Healthy Aging and dementia 
Research Update 2019

Knoebel Institute for Healthy Aging 
Quality in Life, Wellness and Community

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University of Denver
Outline

❖ How to stay healthy
❖ The Aged Brain
❖ How can we study aging?
  ❖ Animal/cell studies
  ❖ Biomarkers
  ❖ Clinical outcome studies
❖ What is dementia?
❖ Different forms of dementia
❖ Down syndrome and AD
❖ Pathological changes
  ❖ Protein aggregation (amyloid/tau)
  ❖ Neuronal loss
  ❖ Inflammation

http://selfhealthguide.blogspot.com/2012/10/the-blue-zones.html
But appearance is only one aspect of aging: It is who you are on the inside that matters!

“You don't stop laughing when you grow old, you grow old when you stop laughing.”

– George Bernard Shaw
How do we age successfully?

“10 Keys”™ to Healthy Aging
University of Pittsburgh
**Blue zones Centenarian Lifestyle**

- Geographic properties
- Philosophical outlook - jovial - purpose
- Eat until 80% full
- Move naturally, no stress
- Fish, vegetables, legumes, barley, goat milk
- Red wine in moderation

A respectful life.com
How can we study aging?

- Animal/cell studies
- Biomarkers
- Clinical outcome studies
Animal studies of aging

- Human long lifespan makes aging studies difficult
- Yeast - days
- Fruit flies (Drosophila) - 50-60 day lifespan
- Worms (C. Elegans) - 20 day lifespan
- Rodents - 2 to 3 year lifespan
- Non-Human primates - 30 year lifespan
Human Aging studies

- Cross sectional
- Longitudinal
- Cross-sequential

https://www.slideshare.net/guest1d8cad/research-3042787
Ledreux et al 2019

> 100 older adults aged 65 and older

4 different interventions

Purpose: life style effects on brain health proteins (BDNF)
The Aged Brain

1. Dementia:
   risk double every 5 years;
   > 40% in people over 85 years of age

2. Motor dysfunction:
   Prevalence of extrapyramidal symptoms:
   15% in 65-74 years of age
   30% in 75-84 years of age
   >50% in > 85 year olds

www.livestrong.com
The many faces of dementia

Margaret Thatcher

#talkdementia

Rosa Parks

Omar Sharif

Salvador Dali

Rita Hayworth

Norman Rockwell

"Success consists of going from failure to failure without loss of enthusiasm." - Winston Churchill
DEMENTIA

An “umbrella” term used to describe a range of symptoms associated with cognitive impairment.

ALZHEIMER’S 50% - 75%
VASCULAR 20% - 30%
LEWY BODY 10% - 25%
FRONTOTEMPORAL 10% - 15%

http://www.dfwsheridan.org/types-dementia
Alzheimer’s Disease

- Most common form of dementia
- Incidence will double next 15 years
- Pathology includes amyloid and tau accumulation

35.5 million people worldwide have dementia

Source - “Dementia: a public health priority” report, World Health Organization and Alzheimer’s Disease International

www.alz.org
Down syndrome

From: Matt Janicki

• Most: extra copy of Chr 21 from mother
• In < 5% of cases extra copy of Chr 21 from the father
• Remaining cases, the error occurs after fertilization
Down syndrome and Alzheimer’s

- Equal in all ethnic groups
- Increased risk and earlier onset
- 80% eventually develop dementia
- Medically underserved population

Hamlett et al., 2016
Biological correlates of dementia

- Protein aggregation - Amyloid and Tau
- Nerve cell (neuronal) Loss
- Inflammation
Protein aggregation

- accumulation of both plaques and tangles
- Similar to Alzheimer pathology
- Oxidative stress, inflammation

Control 63 yrs  DS+AD 61 yrs
Tau grant: aims and prelim data

- Tau levels and species in exosomes and brain tissue in Down syndrome
- Spread of tau pathology in mouse brain
- Aggregation properties of tau \textit{in vitro}
- Mouse and cell models

