Advancing the Science: The Latest in Alzheimer’s Research

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Medical & Scientific Relations

alzheimer's association®
Our Time Today…

• Landscape of Alzheimer’s and Dementia Science
• Highlights in Early Detection and Diagnosis
• Latest Advances in Clinical Trials, Treatments and Lifestyle Interventions
Dementia is a Syndrome

- Dementia is a collection of symptoms related to cognitive decline
- Can include cognitive, behavioral and psychological symptoms
- Due to biological changes in the brain
- Alzheimer’s is most common cause
- Mixed dementia is very prevalent
- Some causes of cognitive decline are reversible and not truly dementia

Alzheimer’s 60%-80%
Vascular 10%-40%
Lewy Bodies 10%-25%
Frontotemporal ~ 10%

Mixed Dementia = >1 Neuropathology - Prevalence ~ 50%

An "umbrella" term used to describe a range of symptoms associated with cognitive impairment.
MCI is a known risk factor for dementia

Everyone who experiences dementia passes through MCI

When you prevent new cases of MCI, you are preventing new cases of dementia
Hallmarks of Alzheimer’s Disease

Neuritic Plaques

Extracellular deposits of beta-amyloid

Neurofibrillary Tangles

Intracellular deposits of hyperphosphorylated tau

Neurodegeneration
Cortical Atrophy

Healthy Brain

Advanced Alzheimer’s
The LATE Debate: A New Cause/Contributor of Dementia?

- TDP-43
- Deposits in memory centers
- More frequent later in life
- Common?
- Symptoms mimic Alzheimer’s dementia and/or accelerate it

Limbic-predominant Age-related TDP-43 Encephalopathy

Risk Factors

Alzheimer’s is not typical aging

- Age
- APOE-e4 gene
- Family history
  - Genetics
  - Shared environmental & lifestyle factors
- Cardiovascular disease
  - Hypertension, diet, diabetes, smoking
- Social & cognitive stimulation
- Education
- Traumatic brain injury

Ages of People with Alzheimer’s Dementia, 2019

- <65 years: 0.2 million (3%)
- 65-74 years: 0.9 million (16%)
- 75-84 years: 2.6 million (45%)
- 85+ years: 2.1 million (36%)

Created from data from Hebert et al.\textsuperscript{A2,51}
Available Therapies

Currently, there are no therapies that can cure Alzheimer’s. Some drugs are available to temporarily improve symptoms.

Disease modification versus symptomatic benefit in the treatment of Alzheimer’s Disease:

- **Disease modification**
  - Arrest
  - Deceleration

- **Symptomatic benefit**
  - No effect

[Graph showing quality of life over time with different treatment outcomes.]
Impact of Alzheimer’s

IN 2019, Alzheimer’s and other dementias will cost the nation $290 BILLION.

BY 2050, these costs could rise as high as $1.1 TRILLION.
We Advocate

Alzheimer’s and Related Dementia Research Funding at the NIH

<table>
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<th>Year</th>
<th>Funding</th>
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Alzheimer’s Association
Global Research Investment

$165 million
500+ projects
27 countries
Connector • Convener • Funder • Catalyst
We have played a role in nearly every significant development in Alzheimer’s science to date.

**Western Carolina Chapter**

**Active and Historical Grants**
- 13 awards between 2005-2019 (7 active)
- Total ~ $32 million (~ $30.2 million active)

**Number of Scientific Reviewers**
- 28 reviewers: 170 critiques

**ISTAART Membership**
- 53 ISTAART members

**Funded Researchers**
- Wake Forest University, UNC Charlotte, UNC Greensboro
Exciting Time in Research
The Hunt for Biomarkers

• Biological marker to measure change
• Reliable predictor and indicator of disease and disease progression
  – Glucose for insulin resistance and diabetes
  – Cholesterol for heart disease

• Uses in Alzheimer’s disease include:
  – Diagnostic: determining diagnosis
  – Enrichment: reinforcing entry criteria into a clinical trial
  – Prognostic: determining course of illness
  – Predictive: treatment outcomes and safety assessment
Biomarkers Are Changing the Game

