Disclosure

I currently receive no money from biotechnology or pharmaceutical companies for my research.
Agenda

• What is Dementia?
• Basic Research
• 2011/2012, New Diagnostic Criteria
• Clinical Trials
• National Alzheimer’s Plan – USA
• National Dementia Plan – Canada
• Upcoming Meetings/ Groups
• Resources
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Dementia Defined

• Image here
Dementia Defined

• A syndrome characterized typically by progressive & global deterioration in intellect
  – loss in, memory, learning, orientation, language, comprehension, judgment

• Symptoms caused by **one or more diseases**
Types of Dementia

Prevalence of Dementia Subtypes

- Alzheimer's Disease (AD)
- Mixed Type
- Lewy Body
- Frontotemporal Lobe
- Vascular Dementia (VaD)
- Reversible

Figure 3: Prevalence of Dementia Subtypes [4]

http://www.genderandhealth.ca/en/modules/dementia/Epi2_Dementia-03.jsp
Worldwide Problem

People living with dementia around the world

- Americas: 9.4m (2015), 15.8m (2030), 29.9m (2050)
- Africa: 4.0m (2015), 7.0m (2030), 15.8m (2050)
- Europe: 10.5m (2015), 13.4m (2030), 18.6m (2050)
- Asia: 22.9m (2015), 38.5m (2030), 67.2m (2050)
- World: 46.8m (2015), 74.7m (2030), 131.5m (2050)

From BUPA, 2015
• The Persistence of Memory – Salvador Dali image here
• Movie: Inside Out image here
• Patient HM image here
• Movie
• Inside the Brain: Unraveling the mystery of Alzheimer’s Disease
• NIA-NIH
• Image of severe brain pathology
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Therapeutic Mechanisms in AD

Modified from Anand et al Neuropharmacology 2014
Therapeutic Strategies in AD

1. Modulating neurotransmission
2. Tau based therapies
3. Amyloid based strategies
4. Modulating intracellular signaling cascades
5. Oxidative stress reduction
6. Mitochondrial targeted therapy
7. Modulation of cellular calcium homeostasis
8. Anti-inflammatory therapy
9. Others, e.g., stem cells

Anand et al Neuropharmacology 2014
Alzheimer’s in a Dish

- Replicated Alzheimer’s outside of the brain
- Creates ability to test thousands of drugs faster than ever before

Dr. Rudy Tanzi, Harvard University
Rest Protein

• During normal ageing, REST is induced
• However, in Alzheimer’s disease, frontotemporal dementia and dementia with Lewy bodies, REST is lost
• REST levels during aging are correlated with cognitive preservation and longevity
Ultrasound

• Opens Blood Brain Barrier (BBB)
• Enhances delivery of anti-amyloid antibodies
• Stimulates neuronal activity
• Reduces plaque burden
  improved memory

Drs Leinenga & Götz, Univ Queensland Australia
Energy Metabolism

Modified From Albenseni and colleagues, Mol Neurobio, 2015
Future Treatment Options

• **Plaques**
  – recruiting the immune system
  – preventing nerve connections destruction
  – reduce amyloid beta production

• **Tau**
  – vaccines
  – prevent tangles

• **Reduce Inflammation**
  – diet, exercise
  – drugs
Treatment Options

• Changes in Metabolism
  – insulin resistance
  – Mitochondrial dysfunction

• Heart-Brain Connections
  – high blood pressure
  – heart disease
  – stroke
  – diabetes
  – high cholesterol
  – smoking
Treatment Options

• **Hormones**
  – gender differences

• **Genetic**
  – early onset
  – late onset
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The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Guy M. McKhann\textsuperscript{a,b,\textsuperscript{*}}, David S. Knopman\textsuperscript{c}, Howard Chertkow\textsuperscript{d,e}, Bradley T. Hyman\textsuperscript{f}, Clifford R. Jack, Jr.\textsuperscript{g}, Claudia H. Kawas\textsuperscript{h,i,j}, William E. Klunk\textsuperscript{k}, Walter J. Koroshetz\textsuperscript{l}, Jennifer J. Manly\textsuperscript{m,n,o}, Richard Mayeux\textsuperscript{m,n,o}, Richard C. Mohs\textsuperscript{p}, John C. Morris\textsuperscript{q}, Martin N. Rossor\textsuperscript{r}, Philip Scheltens\textsuperscript{s}, Maria C. Carrillo\textsuperscript{t}, Bill Thies\textsuperscript{t}, Sandra Weintraub\textsuperscript{u,v}, Creighton H. Phelps\textsuperscript{w}
New Criteria

The new criteria define three stages of AD:

- **Preclinical AD** is characterized by measurable changes in biomarkers and *poor performance* on challenging cognitive tests.

