of the new drugs in development aim to modify the disease process itself, by impacting one or more of the many wide-ranging brain changes that Alzheimer's causes [38]. These changes offer potential "targets" for new drugs to stop or slow the progress of the disease. Many researchers believe successful treatment will eventually involve a "cocktail" of medications aimed at several targets, similar to current state-of-the-art treatments for many cancers and AIDS [39]. For the management of PD, several alkaloids have been explored as potential treatment for the motor symptoms that occur in the disease, via modulation of dopaminergic neurotransmission [37]. Lead compounds for drug discovery include ergot alkaloids from Claviceps purpurea, which provided templates for the development of synthetic drugs such as bromocriptine, used to alleviate PD symptoms [37]. Numerous other alkaloids and their derivatives have been investigated for their ability to alleviate symptoms in neurodegenerative diseases, with some emerging as disease-modifying agents. Nicotine and caffeine, which are alkaloids, have been suggested to provide protective effects against the development of some neurodegenerative diseases and are discussed from an epidemiological perspective, with consideration of their mechanistic effects [38]. Currently, there are several drugs used in the treatment of diseases with their certain limitations such as drug delivery, efficacy, cytotoxicity and most importantly drug resistance. Further, a combinatorial drug approaches have been tried since last few decades in order to improved the treatment, but the outcome is discouraging because of the major side effects and diminished potency in patients where the drug develops resistance [39]. Therefore, there is a need to bring out unique and safer approach in 21st century for the effective treatment strategies.

New trends in drug designing

Although over the last two decades, much attention has been paid on identifying active ingredients from natural products or traditional remedies, or by chemical synthesis in order to discover unique and safer drugs. However, it seems that the trend has been shifted towards new approaches for modern drug design and discovery (Figure 1).

Nanomedicine: Nanotechnology is an emerging multidisciplinary field that is revolutionizing medicinal research. It has an immense potential in radically advancing the treatment and prevention of several diseases [40]. Notably, there have been already significant advancements in the application of various nanotechnology-based approaches towards the diagnostics and therapeutics of cancer [40]. Similarly, nanotechnology offers immense potential in terms of drug delivery and efficacy for the treatment of neurodegenerative diseases. It is very clear that targeted delivery of drugs to neurodegenerative disease is of foremost significance for treating AD and PD [41]. One of the major problems in treating such neurodegenerative disorders is their inability to surpass the natural CNS protective barriers, mainly the BBB [42]. To overcome the impositions of the BBB, new generation

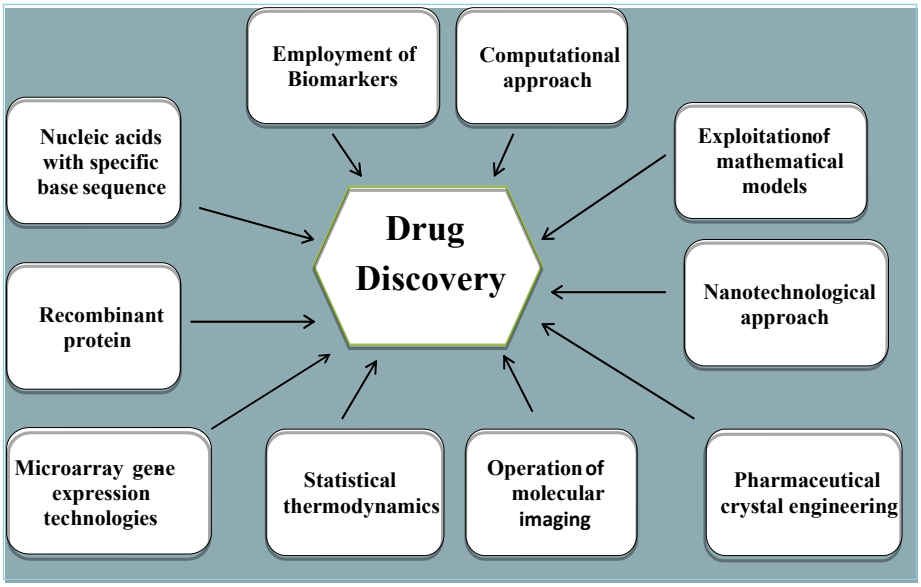

Figure 1: Schematic diagram showing some of the modern tools and techniques used in drug designing and discovery.

