New frontiers in the treatment and diagnosis of memory disorders

Daniel Franc, MD, PhD
Los Angeles Brain Science Project
Pacific Neuroscience Institute
Saint Johns Medical Center
Legitimate hope for a dementia cure?
Advances in the diagnosis of memory loss and dementia
Raw memory declines with age
Dementia prevalence dramatically increases with age
Diagnostic challenges in memory loss

- Normal memory loss in aging
- Depression
- Medication side effects
- Depression
- COPD and insomnia
- Hypertensive disease
- Alcohol abuse (or other substances -- marijuana, opium)
- Late onset neuroinflammatory disease/multiple sclerosis
- Normal pressure hydrocephalus
- B12, Thiamine deficiency
- Vasculitis, HIV, hypothyroidism, tumor, adrenal insufficiency ...
IDEAS
Tau scan
CSF analysis

CSF β-Amyloid$_{1-42}$

CSF Tau

Controls
(n = 72)

Alzheimer Disease
(n = 131)

Controls
(n = 72)

Alzheimer Disease
(n = 131)
Advanced MRI for neurodegenerative disease diagnosis – normal

Courtesy Dr. Sheldon Jordan
Advanced MRI for neurodegenerative disease diagnosis – normal

Courtesy Dr. Sheldon Jordan
Advanced MRI for neurodegenerative disease diagnosis – normal

Courtesy Dr. Sheldon Jordan
Advanced MRI for neurodegenerative disease diagnosis – Alzheimer’s disease diagnosis

Courtesy Dr. Sheldon Jordan
Advanced MRI for neurodegenerative disease diagnosis – Alzheimer’s diagnosis

Courtesy Dr. Sheldon Jordan
Advanced MRI for neurodegenerative disease diagnosis – Alzheimer’s diagnosis

Courtesy Dr. Sheldon Jordan
BOLD ICA
Frontal Temporal Dementia Default Network
BOLD ICA Default Network – Anxiety Disorder

Courtesy Dr. Sheldon Jordan
Advanced neuroimaging: diffusion tensor imaging

Courtesy Dr. Sheldon Jordan
Advanced neuroimaging: quantitative volumetric analysis

Courtesy Dr. Sheldon Jordan
White matter disease/cardiovascular

• Elevated risk of Alzheimer’s with history of hypertension, white matter disease, intracranial atherosclerosis
TCD measures of vasomotor reactivity
Advanced MRI measures of vasomotor reactivity

Courtesy Dr. Sheldon Jordan
Initial memory loss evaluation: seizures

Evaluate for epileptiform discharges
Advances in the treatment of memory loss and dementia
CANCER DRUG IMPROVED COGNITION AND MOTOR SKILLS IN SMALL PARKINSON’S CLINICAL TRIAL

CHICAGO (Oct. 17, 2015) — An FDA-approved drug for leukemia improved cognition, motor skills and non-motor function in patients with Parkinson’s disease and Lewy body dementia in a small phase I clinical trial, report researchers at Georgetown University Medical Center (GUMC) in Washington. In addition, the drug, nilotinib (Tasigna® by Novartis), led to statistically significant and encouraging changes in toxic proteins linked to disease progression (biomarkers).

Complete data were presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience, in Chicago on Oct. 17.

Charbel Moussa, MD, PhD, who directs Georgetown’s Laboratory of Dementia and Parkinsonism, conducted the preclinical research that led to the discovery of nilotinib for the treatment of neurodegenerative diseases. To conduct the clinical study, he partnered with Fernando Pagan, MD, a GUMC associate professor of neurology who directs the Movement Disorders Program at MedStar Georgetown University Hospital.

MEDIA ONLY:
Karen Teber
Km463@georgetown.edu

PATIENT INFORMATION:
Parkinson's disease/Lewy body dementia
Movement Disorders Program
Helen Howard 202-444-2333
HHH102@geunet.georgetown.edu

Alzheimer's disease
Memory Disorders Program
Carolyn Ward 202-784-6671
CW2@georgetown.edu

Click here to download a PDF of
Dementia new therapy: bosutinib
Dementia new therapy: bosutinib

Bosutinib targets tyrosine kinase that keeps proteins from being recycled
Dementia new therapy: tyrosine kinase inhibitors