- **MCI due to AD** is characterized by the first clinical changes. Mild changes in memory and other cognitive abilities are noticeable to patients and families, and can be detected through careful evaluation, but do **not** interfere with *day-to-day activities*.

- **Dementia due to AD** is characterized by changes in *two or more* aspects of cognition and behavior that **interfere** with function in *everyday life*. 
Timelines using New Criteria
Who Should Use the New Diagnostic Guidelines? The Debate Continues...

• How will the new criteria be implemented?
• Are the criteria useful to clinicians everywhere?
• Will their application radiate out appropriately from tertiary into secondary and primary care sites throughout the community?
• Has the time come to apply the new guidelines in those settings?
• What do diagnosticians think who were not part of the expert panels that produced the guidelines?

See discussion online at:
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Clinical Trial Highlights

New blood test predicted with 90% accuracy whether a healthy person would develop Alzheimer’s or cognitive impairment within two or three years.

Dr. Howard Federoff, Georgetown University
Clinical Trial Highlights

• **A4 study** – Anti-amyloid Treatment in Asymptomatic Alzheimer’s Study

• Focuses on those at risk, but currently normal

• Goal of the A4 study is to test whether decreasing amyloid with antibody investigational treatment can help slow the memory loss associated with amyloid buildup

Dr. Reisa Sperling, Harvard Univ.
Clinical Trial Highlights

- **MIND diet** incorporates 2 other diets
  - DASH and Mediterranean
  - 10 healthy food groups
    - Leafy veges, other veges, nuts, berries, beans, whole grains, fish, poultry, olive oil, wine
    - **AVOID**: red meat, butter/margarine, cheese, pastries, candy, fried food
  - Effective, if one adheres

Martha Clare Morris, a nutritional epidemiologist at Rush University Medical Center
Clinical Trial Highlights

- Coconut oil
- To date insufficient data

Dr. Mary Newport
Clinical Trials Worldwide

As of Jan. 2015

• 484 dementia trials (trials other than AD)
• 1423 Alzheimer’s trials
• 128 clinical trials in Winnipeg - no large dementia or AD trials

http://www.centerwatch.com/clinical-trials/
Ongoing Alzheimer’s Clinical Trials across World

- Lu AE58054, Lundbeck, 2012
- EVP-6124, EnVivo Pharmaceuticals, 2012
- Solanezumab, Eli Lilly, 2012
- MK-8931, Merck, 2013
- Circadin, Neurim Pharmaceuticals, 2014
- AVP-923, Avanir Pharmaceuticals, 2014
Lu AE58054, Lundbeck

June 2012

• Phase 2
• 278 pts with moderate AD
• Lu AE58054 (plus donepezil) demonstrated statistically significant improvements in cognitive function in AD compared to placebo (plus donepezil), as assessed by ADAS-cog.

ADAS-cog = AD assessment scale for cognition
July 2012

- Phase 2B
- 409 pts with mild to moderate AD
- The 2.0mg dose obtained statistically significant effects on cognition ($p=0.019$) as measured by ADAS-Cog-13 and clinical function ($p=0.03$) as measured by CDR-SB.
- The 2.0mg dose also showed an improvement in cognition composite ($p=0.004$), memory composite ($p=0.009$) and executive function composite ($p=0.04$). EVP-6124 was well-tolerated.

P values have been rounded off
Solanezumab, Eli Lilly

October 2012

- Phase 3
- 1040 pts with mild to moderate AD
- Results showed a 20% reduction in cognitive decline in patients with mild Alzheimer’s taking solanezumab, but the treatment difference was not statistically significant (p=0.120).
MK-8931, Merck

July 2013

• Phase 1B
• 32 pts with mild to moderate AD
• Administration of MK-8931 at doses of 12mg, 40mg and 60mg resulted in a dose-dependent and sustained reduction in the levels of \( Ab_{40} \), a measure of \( BACE1 \) activity in CSF from baseline of 57%, 79% and 8%, respectively.
• No serious adverse events or study discontinuations due to adverse events were recorded.
June 2014

- Phase 2, *add on drug* to standard therapies
- 80 pts with mild to moderate AD
- Circadin treatment resulted in significant and clinically meaningful effects v. placebo in mean IADL (p=0.032), *MMSE* (+1.5 v. -3 points, p=0.0177) *sleep efficiency* (p=0.04) and median *ADAS-Cog* values (-3.5 v. +3 points, p=0.045).