University of Denver
Karolinska Institutet
Barrow Neurological Institute
Biomarkers

- MRI or PET imaging
- Biomarkers in blood or CSF
- Exosomes in blood containing markers
- Studies of brain tissue post mortem
Towards improved imaging biomarkers

Collaboration with Agneta Nordberg and Laetitia Lemoine
Karolinska Institutet, Stockholm

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B. Hippocampus

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</tbody>
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Exosomes - a novel biomarker method

- Released into the blood stream from all cells
- Contain RNA, proteins, lipids, surface markers
- Function as both signaling to other cells and “garbage disposal”
Neuron-derived exosomes

Aurelie Ledreux

Neuron-derived: L1CAM

A. Brain cortex

B. Liver

Photos: Human Protein Atlas licensed under the Creative Commons Attribution-ShareAlike 3.0 International License (thus not copyrighted). From (Uhlen et al., 2015).
Exosomal biomarkers in a population with Down syndrome

Aβ1-42 levels by Age

P-(S396)-Tau levels by Age

Down syndrome

Controls
Can exosomes be validated as “liquid biopsy”?
Predict onset decades prior to onset of dementia?
Used for longitudinal disease risk biomarkers
Down syndrome and dysfunction of autophagy pathway

MVB = multivesicular body

Endocytosis

Extracellular

Intracellular

Endosome

Enlarged

MVB

Destruction

Expulsion

Exosomes

Increased release

CD65↑ drives expulsion

Lysosome

Disrupted autophagy
How does pathology spread from region to region?

Is it via exosomes?
Aggregation of Tau *in vitro* and *in vivo*

Can Tau pathology spread between species/individuals?

Amplification of Tau fibrils from exosomes obtained from blood. M = marker, C = control exosomes, DS = Down syndrome exosomes.

P-Tau antibodies (S396)
To examine connection between human pathology and behavior: we need mice:

- Study gene-gene interactions
- Develop prevention strategies
- Validate biological function of drugs
- Perform longitudinal intervention studies
Mouse models for DS

~ 100 genes common to these models
http://www.dsrtf.org
Memory loss in Ts65Dn mice

Water Radial arm maze

Spatial memory

Working memory

Novel object recognition task
Gradual loss of nerve cells

18 month

@Interstellate Twitter
Loss of cholinergic cells

Control                  Trisomic

Loss of cells correlates with memory loss

ChAT-positive cells in VDB

R²=0.55
p < 0.001

Memory Errors

Control                  Trisomic
Loss of locus coeruleus noradrenergic neurons

- Rostral LC degenerates in both AD and DS (German et al, 1992)
- LC loss increases AD pathology and inflammation
DREADDs are designer receptors exclusively activated by designer drugs. By replacing endogenous receptors with artificial receptors that respond to an inert compound clozapine-N-oxide (CNO), one can either increase or decrease firing rate in specific neurons. hM3 = increase, hM4 = decrease firing rates of LC neurons
Designer receptors

By giving CNO in drinking water, one can turn ON and OFF the cells.

Hyperactivity

Working memory
Clinical treatment with LC enhancing drugs

- Adrenergic agonists or Droxidopa in clinical trials for ADHD and DS
- These adrenergic-enhancing drugs increase attention and working memory and hold hope for Alzheimer’s disease also in the general population
- Clinical trials networks:

Trial Match® Alz Association

Down Syndrome Clinical Trials Network

Alzheimer’s Association
Neuroinflammation

CD45

GFAP

COX-2

D. Cd45 density

C. Astrocyte branching

Cox-2 staining

Normosomic Trisomic

Relative CoX-2 dens

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2 2.25

12 months 24 month

Ts65

NS TS NS TS

Process crossings

12 months 24 months

TS NS TS

Relative CoX-2 dens

12 months

NS

Ts65
Inflammation resolution

- Resolvins metabolic byproducts of omega-3 fatty acids that help establish homeostasis after an infection.
- Patients with Alzheimer’s disease: lower resolvins and increased receptors.