Saliva Biofluid

Amyloid-β PET Imaging

Tau PET Imaging

Blood Test

CSF – Lumbar Puncture

Retinal Imaging
National study on utility of amyloid PET scans

~18,500 Medicare beneficiaries

With mild cognitive impairment (MCI) or dementia of uncertain cause

**Aim 1:** Impact of scan on management plan at 3 months

**Aim 2:** Impact on major medical outcomes at 12 months

Two-thirds of participants had a change in their diagnosis and/or care management as a result of their PET scan results

RESULTS OF THE IDEAS STUDY JUST PUBLISHED IN JAMA APRIL 2, 2019
Progress Towards a Blood Test

• Global race to uncover and develop blood based biomarkers for Alzheimer’s disease and other dementias
• More research validating amyloid beta in blood by comparing to imaging and cognitive testing
• New research on blood tests for alpha synuclein and neurofilament light
• Not in your doctor’s office tomorrow, but are already being used for clinical trials
Modernizing the Diagnosis

Cognitively Unimpaired

Biomarkers

20 years or more before symptoms appear, the brain changes of Alzheimer's may begin.

Alzheimer's Dementia

History & Cognition

Adapted from Reisa Sperling, BWH, MGH

Cognitive function

Preclinical

Aging

MCI

Dementia

Adapted from Reisa Sperling, BWH, MGH
Progress Toward More Effective Treatment

A future Alzheimer’s therapy will likely include both lifestyle interventions and medicines.
How A Potential Therapy is Developed

Preclinical

Phase 1

Phase 2

Phase 3

Figure adapted from Cancer Institute, New South Wales, Australia (published March 30, 2017)
Current Landscape of Clinical Trials for Alzheimer’s & Dementia

### As of July, 2019

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number</th>
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<tr>
<td>Phase III</td>
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Drugs and Devices

62 cognitive assessment, cognitive training, and computerized devices

Always a Need for Participants
Medicines
Diverse Therapeutic Mechanisms in Phase 3

- **28% Neuropsychiatric Symptoms**
  - Agitation (n=6)
  - Apathy (n=1)
  - Sleep disorders (n=1)

- **61% Disease-Modifying Therapies**
  - Anti-Amyloid (n=8): Immuno-therapy (n=6), BACE inhibition (n=2), Anti-aggregation (n=1)
  - Anti-aggregation (n=1)
  - Anti-Tau (n=1)
  - ↓ Tau phosphorylation and ↓ Amyloid (n=1)

- **11% Symptomatic Cognitive Enhancers**
  - Neuroprotection (n=3)
  - Anti-inflammatory (n=2)
  - Antibiotic (n=1)

- **21% Other MOAs**
  - Antioxidant (n=1)
  - Neurotransmitter based (n=2)

*Cummings J. et al. A&D:TRCI, 2019*
Medicines Focused on Behavioral & Psychological Symptoms of Dementia

FOR IMMEDIATE RELEASE

Merck’s BELSOMRA® (suvorexant) C-IV Meets Primary Efficacy Endpoint in Phase 3 Trial for the Treatment of Insomnia in People with Mild-to-Moderate Alzheimer’s Disease Dementia

First Randomized Controlled Polysomnography Trial of Insomnia Medication in Alzheimer’s Disease Dementia Population

Data to be Filed with FDA for Potential Inclusion in BELSOMRA Prescribing Information

KENILWORTH, N.J., May 7, 2019 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the presentation of results of a Phase 3 trial evaluating the efficacy and safety of BELSOMRA® (suvorexant) C-IV for the treatment of insomnia in people with mild-to-moderate Alzheimer’s disease dementia.
Diversifying the Pipeline

Accelerating transition of research findings from laboratory through clinical trials and into practice
Possibility of Prevention
Lifestyle Interventions
In The News…SPRINT-MIND Study

The New York Times

Study Offers Hint of Hope for Staving Off Dementia in Some People

People who received intensive treatment for hypertension were less likely to develop minor cognitive problems than those receiving standard treatment.

