Brain Power: How Science Is Revolutionizing Cognitive Health

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Cognitive health span

Normal cognition → Age-related cognitive impairment → Mild cognitive impairment (MCI) → Dementia

- Alzheimer’s disease
- Vascular dementia
- Lewy body dementia

Alzheimer’s brain pathology:

- Amyloid plaques
- Tau tangles
- Neuro-inflammation
Synapses and spines – critical but vulnerable elements
Multiple contributors to synaptic degeneration

Amyloid → Tau → Microglia dystrophy and inflammation → Synapse failure/ degeneration

- Resting
- Activated
- Dystrophic
Spine resilience associated with cognitive resilience

Preservation of spine density (DLPFC) associated with preserved cognition

Resilience mechanisms counteracting amyloid and tau effects are possible

Cognitive assessment – Stanford Memory Clinic

- History (dementia onset)
- Neurological exam
- Cognitive exam
- Brain MRI
- Blood: B12, thyroid, others

Recent and emerging biomarkers
- Amyloid and tau PET scans
- Cerebrospinal fluid amyloid and tau
- Blood amyloid and tau (p-tau217)
Amyloid and tau PET scans

Alzheimer's patient

Amyloid PET
Abnormal 15-20 yrs before symptoms

Normal age-matched control

Tau PET
Abnormal just before symptoms
Blood tests for Alzheimer’s detection

Is it Alzheimer’s? Blood tests may offer answers.

Potential applications:
• Patient with cognitive symptoms
• Normal cognition as a screening tool

Accuracy for brain amyloid detection ≥ 95%
Ongoing research in primary care settings
Impacts on care not known

Companies offering blood tests:
• C2N (with symptoms)
• Quest Diagnostics (with symptoms)
• Quanterix (with or without symptoms)
• ALZpath (with or without symptoms)

Source: Washington Post, 2022
Dementia risk factors

- Lack of physical activity
- Unhealthy diet
- Lack of social engagement/mission
- Lack of sleep
- Chronic stress
- Depression
- Hearing loss
- Smoking
- Excessive alcohol consumption
- Anticholinergic medications
- Hypertension
- Diabetes
- Hyperlipidemia
- Obesity
- Traumatic brain injury
- Low education
- Air pollution
- Genetics

Source: Livingston et al. – Lancet Commission Report 2020
Alzheimer’s genetics

Familial AD (< 2%) onset 40-50s
Sporadic AD (> 98%) onset > 65 yo  Sporadic: Many genes + environment

Gene with highest impact for sporadic: ApoE gene: ApoE2 / ApoE3 / ApoE4

No family hx:
Life-time risk 15%
- E4: 9%
+ E4: 30%

One parent with AD:
E3/E3: 30%
E3/E4: 45%
E4/E4: 60%
Possible implications of genetic testing

- Life planning
- Risk management
- Self-stress
- Relationships
- Insurance
- Treatment implications?

A4-5 study in E4 asymptomatic subjects is ongoing
Dementia prevention strategies

No prevention evidence for current drugs

Physical exercise  Diet  Cognitive exercise  Sleep
Exercise and risk of dementia

Step count study – UK Biobank Registry
- 78,430 adults aged 40-79
- Wrist accelerometer; 7-year follow up

3800 steps: 25% risk reduction
9800 steps: 50% risk reduction

Meta analysis – 29 published studies

Moderate-vigorous exercise

25% risk reduction < 15-year follow up

Examples of light exercise:
- Leisurely walking
- Gardening

Source: Poso Cruz et al. JAMA Neurology 2022 | Zhang et al. Aging Res Rev 2023
High physical activity – resilience to amyloid

Meta analysis: no effect of exercise on amyloid accumulation

Exercise as *cause* of reduced disease/aging mechanisms

- Improved memory function
- Decreased brain inflammation

Multi-omic testing
- Immune
- Metabolic
- Mitochondrial function

Sex-based differences in response

Source: De Miguel et al. Nature 2021; MoTrPAC Group Nature 2024
Mediterranean diet: longitudinal studies

20-40% risk reduction for dementia

Mediterranean diet: longitudinal studies

Alzheimer’s onset

Survivor function estimate

Diet compliance:
High
Medium
Low

UK Biobank cohort
60,000 subjects diet/dementia assessment:
23% risk reduction

Mediterranean diet associated with reduced Alzheimer’s pathology

Rush Memory and Aging Project – autopsy study; assessment of dietary scores to determine diet pattern

Source: Agarwal et al. Neurology 2023
Prospective Trial: MIND diet for prevention of cognitive decline in older persons

MIND diet: Mediterranean-DASH Intervention for Neurodegenerative Delay

604 subjects enrolled
- Normal cognition
- ≥ 65
- FH dementia
- Suboptimal MIND diet score
- BMI ≥ 35

3 years with coaching
- Control: mild caloric restriction
- MIND: mild caloric restriction + MIND

Source: Barnes et al. NEJM 2023
Ultra-processed food and dementia risk

Framingham Heart Study – Population-based cohort
Food frequency questionnaire, 2909 adults, mean follow up 14.4 years

Source: Wang et al. Alz and Dem 2023
Effects of sleep on Alzheimer’s risk

Evidence of amyloid clearance during sleep

Which is first?