Are people with Alzheimer’s less able to handle inflammation?

Wang et al., 2015
DS Biobank Consortium

Sites involved in the DS Biobank Consortium

- UC Irvine
- DU
- CU
- Arizona
- UKY
- Harvard
- MUSC
- Stockholm
- Barcelona

- Train graduate students and physicians
- Provide tissues and biofluids to other researchers
- Generate standard neuropathology staging
- Advocate for brain donation
Effects of concussions on dementia later in life
Concussion and AD biomarkers

- High impact sports: football/Lacrosse/soccer/hockey players
- Veterans with blast injuries
- Increased risk for psychiatric and neurological conditions
Concussion program at DU

- Interdisciplinary DU group
- Human dynamics lab
- Cognitive performance
- Biomarkers - longitudinal study

Human Dynamics lab DU - Brad Davidson, Kevin Shelburne
# Cohort demographics DU Concussion

## Table 1: Cohort demographics by sport played

<table>
<thead>
<tr>
<th>Sport</th>
<th>Total participants recruited</th>
<th>Male/Female</th>
<th>Percent Male/Female</th>
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<tbody>
<tr>
<td>Total</td>
<td>317</td>
<td>170/147</td>
<td>54/46</td>
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<tr>
<td>Lacrosse</td>
<td>94</td>
<td>52/42</td>
<td>55/45</td>
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<tr>
<td>Soccer</td>
<td>42</td>
<td>21/21</td>
<td>50/50</td>
</tr>
<tr>
<td>Hockey</td>
<td>40</td>
<td>40/0</td>
<td>100/0</td>
</tr>
<tr>
<td>Swimming</td>
<td>29</td>
<td>18/11</td>
<td>62/38</td>
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<tr>
<td>Basketball</td>
<td>29</td>
<td>15/14</td>
<td>52/48</td>
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<tr>
<td>Skiing</td>
<td>22</td>
<td>8/14</td>
<td>36/64</td>
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<tr>
<td>Tennis</td>
<td>20</td>
<td>10/10</td>
<td>50/50</td>
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<td>Golf</td>
<td>11</td>
<td>4/7</td>
<td>36/64</td>
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<tr>
<td>Gymnastics</td>
<td>14</td>
<td>0/14</td>
<td>0/100</td>
</tr>
<tr>
<td>Volleyball</td>
<td>11</td>
<td>0/11</td>
<td>0/100</td>
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<tr>
<td>Diving</td>
<td>5</td>
<td>2/3</td>
<td>40/60</td>
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Demographic data

Percent athletes with mTBI history

- Total: 35.6%
- Soccer
- Hockey
- Lacrosse
- Basketball
- Diving
- Skiing
- Volleyball
- Gymnastics
- Swimming
- Tennis

Number of acute mTBIs per sport

- Total: 29
- Diving: 11
- Basketball: 3
- Swimming: 3
- Hockey: 2
- Gynmastics: 4
- Soccer: 3
- Lacrosse: 2

Image of athletes playing lacrosse for Denver University.
Exosome biomarkers concussion

**Plasma Tau**

![Bar chart](chart1.png)

At baseline and after mTBI

**Exosomal cargo**

![Bar chart](chart2.png)

Recent mTBI <12 months

> than 12 months

Goetzl et al FASEB J. 2019
Future goals

- New technology diagnosis/treatment/prevention
- Include DU athletes 10, 20, 30 years after sports career
- Validate exosome biomarker technology
The perfect storm

- Memory loss
- Protein aggregation
- Nerve cell (neuronal) Loss
- Inflammation

What can we do?

- Early detection
- Exercise/diet
- Reduce stress
- Battle inflammation
- Reduce systemic conditions
Thank you!!

Join the Alzheimer’s Walk Pioneer Team!

Funding: Alzheimer’s Association, National Institutes on Aging, LeJeune Foundation, Global Down syndrome Foundation, University of Denver, Bright Focus Foundation
Together we can stop Alzheimer’s

Thank you for your Attention