of drugs discovered through innovative nanotechnology approaches such as polymeric biocompatible drug carriers have been applied to the central nervous system for many applications [42]. Polymeric nanoparticles are promising candidates in the investigation of AD because nanoparticles are capable of opening tight junctions, crossing the BBB, high drug loading capacities, targeting towards the abberant proteins of AD [43]. In order to strengthen the pharmacological activity of antiparkinsonian drugs, enhancing their penetration of the BBB, different approaches are possible. Among these, the prodrug approach appeared to be the most promising, and many prodrugs have been prepared in an effort to optimize physicochemical characteristics [44]. In addition, novel therapeutic strategies based on formulations linking dopaminergic drugs with neuroprotective agents, increases LD striatal levels. These strategies offer sustained release of the drug without any fluctuation of brain concentration, presenting promising avenues for development of other effective new treatments for PD [44].

Bioinformatics or computational approach in drug designing

The completion of Human genome project has revolutionized the biomedical research and has had great impact on the basic biological research especially, in the area of genomics and proteomics that led to discovery of new drugs [45]. For such innovative drug discovery and design, a lot of genomics and proteomics experimental data are compared with established genomics and proteomics databases, with the help of computer software enabling quick and accurate searches within these databases. In order to pursue an innovative approach for supporting the design of clinical trials, a bioinformatics approach offers immense scope in drug discovery. It is possible to simulate various aspects of the drug discovery and design through *in silico* analysis rather than undertake experiments or trials in the laboratory [46]. Such a computational approach may lead to reasonable savings both in time and in cost. ND. Indeed it is a computational neuropharmacology, which could address the possible problem of add-on neuroleptics (antipsychotic drugs) and antidepressant treatment for behavioral problems in the relevant patient populations [47]. As for example, G protein-coupled receptors, which are the target of psychoactive drugs, such as the neuroleptic Haldol--are known to interfere with intracellular pathways typically associated with disease-modifying approaches, and vice-versa. Computational neuropharmacology allows a quantitative estimation of the effect of additional medication on disease-modifying therapeutic approaches and, as such, can be helpful in optimizing clinical trial design.

Conclusion

Currently many drugs are available to treat the neurodegenerative disorder especially, AD and PD with different targets and mechanisms of action. However, none of these drugs has proven to be significant in terms of efficacy owing to their various limitations. The current medication for AD such as the anticholinesterase inhibitors and the latest NMDA receptor inhibitor, Namenda offer moderate symptomatic relief at various stages of the disease, but do not hold progression of this neurodegenerative disorder. Similarly, the most common drugs used to treat PD are Sinemet and (Levodopa/Carbidopa). Levodopa is the most commonly prescribed and effective drug for controlling the symptoms of PD, particularly bradykinesia and rigidity. Levodopa is transported to the nerve cells in the brain that later on converted into dopamine to be used as a neurotransmitter. On the other hand, Sinemet is the most effective medication and has the least short-term side effects; it is associated with high risks of long-term side effects, such as involuntary movements (dyskinesia). When used on a long-term basis, levodopa may also cause restlessness, confusion, or abnormal movements. Therefore, considering multifactorial nature of the disease, a number of factors have to be taken care of while tackling such disease. Thus, there is a need to adopt new strategies such as nanotechnological and gene therapy approaches for targeted drug delivery as well as pharmacological compounds with many properties that could be able to exert their effect heterogeneously on multiple factors implicated with AD and PD. In this endeavor, the growing importance of nanotechnology has become potential choice, due to its substantial popularity in the field of nanomedicine. There are a number of biocompatible nanoparticles reported to be effective to overcome these limitations and could serve as an effective drug delivery system with slight optimization of

physical, chemical and biological properties. These newer generations of drug delivery systems have major advantages over conventional drug delivery systems. In short, nanoparticles offer a great potential in drug delivery across BBB due to their small sizes and ease of surface modifications.