Disrupted sleep vs early effects of pre-symptomatic AD

Source: Massey et al. Int J Mol Sci 2022
Health lifestyle associated with lower Alzheimer’s risk

Possible health factors
- MIND diet
- Cognitive activity
- Moderate/vigorous exercise ≥150 min/wk
- Not smoking
- Low/moderate alcohol consumption

Source: Dhana et al. BMJ 2022

Chicago Health and Aging Project
Population-based cohort study

Source: Dhana et al. BMJ 2022
Health lifestyle – Combination approaches

FINGER Study: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

Brain health – at your fingertips
Miia Kivipelto

Illustration: Martina Krona from the book "Brain Health" (Miia Kivipelto, Mai-Lis Hellénius)
FDA-approved Alzheimer’s treatments

Symptomatic therapy
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Memantine (Namenda)

Disease modifying therapy
(Slow progression, delay or prevent onset)
- amyloid reduction with amyloid antibody treatment
Supplements

Dementia-free survival probability

Source: Ghahremani et al. Alz Dem 2023
Metformin – no consistent effects on AD risk

Age ≥ 66

Early initiation of metformin monotherapy
n = 12,331

Incidence of dementia per 1000 person years
14.9

Delayed or no initiation of diabetes drugs
n = 22,369

Incidence of dementia per 1000 person years
14.2

New diabetes diagnosis
HbA1c ≥ 6.5% < 8.0%

5% higher risk
(no significant association)

No association between metformin initiation and incident dementia in older adults newly diagnosed with diabetes
**Lecanemab amyloid antibody – MCI/mild AD**

Phase 3 trial, 1795 participants – 18-month treatment

**Inclusion criteria**
- MCI or mild AD (MMSE 22-30)
- Positive amyloid test

**Exclusion/caution**
- Microhemorrhages, bleeding disorders
- Anticoagulation
- Potential stroke treatment

**Amyloid PET scan**
- Pre-Investigational Treatment
- Post-Investigational Treatment
- Less amyloid

**CDR-SB cognition score**
- 27% reduction in decline
- **Adjusted Mean Change from Baseline**
- **Visit (mo)**
  - Placebo
  - Lecanemab

**0.45 points – clinical significance?**

- Large clearance of amyloid but small clinical effects
- IV treatment, 20% ARIA; about 12% brain edema side effect
- Major need for more effective therapies

Source: Van Dyck et al. NEJM 2022
Developing a more powerful drug – addressing multiple mechanisms

Amyloid plaques  
Tau tangles  
Neuro-inflammation
Basic studies in cell cultures

Neurons from mice or humans

Culture media  Amyloid  Amyloid + C31

“Resilience in a dish”
LM11A-31 inhibits amyloid- and tau-induced spine loss

**Amyloid**
- Recombinant human Aβ oligomers

**Mouse hippocampal neurons 21DIV**

**Tau**
- Recombinant human tau oligomers

Source: Yang/Longo Lab SFN 2022 | Yang et al. – Sci Reports 2020
First human testing

FDA approval for ‘first in man’

Phase 1
First human testing
Phase 2a RCT safety and exploratory endpoint trial

Mild-moderate Alzheimer’s disease

PI: M. Windisch (PharmatrophiX-NeuroScios)
Co-PI: A. Börjesson-Hanson (Karolinska)

- Subjects enrolled in 18 sites in 5 countries
- 6-month treatment trial
Barcelona Alzheimer’s Treatment and Research Center
Placebo vs drug – FDG-PET
Shanks, Schmitz, Chen, Reiman

- [Placebo time1 > time2] FWE p < 0.05, k > 100
- Drug decreasing signal loss uncorrected p < 0.05, k > 100

Placebo brain degeneration areas

Drug protection areas

Suprathreshold Voxels

\[ p = 0.05 \]
\[ p = 0.01 \]

- Purple: Decline: drug < placebo
- Yellow: Decline: drug > placebo

Ratio hypothesis consistent/inconsistent p < 0.001

Source: Shanks et al Nature Medicine 2024
AD Prevention

Spinal fluid proteins change 10-20 years prior to cognition changes

In AD subjects with cognitive impairment, LM11A-31 normalized many of these proteins

Source: Johnson et al Nat Med 2023
Planned phase 2b/3 trial – 1600 subjects

U.S. and Europe

18-month blinded treatment period
Randomized 1:1

Placebo twice daily 800 subjects

LM11A-31 twice daily 800 subjects

Phase 2b

Phase 3

Biomarker analysis
(500 subjects reaching 6-mo treatment)

Biomarker and clinical analysis
(50% of subjects reaching 18-mo treatment)

Final efficacy analysis
• Clinical measures
• Biomarker measures

12-month open-label extension
All subjects on drug

LM11A-31 twice daily

Screen/enroll
MCI + mild AD subjects
Progress in Alzheimer’s/Neurodegeneration prevention and treatment

- Age-related neurodegenerative mechanisms
- Imaging and large-scale blood biomarkers
- Deep biology treatment and prevention approaches

Iqbal Farrukh and Asad Jamal Alzheimer’s Disease Research Center at Stanford
Thank you!