From: [redacted] <[redacted]>
To: [redacted] <[redacted]>, [redacted] <[redacted]>
Subject: Fwd: Alzheimer's R&D updates - March 2017
Date: Sat, 08 Apr 2017 13:30:11 +0000

Morning!

please forward below to [redacted] ... tell him Gates has decided to spend some money on alzhhiemers, that is what Jeffrey wanted to talk to him about Thanks, [redacted]
---------- Forwarded message ----------
From: [redacted] <[redacted]>
Date: Sat, Apr 8, 2017 at 9:17 AM
Subject: Fwd: Alzheimer's R&D updates - March 2017

Begin forwarded message:

From: [redacted] <[redacted]>
Date: April 8, 2017 at 3:38:14 AM EDT
To: [redacted] <[redacted]>
Subject: FW: Alzheimer's R&D updates - March 2017

[redacted] –

Here is the most recent update we shared with Bill. I am sure you have seen the Kitamura paper in Science this week re: memory and silent copies in the pre-frontal cortex.

The F1000 link will not work for you since it is an internal password protected place where we store PDF copies. Let me know if you need PDF copies and I can send them along.

LRP1 Mediated Aβ Clearance (in a mouse model)

A study led by researchers at the Mayo Clinic in Jacksonville, FL identified a link between the clearance of Aβ and the protein LRP1, a low-density lipoprotein receptor-related protein. LRP1 levels tend to be lower in the brains of Alzheimer's Disease (AD) patients and it is thought to be involved with insulin signaling, lipid handling, and Aβ metabolism. Liu et al showed that LRP1 functions in the uptake and metabolism of Aβ in astrocytes (a type of glial cell in the brain that helps support and maintain neurons) using both cell and mouse model systems. Deleting LRP1 from astrocytes in an AD mouse model system led to increased levels of both soluble and insoluble forms of Aβ and increased in inflammatory markers in the cortex and hippocampus. While they could not verify direct interaction of Aβ and LRP1 in the cellular internalization and degradation of Aβ, they demonstrated that LRP1 plays a critical role in the process. Future work to verify and expand upon the mechanistic understanding of the effects observed here could result in LRP1 as a potential drug target.

Yes, it is in a mouse model…so may not be 100% predictable or translatable in humans. David Holtzman (St Louis), who you met last year is a co-author on this study.

Liu CC, Hu J, Zhao N, Wang J, Na W, Cirrito JR, Kanekiyo T, Holtzman DM, Bu G. 2017. Astrocytic LRP1 Mediates Brain Aβ Clearance and Impacts Amyloid Deposition. J Neurosci; pii: 3442-16.

F1000 Link

Novel Chimeric Model System Utilizing Transplanted Human Neurons

A group successfully transplanted human stem cell-derived neurons into the brain of an Alzheimer's mouse model. The transplantation of neural precursors in rodent brains has previously been characterized to result in mature, connected, and active neurons. This approach enabled the creation of a chimeric disease model capable of exhibiting human-specific neuronal pathologies. One key pathological hallmark of AD that has not been recapitulated in Alzheimer's animal models is the significant loss of neurons. Using this chimeric model system, the group found that matured human neurons were much more fragile than matured mouse neurons when exposed to A in the Alzheimer's mouse model (compared to matured human or mouse neurons derived from stem cells in non-AD mouse model controls). The transplanted human neurons exhibited dystrophic structures 4 months after transplantation and significant (~50%) losses by the 6 month mark. Tau-related tangle pathologies were not noticeably detectable in the study, the authors noted that more time may be required to observe these types of effects. While only three human neuronal cell lines were investigated and no tau-tangles were evident in this study, this model system has created new ways to look at the effects that different human genetic backgrounds and mutations may have on AD pathologies *in vivo*.

Espuny-Camacho I, Arranz AM, Fiers M, Snellinx A, Ando K, Munck S, Bonnefont J, Lambot L, Corthout N, Omodho L, Vanden Eynden E, Radaelli E, Tesseur I, Wray S, Ebneth A, Hardy J, Leroy K, Brion JP, Vanderhaeghen P, De Strooper B. 2017. Hallmarks of Alzheimer's Disease in Stem-Cell-Derived Human Neurons Transplanted into Mouse Brain. *Neuron*; 93(5):1066-1081.

F1000 Link

Disruption of Fatty Acid Metabolism Occurs in the Brains of Alzheimer's Patients

Omega-3 and omega-6 fatty acids have been implicated in both playing both positive and negative roles in relation to AD. In this study, the authors assessed metabolites in brain tissue (by mass spectrometry) collected from: 14 individuals that had been diagnosed with AD; 14 controls; and 15 "asymptomatic subjects," meaning that they were not diagnosed with AD but their brains exhibited pathological hallmarks of disease. 4,897 metabolites were assessed and levels were compared in three different regions of the brain: 1) an area that does not typically display tau or amyloid-related pathologies (cerebellum); 2) a region that is susceptible to tau pathologies (inferior temporal gyrus); 3) a section that is vulnerable to presentation of amyloid plaques (middle frontal gyrus). The levels of six unsaturated fatty acids emerged as being significantly different in these three areas of the brain: Linoleic, Oleic, Docosahexanoic (DHA), Arachidonic, Linolenic, and Eicosapentaenoic (EPA). While the data were gathered from a small study population, it is notable that the metabolite profiles not only separated: the controls; the "asymptomatic subjects;" and the patients that had been clinically diagnosed with AD, but that the gradations in the metabolite profiles also aligned with the severity of disease. It will be important to verify the results in a larger population, but this group offers compelling evidence from an unbiased metabolome investigation that several unsaturated fatty acids are

related to AD pathogenesis. More work must be done to understand the mechanistic abnormalities associated with the metabolism of these fatty acids.

Snowden SG, Ebshiana AA, Hye A, An Y, Pletnikova O, O'Brien R, Troncoso J, Legido-Quigley C, Thambisetty M. 2017. Association between fatty acid metabolism in the brain and Alzheimer disease neuropathology and cognitive performance: A nontargeted metabolomic study. PLoS Med;14(3):e1002266.

F1000 Link

Development of a Polygenic Hazard Score Based on Genetic and Age-Associated Risk of Alzheimer's

Using genotypic data from >70,000 AD patients and aged controls to develop a polygenic hazard score (PHS) as a measure of genetic and age-associated risk of AD. For the genetic component, the researchers used a survival model framework to account for single nucleotide polymorphisms (SNPs) linked to AD in a PHS for every patient; the status of APOE alleles was also included. They merged this with population-based incidence rates (accounts for age; based on data from the US) to arrive at an estimate of risk of developing AD. When tested on two independent cohorts, the PHS "strongly predicted" age of onset and longitudinal progression. While the authors acknowledge that prospective validation will need to be performed on non-Caucasian, non-US populations, this type of approach could prove to be very useful for screening, stratifying, and enrolling subjects for drug trials.

Desikan RS, Fan CC, Wang Y, Schork AJ, Cabral HJ, Cupples LA, Thompson WK, Besser L, Kukull WA, Holland D, Chen CH, Brewer JB, Karow DS, Kauppi K, Witoelar A, Karch CM, Bonham LW, Yokoyama JS, Rosen HJ, Miller BL, Dillon WP, Wilson DM, Hess CP, Pericak-Vance M, Haines JL, Farrer LA, Mayeux R, Hardy J, Goate AM, Hyman BT, Schellenberg GD, McEvoy LK, Andreassen OA, Dale AM. 2017. Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. PLoS Med;14(3):e1002258.

F1000 Link

Best,

Bose