Acknowledgement

Authors are grateful to Mr. Mohammad S. Gazdar, Librarian, and KFMRC for providing assistance in retrieving research articles from journals available in the library and as well from different web resources.

References

1. Flier JS (2004) Obesity wars: molecular progress confronts an expanding epidemic. Cell 116: 337-350.
2. Maher PA, Schubert DR (2009) Metabolic links between diabetes and Alzheimer's disease. Expert Rev Neurother 9: 617-630.
3. Rubinsztein DC (2006) The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 443: 780-786.
4. Ferrari CKB (2000) Free radicals, lipid peroxidation and antioxidants in apoptosis: implications in cancer, cardiovascular and neurological diseases. Biologia 55: 581-590.
5. Cole GM, Frautschy SA (2007) The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease. Exp Gerontol 42:10-21.
6. Venda LL, Cragg SJ, Buchman VL, Wade-Martins R (2010) α-Synuclein and dopamine at the crossroads of Parkinson's disease. Trends Neurosci 33: 559-568.
7. Bronstein J, Lawrence RD (1951) Two types of diabetes mellitus, with and without available plasma insulin. Br Med J 1: 732-734.
8. de la Monte SM, Wands JR (2008) Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol 2: 1101-1113.
9. Priyadarshini M, Kamal MA, Greig NH, Realef M, Abuzenadah AM, et al. (2012) Alzheimer's disease and type 2 diabetes: exploring the association to obesity and tyrosine hydroxylase. CNS Neurol Disord Drug Targets 11: 482-489.
10. Jiang Q, Heneka M, Landreth GE (2008) The role of peroxisome proliferator-activated receptor-gamma (PPARgamma) in Alzheimer's disease: therapeutic implications. CNS Drugs 22: 1-14.
11. Silva GA (2006) Neuroscience nanotechnology: progress, opportunities and challenges. Nat Rev Neurosci 7: 65-74.
12. Tabrez S, Jabir NR, Shakil S, Greig NH, Alam Q, et al. (2012) A synopsis on the role of tyrosine hydroxylase in Parkinson's disease. CNS Neurol Disord Drug Targets 11: 395-409.
13. Khan W, Priyadarshini M, Zakai HA, Kamal MA, Alam Q (2012) A brief overview of tyrosine hydroxylase and α-synuclein in the Parkinsonian brain. CNS Neurol Disord Drug Targets 11: 456-462.
14. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, et al. (2004) Levodopa and the progression of Parkinson's disease. N Engl J Med 351: 2498-2508.
15. Feve AP, Bathien N, Rondot P (1992) Chronic administration of L-dopa affects the movement-related cortical potentials of patients with Parkinson's disease. Clin Neuropharmacol 15: 100-108.
16. Feve AP, Bathien N, Rondot P (1991) Changes in movement-related cortical potentials in Parkinson's patients before and after treatment with levodopa. Neurophysiol Clin 21:105-119.
17. Fahn S (1999) Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs Later L-DOPA. Arch Neurol 56: 529-535.
18. Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci 991: 1-14.
19. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Macias R, Alvarez L, et al. (2000) Pathophysiologic basis of surgery for Parkinson's disease. Neurology 55: S7-12.
20. Ballabh P, Braun A, Nedergaard M (2004) The blood-brain barrier: an overview: structure, regulation, and clinical implications. Neurobiol Dis 16: 1-13.
21. Rishton GM (2008) Natural products as a robust source of new drugs and drug leads: past successes and present day issues. Am J Cardiol 101: 43D-49D.
22. Reichert JM (2003) Trends in development and approval times for new therapeutics in the United States. Nat Rev Drug Discov 2: 695-702.
23. Munos B (2009) Lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov 8: 959-968.
