
From: jeffrey E. <jeevacation@gmail.com>
Sent: Tuesday, August 29, 2017 9:58 AM
To: [REDACTED]
Subject: Re: Alzheimer's

well done

On Tue, Aug 29, 2017 at 1:28 AM, [REDACTED] <[REDACTED]> <mailto:[REDACTED]> > wrote:

FYI

----- Forwarded message -----

From: [REDACTED] <[REDACTED]> Bill and Larry - hi. =nd just to you both - I will send to the others and copy Larry later
tonig=t. <mailto:[REDACTED]>

Given my experience building and manag=ng learning initiatives and my understanding of this landscape, I've
t=ied to think about your competitive/comparative advantage while giving you=a little more time to learn in the
background.

At the end of this learning y=u could exit the space easily, go deeper or even change strategies based o= what
you learn. In 2-3 years a few things will unfold - and I would just =aution you to tread lightly because all sorts of new
data is emerging - no= only about mechanisms of disease but about whether AD is a distinct patho=ogic entity. Lord
knows = I just don't want you to get caught into a=polio type vortex until you are ready.

McKinsey has been hired to help build y=ur strategy and I will pass all of this along to the McKinsey team, Bose
a=d Jonah under separate cover. I will also continue to support them, make i=trroductions and join their sessions - next
one September 8. In my honest o=inion, McKinsey maybe not the right partner but we will all rally behind t=em.

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See you both soon... [REDACTED]

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Aspiration

1. Segment the landscape until we have a natural advantage
2. Opportunity: small enough to win, large enough to matter
3. Measurable points on the board

Situation

- Alzheimer's is not a typical disease with a single causal factor / etiology
- Polarized scientific community
- No shortage of R&D resources
- Requires longitudinal investments in health and hard to quantitatively track pathology
- What needs fixing

o A0 Institutions – processes, policies

o A0 Tools & technologies – validation, standardization

o C2 Science – exploration, cross-sector ideas

Informed Entry into Alzheimer's Landscape

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\$100 million, 3 year learning initiative managed quietly from bgc3 that will explore:

1. Performance of existing institutions vs. need for creation of new (or hybridized) ones
2. Opportunity for cost savings and market building
3. Barriers to clinical trial participation
4. Processes for data sharing and standardization
5. Novel mechanistic approaches

Specific Targets for Exploration

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Target 1: Underwrite risk for private sector; keep data in the public domain

\$20 million

AMC-AD, National Institutes on Aging (NIA)

Matchin= grant (1:2 for government, 1:1 for private sector)

Propose= Outcomes

In 3 years, study and trial data for 2016++ pipeline fully public and curated by NIA

Stronger NIA

Open trial data

- 10 new candidate drugs put into later stage discovery process

Cost

Recipient

Form

Possible Partner: IMI

Propose= Outcomes

In 3 years, 5 validate biomarkers

Standardized validation processes

Open and shared trial and registry data

- Aligned US/Europe regulatory and study processes

What we learn

Coherence of standards

Appetite for shared data

- Ability of new institution to attract additional resources

Target 3: Build microbiomic fundamentals

\$20 million across 3 recipients

Recap

1. \$5m to NIA/NIH to RFP pre-inflammatory and inflammatory markers (\$5m)
 2. \$5m to ICDDR,B to classify non-pathogenic colonists and create a digital library
 3. \$10m TBC via BMGF to redraw bacterial taxonomy based on genetic criteria to supplement traditional identification and classification
- Grants

Proposed Outcomes

· Identify non-pathogenic colonist strains for use in health and also food and supplement industry

· World Gut library

· Update bacterial classification systems to include genomics

What we learn

· Build a deeper understanding of the microbiome with applications across health, pharma and food sciences

· Modern bacterial taxonomy based on genetic characteristics

· Microbiome non-pathogenic library offers biomarkers for health but also potential prebiotic and endobiotic candidates for food and pharmaceutical industries (monetizable = creates new market)

Target 3:

Target 4: Invest in computational repurposing of failed candidate drugs

\$18 million

TBC

1. \$1m scoping (go/no go) effort with McKinsey
2. \$2m pilot
3. \$15m initial investment in repurposing fund either as part of a new entity versus with the NIA AMP-AD

1 contract, 1 grant and 1 investment

Proposed Outcomes

· Scope potential of market and collaboration with McKinsey

· 20 repurposed medications

· Creates new market opportunity for failed drugs

Target 5: Investigate and build social biomarkers correlated with aging and dementia

\$2 million

Israel =rain Technologies

Grant for Grand Challenge-style competition

What we learn

- Scale and scope of potential for digital biomarkers in cognitive disease

Target 6: Bring the financial industry into the conversation

\$1 million

\$1 million to Dr. Jason Karlawish at University of Pennsylvania Medical School / Wharton School

Grant

What we learn

· Possibility of using financial markets to reduce cost and ease burden of care

· Create a new financial product

· Create automated checks and balances or financial standards for demented adults or retiree over age 65 with cognitive challenges

- Share actuarial burden between long term facility care-caregivers

Target 7: Reduce CMS facility and hospital admission costs

\$1 million

RAND

Grant

What we learn

· Save tons of money

· Reduce hospital admissions

- Share burden of care

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<=ont face="verdana, sans-serif">Target 8: Improve trial enrollment<=span>

\$2 mill=on

Lon Sch=eider, USC School of Medicine

Grant

Propose= Outcomes

<=ont face="verdana, sans-serif">· Linkage across trials

=font face="verdana, sans-serif">· Improved (and shared) recruiting tools

=font face="verdana, sans-serif">· Corporate advocacy

· Involvement of search engines (Google, Bing, etc) in stacking searches

What we=learn

<=ont face="verdana, sans-serif">· Barriers to participation

=font face="verdana, sans-serif">· Corporate appetite to contribute

· Institutional appetite to widen trials and/or share controls=/p>

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<=ont face="verdana, sans-serif">Target 9: Novel mechanisms for exploration

\$25 mil=ion

Either =ia intermediary such as Cure Alzheimer's Fund or 8-10 individual recipients (see below)<=span>

Grant

What we=learn

<=ont face="verdana, sans-serif">· Dysregulation of neural pH dynamics: Aimee Kao, Ph.D. / University of California, San Francisco

=font face="verdana, sans-serif">· Human age equivalency and functional phenotypes: Fred "Rusty" Gage, Ph.D.=/ Salk Institute for Biological Studies

=font face="verdana, sans-serif">· Gliovascular changes and waste (glymphatics): Jeffrey Iliff, Ph.D. and William Rooney, Ph.D. / Oregon Health & Science University=/p>

=font face="verdana, sans-serif">· White matter dysfunction as a biosensor: Ragnhildur Thóra Káradóttir, P=.D. / University of Cambridge

Cellular networks controlling proteinopathy: Martin Kampmann, Ph.D., Michael Keiser, Ph.D., David Kokel, Ph.D. / University of California, San Francisco

Immunological gating pathways and denegeration: Dr. Michael Schwartz / Weizmann Institute

Rejuvenation of the nervous and vascular systems: Dr. Shai Efrati / Sagol Center

Filamentous bacteriophages as therapeutics: Proclara biosciences (may be better fit for DDF)

Target 10: Convene a 3 year Task Force to guide your learning

\$ 1 million

NACC, Dr. Bud Kukul / University of Washington

Grant

What we learn

Expert opinion(s) on emerging data, trends and science

Progress and perspective on our own learning from Targets 1-9 as listed above

Managing the Process

\$ 500,000 per year

TBC

Contract or Staff (bgC3) as under the radar manager or advisor + .25 FTE administrative support

Proposed Process

Perform due diligence on proposals

Manage portfolio of learning grants (and contracts)

Report to Bose/Jonah/Larry quarterly or as required otherwise

Attend or delegate attendance for major meetings

Submit quarterly summary report and annual learning report

Serve as primary point of contact with partners / quarterly calls

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=A0 please note

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