Translating CD33 genetic mechanism into a novel Alzheimers therapeutic

https://neurodegenerationresearch.eu/survey/translating-cd33-genetic-mechanism-into-a-novel-alzheimers-therapeutic/

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Country

USA

Title of project or programme

Translating CD33 genetic mechanism into a novel Alzheimers therapeutic

Source of funding information

NIH (NIA)

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15/04/2014

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3

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)... Biotechnology... Brain Disorders... Dementia... Genetics... Immune System... Leukemia for Childhood Leukemia Subset... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): The overarching theme of this proposal is that polymorphisms identified by recent Alzheimer's disease (AD) genome wide association studies biologically define rate-limiting steps in AD pathways. Hence, elucidating their mechanism of action will identify robust pharmacologic targets. Notably, a SNP with modest molecular actions may reduce AD risk by 10% but a drug that acts strongly at the same target may have a large effect on AD risk. This proposal will elucidate the mechanism of action of rs3865444 (rs444), an AD-associated SNP in CD33, and translate this mechanism into a proof of concept AD treatment. In our highly compelling preliminary results, we associate the AD-protective minor allele of rs444 with (i) a robust increase in the proportion of CD33 lacking exon 2 (D2-CD33) which appears critical to CD33 function. Large pharma have developed humanized monoclonal antibodies against CD33 for acute myeloid leukemia (AML); these antibodies and their derivatives have potential AD relevance as CD33 antagonists. This leads to our global hypothesis: Reduced CD33 function decreases AD risk whether CD33 inhibition is due to genetics or pharmacologic agents. To test our hypothesis, we will (i) Elucidate the mechanism underlying the CD33 AD SNP, (ii) Compare CD33 and D2- CD33 function, especially relative to AD pathogenic mechanisms, and (iii) Translate CD33 genetics into a novel AD therapeutic mimic. Overall, this focused proposal will develop our compelling mechanistic genetic results, elucidate the differences in D2-CD33 and CD33 function, and begin to translate these changes into an AD-preventive agent. In work beyond the scope of this focused proposal, we anticipate that these therapeutic agents will be tested in “”AD”” murine models that are transgenic for human CD33 and, eventually, humans.

Lay Summary

PUBLIC HEALTH RELEVANCE: The significance of this proposal to public health is that we will identify the mechanism whereby a genetic factor modulates the risk of Alzheimer's disease. We will then perform studies to identify agents that target this mechanism as proof-of-concept pre-clinical Alzheimer's disease prevention studies.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

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