*MMSE* = Mini mental state evaluation
AVP-923, Avanir Pharmaceuticals

Nov. 3, 2014

• Phase 2
• For treatment of *agitation* in 220 pts with AD
• AVP-923 was generally safe and well-tolerated and associated with a low rate of discontinuation from the study (11.8%).
Alzheimer’s Disease Neuroimaging Initiative 2 (ADNI2)

- Now in its third phase (ADNI, ADNI GO and ADNI 2)
- ADNI 2 is studying the *rate of change of cognition, function, brain structure, and biomarkers* in 150 elderly controls, 450 subjects with mild cognitive impairment, 150 with mild to moderate AD
- And a new group of 100 people with significant, yet subtle, memory complaints, referred to as the significant memory concern cohort

http://www.adni-info.org/
Further Information on ADNI2

• This website is informational and is intended to provide an introduction of ADNI study basics - http://www.adni-info.org/

• Scientists and researchers seeking access to ADNI data should visit USC’s Laboratory of Neuroimaging ADNI database - http://adni.loni.usc.edu/
Phase 2/3 Clinical Trials Canada

- Edmonton – T5X3N5
- Gatineau – J8T8J1
- Greenfield Park – J4V2J2
- Halifax – B3S1M7
- Kamloops – V2C1K7
- Kelowna - V1Y 1Z9
- Montreal - H1T 2M4
- Ottawa - K1N 5C8

Contact 1-888-545-5972

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Phase 2/3 Clinical Trials Canada

- Peterborough - K9H 2P4
- Quebec City - G1J 1Z4
- Sherbrooke – J1J 2G2
- Toronto - M3B 2S7
- Vancouver - V6T 2B5

Contact 1-888-545-5972

CenterWatch – Feb 2016
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National Plans in North America

• National Alzheimer’s Plan Act – USA
  – New budget in USA almost doubled AD research money to close to 1 billion dollars/year

• National Dementia Plan – Canada
  – No agreed on plan as of yet
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Upcoming Meetings
North America

• 2016 Annual Meeting of USA & Canadian Academy of Pathology, 12-18 March 2016, Seattle, WA, USA
• 2016 Zilkha Symposium on Alzheimer Disease & Related Disorders, 10 April 2016, Los Angeles, CA, USA
• Epigenetic and Metabolic Regulation of Aging and Aging-Related Diseases, 1-5 May 2016, Santa Fe, NM, USA
• Alzheimer Assoc. Int. Conf., Toronto, ON July 2016
• 4th World Parkinson Congress (WPC 2016), 20-23 September 2016, Portland, OR, USA
• World Congress & Expo on Dementia & Neuroscience, 26-28 September 2016, Los Angeles, CA, USA
Organizations

- **Alzheimer Society of Manitoba**
  - http://www.alzheimer.mb.ca/

- **Alzheimer Society of Canada**
  - http://www.alzheimer.ca/en/We-can-help?gclid=CKnK2572rMsCFQMQaQod9kMA2w

- **Alzheimer’s Association**, USA
  - http://www.alz.org/

- **National Inst. of Health**, NIH-NIA, USA
  - https://www.nia.nih.gov/alzheimers
Organizations

• *Alzheimer’s Disease International (ADI)* is a worldwide organization – of which the Alzheimer’s Association is a founding member
  – World Alzheimer Report: Dementia and Risk Reduction

• *Coalition Against Major Diseases (CAMD)*
  – Alliance of pharmaceutical companies
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Brain Health Registry

• Neuroscience **online project**
• Members return to the website every 3 to 6 months.
• Goal to understand human brains as they age and change over time
• Sponsored by Dr. Mike Weiner and others (Drs. Mackin, Nosheny) at UCSF (Univ. Calif. San Francisco)

Dr. Mike Weiner

http://www.brainhealthregistry.org/
At 90, in Nov 2013, my mom diagnosed with dementia

- Can no longer carry on a coherent conversation
- Angers easily, frequently chemically restrained to control behavior
- Wants to go home, frequently attempts to leave nursing home
- Initiates or is a victim of confrontations with others

Photo taken for 91st birthday, 9/2014
Questions?

Thanks for listening

balbensi@sbrc.ca
204-235-3942