24. Rishton GM (2005) Failure and success in modern drug discovery: guiding principles in the establishment of high probability of success drug discovery organizations. Med Chem 1: 519-527.
25. Kuhlmann J (2007) The applications of biomarkers in early clinical drug development to improve decision-making processes. Ernst Schering Res Found Workshop 29-45.
26. Westerhoff HV, Mosekilde E, Noe CR, Clemensen AM (2008) Integrating systems approaches into pharmaceutical sciences. Eur J Pharm Sci 35: 1-4.
27. Rescigno A (2010) The two faces of pharmacokinetics. J Pharm Pharm Sci 13: 38-42.
28. Peterson ML, Hickey MB, Zaworotko MJ, Almarsson O (2006) Expanding the scope of crystal form evaluation in pharmaceutical science. J Pharm Pharm Sci 9: 317-326.
29. Niu G, Chen X (2008) Has molecular and cellular imaging enhanced drug discovery and drug development? Drugs R D 9: 351-368.
30. Michel J, Essex JW (2010) Prediction of protein-ligand binding affinity by free energy simulations: assumptions, pitfalls and expectations. J Comput Aided Mol Des 24: 639-658.
31. Custer LL, Sweder KS (2008) The role of genetic toxicology in drug discovery and optimization. Curr Drug Metab 9: 978-985.
32. Grand JH, Caspar S, Macdonald SW (2011) Clinical features and multidisciplinary approaches to dementia care. J Multidiscip Healthc 4: 125-147.
33. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, et al. (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56: 303-308.
34. http://www.afro.who.int/mentalhealth/related_disease/alyheimer_disease.html
35. Howes MJ, Perry E (2011) The role of phytochemicals in the treatment and prevention of dementia. Drugs Aging 28: 439-468.
36. Kalinderi K, Fidani L, Katsarou Z, Bostantjopoulou S (2011) Pharmacological treatment and the prospect of pharmacogenetics in Parkinson's disease. Int J Clin Pract 65: 1289-1294.
37. Melanie-Jayne RH (2013) Alkaloids and Drug Discovery for Neurodegenerative Diseases. Natural Products: 1331-1365.
38. Robak T (2008) Treatment of chronic lymphoid leukemias with monoclonal antibodies: current place and perspectives. Drug Dev Res 69: 373-387.
39. Jabir NR, Tabrez S, Ashraf GM, Shakil S, Damanhouri GA, et al. (2012) Nanotechnology-based approaches in anticancer research. Int J Nanomedicine 7: 4391-4408.
40. Kamal MA, Greig NH, Alhomida AS, Al-Jafari AA (2000) Kinetics of human acetylcholinesterase inhibition by the novel experimental Alzheimer therapeutic agent, tolserine. Biochem Pharmacol 60: 561-570.
41. Sahni JK, Doggui S, Ali J, Baboota S, Dao L, et al. (2011) Neurotherapeutic applications of nanoparticles in Alzheimer's disease. J Control Release 152: 208-231.
42. Kamal MA, Qu X, Yu QS, Tweedie D, Holloway HW, et al. (2008) Tetrahydrofurobenzofuran cymserine, a potent butyrylcholinesterase inhibitor and experimental Alzheimer drug candidate, enzyme kinetic analysis. J Neural Transm 115: 889-898.
43. Kamal MA, Klein P, Luo W, Li Y, Holloway HW, et al. (2008) Kinetics of human serum butyrylcholinesterase inhibition by a novel experimental Alzheimer therapeutic, dihydrobenzodioxepine cymserine. Neurochem Res 33: 745-753.

44. Bentley DR. The Human Genome Project--an overview. Med Res Rev. 2000; 20: 189-196.

45. Clark M, Meshkat S, Talbot G, Konteatis Z, Ludington J, et al. (2009) Developing technologies in biodefense research: computational drug design. Drug Dev Res 70: 279-287.

46. Geerts H, Trojanowski JQ, Lee VM (2005) Drug discovery in neurodegenerative diseases. Sci Aging Knowledge Environ 2005: pe4.

47. Heilker R, Wolff M, Tautermann CS, Bieler M (2009) G-protein-coupled receptor-focused drug discovery using a target class platform approach. Drug Discov Today 14: 231-240.