Design And Development Of Experimental Therapeutics

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Title of project or programme

Design And Development Of Experimental Therapeutics

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NIH (NIA)

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Intramural... Clinical Trials and Supportive Activities... Dementia... Injury (total) Accidents/Adverse Effects... Injury - Trauma - (Head and Spine)... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

1. Alzheimers Disease: Three series of agents are being developed to treat AD. Selective

inhibitors of amyloid-beta peptide (abeta) production and inhibitors of the enzymes acetylcholinesterase (AChE) and butrylcholinesterase (BChE) 1.1. Molecular events associated with AD: A reduction in levels of the potentially toxic amyloid-beta peptide (Abeta) has emerged as an important therapeutic goal in AD. Targets to achieve this goal are factors that affect the expression and processing of the Abeta precursor protein (APP). Our studies have generated compounds to lower APP and Abeta levels in neuronal cultures and the brain of animal models without toxicity. This activity is independent of cholinergic action, but is post-transcriptional: lowering APP protein levels without affecting mRNA levels via translational regulation. This is mediated, in part, via the 5-untranslated region (UTR) of APP mRNA. Current studies are characterizing mechanisms involved and focusing on these in the design and synthesis of agents that lower APP levels as a way of lower Abeta peptide (collaborators: Drs. Lahiri, Sambamurti, Rogers). The compound, Posiphen, has advanced to clinical trials and backup compounds are being assessed to define molecular mechanisms underpinning activity. Posiphen was well tolerated in phase 1 clinical trials, demonstrating target engagement and effectively lowering APP, Abeta, tau and other key AD CSF markers (collaborator: Dr. Maccecchini). Recent parallel studies (collaborator: Drs. Rogers, Lahiri, Sambamurti, Maccecchini) indicate that Posiphen has a broader action that impacts a number of misfolded proteins, including alpha-synuclein. Hence Posiphen and metabolites are being assessed in cellular and animal models of Parkinson's disease (PD) as well as other neurological disorders. 1.2. Cholinesterase inhibitors: Compounds were developed to optimally augment the cholinergic system in the elderly and raise levels of the neurotransmitter, acetylcholine (ACh). Extensive studies involving chemistry, X-ray crystallography, biochemistry and pharmacology resulted in the design and synthesis of novel compounds to differentially inhibit either AChE or BChE in the brain or periphery for an optimal duration for the potential treatment of a variety of disorders (AD, myasthenia gravis, and as chemical warfare prophylactics (collaborators: Drs. Becker, Marini, Lahiri, Kamal, Reale, Sambamurti, Descamp). Also, specific and highly selective BChE inhibitors have been developed to define this enzyme's role in brain during health, aging and disease. 1.2A. AChE: Long-acting, centrally active, selective inhibitors of AChE have been developed to define its role in health and disease and move compounds into clinical studies. Extensive chemistry on the template of eserine has been undertaken. Novel phenylcarbamates were developed that are highly selective for AChE vs. BChE, have favorable toxicologic profiles, robustly enhance cognition in animal models and are neurotrophic/protective. In collaborative studies phenserine was translated into clinical trials in AD (collaborators: Drs. Becker, Nordberg, Friedhoff, Winblad, Sambamurti, Lahiri, Bruinsma). Generation of a slow-release formulation has been undertaken – for future human studies (Collaborators, Drs. Becker, Chigurupati, Flanagan). Recent studies additional have demonstrated that key agents are effective in protecting against soman-induced neurotoxicity/death, and new analogues have been synthesized and are under evaluation. 1.1B. BChE: In healthy brain, 80% of cholinesterase activity is in the form of AChE and 20% is BChE. AChE activity is concentrated chiefly in neurons, and BChE primarily with glial cells. Kinetic evidence indicates a role for BChE, in hydrolysing excess ACh. In advanced AD, AChE activity declines to 15% of normal levels in affected brain regions, whereas BChE activity rises 2-fold. The normal BChE/AChE ratio becomes mismatched in AD causing excess metabolism of already depleted ACh. The first reversible, centrally-active BChE inhibitors have been synthesized and appear favorable in AD preclinical models. Bisnorcymserine has been advanced through required preclinical studies and into clinical phase 1 studies where its safety, pharmacokinetics and -dynamics are being assessed (collaborators: Drs. Kapogiannis, Maccecchini, Lahiri, Kamal) 1.3. Utilizing the

compounds generated above, the relationship between the cholinergic system and inflammation is being characterized in health and disease (collaborators: Drs. Reale, Kamal). Our recent studies suggest that the cholinergic anti-inflammatory pathway is compromised in AD, but can potentially be effectively “”reset”” by select cholinergic compounds. 2. Stroke, PD, brain trauma: Drugs currently used provide temporary relief of symptoms, but do not prevent the occurrence of cell death. Our target for drug design is the transcription factor, p53 and its down-stream effectors. p53 up-regulation is a common feature of many neurodegenerative disorders and a gate keeper to the biochemical cascade that leads to apoptosis. We have developed novel tetrahydrobenzothiazole/oxazole analogs that inhibit p53 activity. Agents are in current assessment for neuroprotective/regenerative actions in cellular and animal models (collaborators: Drs. Pick, Hoffer, Wang, Luo) to select ones of potential as clinical candidates and agents to characterize disease. Agents have demonstrated potent activity in models of stroke, AD, PD, and are in assessment in other disorders – including traumatic brain injury (TBI) – to define their optimal use. 3. Clinical translation and assessment of experimental drugs in neuropsychiatric conditions: Despite promising advances in understanding possible mechanisms of disease in recent years, clinical investigators still struggle with methods and practices too open to effects from measurement errors, biases, carelessness at research sites distant from the sponsor, and with commercial pressures to as quickly as possible enter human trials – a priority that is acknowledged to allow frequently insufficient preclinical investigations and suspected as one cause for failures in human clinical trials. Hence, drug discovery/development is acknowledged as at great risks of failing due to lack of efficacy or compromises to safety. Less than 11% of all new agents that enter clinical development reach the marketplace. For neurological drugs, attrition is considerably higher still, less than 7%. To understand and optimize clinical development the numerous factors that impair the process and generate type 2 errors are being critically reviewed and assessed (Collaborator: Dr. Becker). Rational approaches to optimize the clinical drug development process of neuropsychiatric drugs are being developed to aid reduce the currently too high attrition rate in neurological drug development, and particularly in AD.

Lay Summary
Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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2016

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