**Announcements**

**NEW CLINICAL TRIAL WILL TEST CANCER DRUG AS ALZHEIMER’S TREATMENT**

The Alzheimer’s Drug Discovery Foundation (ADDF) announces a $2.1 million grant awarded to R. Scott Turner, MD, PhD, of Georgetown University Medical Center to conduct a phase II clinical trial of low-dose nilotinib (marketed as Tasigna® for use as a cancer therapy) in patients with Alzheimer’s disease.
Dementia therapy trial: nilotinib

- Ongoing Phase 1+ boisutinib trial
  - In conjunction with Dr. Sheldon Jordan, Dr. Santosh Kesari and other Saint Johns physicians
  - Ongoing trial of 20 patients patients with mild, moderate, and severe dementia including Alzheimer’s and frontotemporal dementia
  - MRI, spinal fluid and neurocognitive testing
  - Will follow memory and MRI scores

- Plan for Phase 3-4 clinical trial
Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer’s disease mouse model

Gerhard Leinenga and Jürgen Götz*

Amyloid-β (Aβ) peptide has been implicated in the pathogenesis of Alzheimer’s disease (AD). We present a non-pharmacological approach for removing Aβ and restoring memory function in a mouse model of AD in which Aβ is deposited in the brain. We used repeated scanning ultrasound (SUS) treatments of the mouse brain to remove Aβ, without the need for any additional therapeutic agent such as anti-Aβ antibody. Spinning disk confocal microscopy and high-resolution three-dimensional reconstruction revealed extensive internalization of Aβ into the lysosomes of activated microglia in mouse brains subjected to SUS, with no concomitant increase observed in the number of microglia. Plaque burden was reduced in SUS-treated AD mice compared to sham-treated animals, and cleared plaques were observed in 75% of SUS-treated mice. Treated AD mice also displayed improved performance on three memory tasks: the Y-maze, the novel object recognition test, and the active place avoidance task. Our findings suggest that repeated SUS is useful for removing Aβ in the mouse brain without causing overt damage, and should be explored further as a noninvasive method with therapeutic potential in AD.
Focused ultrasound for treatment of Alzheimer’s dementia

• Ongoing Phase 1+ trial
  • In conjunction with Dr. Sheldon Jordan, Dr. Santosh Kesari and other Saint Johns physicians
  • Ongoing trial of 20 patients patients with mild, moderate, and severe dementia including Alzheimer’s and frontotemporal dementia MRI, spinal fluid and neurocognitive testing
  • Will follow memory and MRI scores

• Future focused ultrasound trials with Pacific Neuroscience and Saint Johns Medical Center
Dementia therapy trial: transcranial magnetic stimulation

TMS can be used to stimulate brain networks affected by Alzheimer’s dementia
Dementia therapy trial: transcranial magnetic stimulation

- Empiric treatment of memory loss in patients with diagnosed neurodegenerative disease
  - MRI, spinal fluid, neurocognitive testing
  - EEG to assess for seizures or discharges
  - 12-18 month follow up
- Please contact if interested in more information
Reversal of cognitive decline: A novel therapeutic program

Dale E. Bredesen, MD

Mary S. Easton Center for Alzheimer’s Disease Research, Department of Neurology, University of California, Los Angeles, CA 90095;
Buck Institute for Research on Aging, Novato, CA 94945.

Key words: Alzheimer’s, dementia, mild cognitive impairment, neurobehavioral disorders, neuroinflammation, neurodegeneration, systems biology

Received: 9/15/14; Accepted: 9/26/14; Published: 9/27/14

Correspondence to: Dale E. Bredesen, MD; E-mail: dbredesen@mednet.ucla.edu; dbredesen@buckinstitute.org

Abstract: This report describes a novel, comprehensive, and personalized therapeutic program that is based on the underlying pathogenesis of Alzheimer’s disease, and which involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilized this program include patients with memory loss associated with Alzheimer’s disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI). Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD. Six of the patients had had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Improvements have been sustained, and at this time the longest patient follow-up is two and one-half years from initial treatment, with sustained and marked improvement. These results suggest that a larger, more extensive trial of this therapeutic program is warranted. The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes. Furthermore, given the failure of monotherapeutics in AD to date, the results raise the possibility that such a therapeutic system may be useful as a platform on which drugs that would fail as monotherapeutics may succeed as key components of a therapeutic system.
Dementia treatment: holistic approach