Lowering blood pressure could cut risk factor for dementia
The SPRINT-MIND Study
First Study to Demonstrate Reduction of New Cases of Cognitive Impairment

- 9,000+ people, Over age 50, All-cause dementia risk
- Standard vs. Intensive Blood Pressure Intervention
- Intensive treatment 120 systolic vs. 140 systolic
  - 19% reduced risk for MCI
  - 17% reduced risk for dementia * Not Statistically Significant
  - 15% reduced combined risk for MCI and dementia
- Dramatic reduction of small vessel disease on MRI
SPRINT-MIND 2.0

• **SEED** SPRINT-MIND 2.0 to clarify impact on dementia with 2 years additional follow up
• Over 7,000 will be contacted for additional follow up
• Initiating study **NOW** to allow for maximum participant retention
Why Is This Important?

There are things you can do to reduce your risk of MCI and dementia – especially regarding cardiovascular disease risk factors.
Lifestyle Research at AAIC 2019

- Combining multiple healthy lifestyle factors may be more impactful for reducing dementia risk
  - Healthy diet
  - Moderate to vigorous physical activity
  - Light to moderate alcohol intake
  - Smoking
  - Cognitive stimulation

- 4 or 5 → 59% lower risk of Alzheimer’s dementia
- 2 or 3 → 39% lower risk
- May even offset risk associated with genetics

Can Alzheimer's be stopped? Five lifestyle behaviors are key, new research suggests

Following four out of five lifestyle behaviors can protect against mental decline, even in people with increased genetic risk.

July 24, 2019, 10:00 AM EDT / Updated July 24, 2019, 10:18 AM EDT
By Linda Carroll

There's no cure for or drug to stop Alzheimer's disease, but it may be possible to hold off dementia — even in people who have a genetic risk, researchers reported Sunday at the Alzheimer's Association International Conference. The key is not any one factor; several studies show, but following a combination of healthy lifestyle habits. And the more healthy habits a person adopts, the lower the risk of cognitive decline.

People who followed four out of five lifestyle behaviors, including regular exercise, cognitive stimulation and a brain-healthy diet and not smoking, over a six-year period had a 60 percent lower risk of developing Alzheimer's dementia when compared to people who practiced only one or none of these habits, according to researchers from Rush University in Chicago.

Similarly, a UK study found that among people with a heightened genetic risk of cognitive decline, dementia was 32 percent lower in those with a healthy lifestyle.
U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk

Two year multi-center randomized clinical trial

Self-Guided and Structured Lifestyle Groups

2,000 Participants at five U.S. sites
• Landmark study
• Uniquely positioned
  – Embedded in community systems
  – Ready for implementation if the intervention works
• Goal of 23% diversity
• Adults 60-79, with parent or sibling with memory loss or dementia
• Several additional ancillary studies applying to NIH
$47 million grant to explore how a healthy lifestyle changes the aging brain

By Kara Marcink | JULY 19, 2019

The new funding will add positron emission tomography (PET) and magnetic resonance imaging (MRI) to the upcoming U.S. POINTER study, which will explore how lifestyle changes affect memory and thinking in older adults. (UC Berkeley photo by Malachi Tran)

U.S. POINTER

IN THE NEWS

• $47 Million granted from NIA to UC Berkeley for U.S. POINTER Neuroimaging Ancillary Study
• Adding PET and MRI
• Underscores our Seed, Speed, Scale strategy
The Importance of WW-FINGERS

- Focus on modifiable risk factors and brain health
- Dementia can potentially be reduced impacting disability
- Crucial for LMIC areas
- Global diversity
  - Ethnic differences, customs, food, culture, and attitude
- Potential for **FASTER** dissemination/uptake to impact cognitive health
Changing the Trajectory of Alzheimer’s Disease

DELAYED ONSET
If we develop a treatment by 2025 that delays the onset of Alzheimer’s by just 5 years, then:

5.7 MILLION people expected to develop Alzheimer’s would not in 2050.
Take Action Today
10 Ways to Love Your Brain

START NOW

It’s never too late or too early to incorporate healthy habits.
How to Get Involved in Research

TrialMatch is a free clinical studies matching service designed to provide a customized list of potential study matches to each user.
In Summary …

• Alzheimer’s Association is a global leader for Alzheimer’s and dementia science

• Exciting time in research
  – New tools for detection and diagnosis
  – Growing diversity of therapies under investigation

• New research leading to future of therapy that combines drugs and modifiable risk factor interventions

• There is **HOPE** in research !!