From: [redacted]>
To: Jeffrey Epstein <jeevacation@gmail.com>, Richard Kahn <[redacted]>
Subject: Funding Proposal-- could we meet?
Date: Thu, 05 Mar 2015 04:32:05 +0000
Attachments: telomere_article.docx

Hi Jeffrey,

Could we meet? I hope you are alright.

Below is the beginning of a funding proposal for the foundation. It suggests 3 groundbreaking research projects in Alzheimer's, Cancer (pathway resistance) and Age regeneration. See below. I've also attached a supporting article I wrote on the aging research. I like the cancer project because it's a much needed field of research and ties into Martin Nowak's work.

I look forward to discussing this with you.
[redacted]

Alzheimer's

Dr. Berislav Zlokovic, MD, PhD
Director, Zilkha Neurogenetic Institute
Professor and Chair,
Department of Physiology & Biophysics
Director, Center for Neurodegeneration & Regeneration
Zilkha Neurogenetic Institute
Keck School of Medicine of USC

1. **Alzheimer's and the blood brain barrier:** Recent research shows a major correlation between Alzheimer's and leaks in the blood brain barrier: Zlokovic's team compared brain scans from 63 people of different ages taken with magnetic resonance imaging, or MRI. The MRI scans tracked an element called gadolinium in healthy people aged 23 to 91 years old. Gadolinium serves as a marker to track where blood flows. Zlokovic's team watched as it passed through the blood-brain barrier. The barrier's leakiness first showed up in the hippocampus. And leaks were more likely to show up in older brains. People 55 to 85 years old with some memory problems had leakier blood-brain barriers than healthy people their age. Zlokovic's team reported its new findings on January 21 in the journal *Neuron*.
2. **Alzheimer's and a genetic excess of Cyclophilin A:** People who carry two copies of the ApoE4 gene have approximately 8 to 10 times the risk of getting Alzheimer's than those who do not have the gene. Scientists from Rochester University and the University of Southern California have shown how ApoE4 can unleash an excess of the protein cyclophilin A into the cardiovascular system, causing inflammation in atherosclerosis and other conditions. Cyclophilin A also accumulates in cells that help maintain the blood-brain barrier, reducing blood to the brain and allowing toxic substances to infiltrate. Cyclophilin A causes a breakdown of cells lining the blood vessels in the brain in the same way as found in cardiovascular disease or abdominal aneurysm. Specifically, the study found that mice carrying the ApoE4 gene had five times as much cyclophilin A in their pericyte cells, cells that maintain the integrity of the blood-brain barrier. The

cyclophilin A caused an increase in the inflammatory molecule NF Kappa B which increased levels of MMP molecules or matrix metalloproteinases that are known to damage blood vessels and reduce blood flow. The mice's blood vessels died, blood did not flow as completely through the brain as it did in other mice, and harmful substances like thrombin, fibrin, and hemosiderin, entered the brain tissue. When the team stopped the excess of cyclophilin A by removing the ApoE4 gene or by using cyclosporine A to inhibit it, the brain damage in the mice was reversed. Blood flow resumed to normal and toxins from blood vessels into the brain was reduced by 80%. In the past, amyloid beta, a protein that accumulates in the brains of Alzheimer patients was seen as the main culprit for damage. However, this recent study shows that there is also a serious vascular origin. "Our study has shown major neuronal injury resulting from vascular defects that are not related to amyloid beta," said Dr. Berislav Zlokovic, an adjunct professor at Rochester and director of the Center for Neurodegeneration and Regeneration and professor. "This damage results from a breakdown of the blood-brain barrier and a reduction in blood flow. Amyloid beta has an important role in Alzheimer's disease," added Zlokovic. "But it's very important to investigate other leads, perhaps where amyloid beta isn't as centrally involved."

Aging Reversal

Dr. Helen Blau—PhD
Professor and Director of the Baxter Laboratory for Stem Cell Biology in the Microbiology and Immunology Department and the Stanford Institute for Stem Cell biology and Regenerative Medicine in the Stanford University School of Medicine.

1. **Dramatic Telomere rejuvenation of human cells and adult stem cells in culture:** Researchers at Stanford's Baxter Laboratory lengthened the DNA telomeres in human cell cultures, using a plasmid mRNA infusion. Cell's lifespan increased more than 10-fold. Population doubling increased more than 10 to the 12(exponent). Critically, the telomeres resumed shortening at normal rates after the end of treatment. The rate of replication remained consistent with younger cells after treatment, and all cells eventually showed the natural markers of mortality reducing the concern of causing cancerous cells. mRNA transfection was done in an immuno-safe, organic way and tackles the very real problem of low cell volume in cell culture tissue regeneration. It critically addresses rejuvenating adult stem cells as well. Overall, the ability to quickly generate a large pool of telomere robust cells, without immortalizing them, is a tremendous step for regenerative medicine, it could have a huge impact on tissue rejuvenation as well drug screening to disease modeling: rejuvenating cell types that mediate certain conditions and diseases for example, such as hematopoietic stem cells or progenitors in cases of immuno senescence or bone marrow failure. Helen Blau, PH.D., who led the research at the Baxter Laboratory stated, “We have found a way to lengthen human telomeres by as much as 1,000 nucleotides, turning back the internal clock in these cells by the equivalent of many years of human life. This [also] greatly increases the number of cells available for studies such as drug testing or disease modeling.”

Cancer

Dr. Roger Lo, MD, PhD—funding from the Melanoma Alliance.

UCLA/ Jonson Comprehensive Cancer Center

1. **Preempting resistance—** cancer cells quickly evolve to become resistant to inhibitor drugs. A research team from UCLA/JCCC, has mapped out how melanoma tumors resist BRAF inhibitors: the cell-signaling pathways BRAF-mutant melanoma cells use to become resistant to inhibitor drugs, and how the limited focus of BRAF inhibitors allows melanoma cells to evolve and develop drug resistance. The study was based on the analysis of 100 biopsies from patients treated with BRAF inhibitors, and it highlights that BRAF inhibitor-resistant tumors use a variety of different signaling routes to learn resistance. "By helping us understand the core resistance pathways and tumor heterogeneity, fitness and mutational patterns that emerge under drug selection." Lo said. "This study lays a foundation for clinical trials to investigate the mechanisms of tumor progression in these melanoma patients." The second study, also led by Lo, found that as soon as melanomas face BRAF inhibitors they are able to quickly turn on drug resistance pathways (a process called early adaptive resistance). Over time, these early adaptive resistance pathways are further fortified, allowing the tumor cells to break free of the BRAF inhibitor and resume growth. Discovering the common denominator or core melanoma escape pathways is an important conceptual advance when fighting BRAF inhibitor resistance. "We now have a landscape view of how melanoma first adapts and then finds ways to overcome what is initially a very effective treatment" said Antoni Ribas, JCCC member and professor of medicine co-investigator in these articles. "We have already incorporated this knowledge to the testing of new combination treatments in patients to get us back ahead of melanoma and not allow it to escape."

2. This work represents an international collaboration led by Dr. Lo, which includes scientists from Vanderbilt University in Nashville, Tennessee, the Melanoma Institute of Australia in Sydney, Australia, and the Ludwig Institute for Cancer Research in Brussels, Belgium. These studies highlight the work of UCLA's translational physician-scientists who are taking laboratory discoveries to cancer patients as quickly as possible.

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