<table>
<thead>
<tr>
<th>Goal</th>
<th>Approach</th>
<th>Rationale and References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize diet: minimize simple CHO, minimize inflammation.</td>
<td>Patients given choice of several low glycemic, low inflammatory, low grain diets.</td>
<td>Minimize inflammation, minimize insulin resistance.</td>
</tr>
<tr>
<td>Enhance autophagy, ketogenesis</td>
<td>Fast 12 hr each night, including 3 hr prior to bedtime.</td>
<td>Reduce insulin levels, reduce Aβ.</td>
</tr>
<tr>
<td>Reduce stress</td>
<td>Personalized—yoga or meditation or music, etc.</td>
<td>Reduction of cortisol, CRF, stress axis.</td>
</tr>
<tr>
<td>Optimize sleep</td>
<td>8 hr sleep per night; melatonin 0.5mg po qhs; Trp 500mg po 3x/wk if awakening. Exclude sleep apnea.</td>
<td>[36]</td>
</tr>
<tr>
<td>Exercise</td>
<td>30-60&quot; per day, 4-6 days/wk</td>
<td>[37, 38]</td>
</tr>
<tr>
<td>Brain stimulation</td>
<td>Posit or related</td>
<td>[39]</td>
</tr>
<tr>
<td>Homocysteine &lt;7</td>
<td>Me-B12, MTHF, P5P; TMG if necessary</td>
<td>[40]</td>
</tr>
<tr>
<td>Serum B12 &gt;500</td>
<td>Me-B12</td>
<td>[41]</td>
</tr>
<tr>
<td>CRP &lt;1.0; A/G &gt;1.5</td>
<td>Anti-inflammatory diet; curcumin; DHA/EPA; optimize hygiene</td>
<td>Critical role of inflammation in AD</td>
</tr>
<tr>
<td>Fasting insulin &lt;7; HgbA1c &lt;5.5</td>
<td>Diet as above</td>
<td>Type II diabetes-AD relationship</td>
</tr>
<tr>
<td>Hormone balance</td>
<td>Optimize fT3, fT4, E2, T, progesterone, pregnenolone, cortisol</td>
<td>[5, 42]</td>
</tr>
<tr>
<td>GI health</td>
<td>Repair if needed; prebiotics and probiotics</td>
<td>Avoid inflammation, autoimmunity</td>
</tr>
<tr>
<td>Reduction of A-beta</td>
<td>Curcumin, Ashwagandha</td>
<td>[43-45]</td>
</tr>
<tr>
<td>Cognitive enhancement</td>
<td>Bacopa monniera, MgT</td>
<td>[46, 47]</td>
</tr>
<tr>
<td>25OH-D3 = 50-100ng/ml</td>
<td>Vitamins D3, K2</td>
<td>[48]</td>
</tr>
<tr>
<td>Increase NGF</td>
<td>H. erinaceus or ALCAR</td>
<td>[49, 50]</td>
</tr>
<tr>
<td>Provide synaptic structural components</td>
<td>Citicoline, DHA</td>
<td>[51]</td>
</tr>
<tr>
<td>Optimize antioxidants</td>
<td>Mixed tocopherols and tocotrienols, Se, blueberries, NAC, ascorbate, α-lipoic acid</td>
<td>[52]</td>
</tr>
<tr>
<td>Optimize Zn:fCu ratio</td>
<td>Depends on values obtained</td>
<td>[53]</td>
</tr>
<tr>
<td>Ensure nocturnal oxygenation</td>
<td>Exclude or treat sleep apnea</td>
<td>[54]</td>
</tr>
<tr>
<td>Optimize mitochondrial function</td>
<td>CoQ or ubiquinol, α-lipoic acid, PQ, NAC, ALCAR, Se, Zn, resveratrol, ascorbate,</td>
<td>[55]</td>
</tr>
</tbody>
</table>

- Improve sleep
- Treat stress and anxiety
- Regular exercise
- Improve diet
- Cognitive exercises
- Supplements
  - Coconut oil, MCT oil
  - Curcumin
  - Resveratrol
- Beyond Alzheimer’s patient support group founded by Patti Davis moving to Saint Johns Medical Center in May 2016
  - Support for family members of patients with Alzheimer’s and other neurodegenerative diseases
- Please contact if interested in more information
Thanks for your interest!