Let’s Focus on Prevention – International Research Projects and the Importance of Interdisciplinary Collaboration

Dementia and Neurodegeneration Ireland (DNNI)
30th November 2017

Prof Craig Ritchie
Centre for Dementia Prevention
Centre for Clinical Brain Sciences
University of Edinburgh

@cwrit42w
Disclosures

• I have recently sat on paid advisory boards for Merck, Pfizer, Eisai, Actinogen, Kyowa, Roche and Eli Lilly
Talk Summary

• The emerging reality of prevention
• International Collaboration – EPAD as exemplar
• Progress and next steps
Learning Objectives

• To understand the epidemiological and biological basis underpinning the optimism towards preventing dementia

• To recognise the value in globally aligned projects and partnerships

• How to collaborate and generate new knowledge from these projects
Alzheimer’s Dementia?
Alzheimer’s Disease?
Alzheimer’s Disease (Pathology/Biomarkers)
Alzheimer’s Dementia
(Pathology/Biomarkers)

- Amyloid Pathology
- Tau Pathology
- Cerebrovascular Changes
- α-synuclein
- Blood Brain Barrier Integrity
- Glial activation and inflammation
- Oxidative stress
- Mitochondrial dysfunction
- Synaptic dysfunction
- Metal dyshomeostasis
- Apoptosis
- Insulin resistance
- mTOR signalling
- β-HSD function
Different Profiles (Normal Ageing)

<table>
<thead>
<tr>
<th>Processes</th>
<th>40-50</th>
<th>50-60</th>
<th>60-70</th>
<th>70-80</th>
<th>80-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abeta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortl*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflm*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mito</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxdn*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>αsyn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Different Profiles (Alzheimer’s disease/dementia)

<table>
<thead>
<tr>
<th>Processes</th>
<th>40-50</th>
<th>50-60</th>
<th>60-70</th>
<th>70-80</th>
<th>80-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABeta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortl*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflm*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mito</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxdn*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>αsyn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specific interventions at a critical (early) time point on background of general approach to modification of risk...
Specific interventions at a critical (early) time point on background of general approach to modification of risk...

**Alzheimer’s Disease**

1. More specific pathology present
2. Biomarkers to diagnose
3. Asymptomatic
4. Modifiable stage for disease

<table>
<thead>
<tr>
<th>Processes</th>
<th>40-50</th>
<th>50-60</th>
<th>60-70</th>
<th>70-80</th>
<th>80-90</th>
</tr>
</thead>
</table>

**Different Profiles: Highlights Distinction**
Specific interventions at a critical (early) time point on background of general approach to modification of risk...
Risk factors

Across the lifespan

- APOE, other genes
- Familial aggregation

0
Adult life

20
Education

60
Cognitive and social activity

75
Brain reserve

Late-life

Risk factors

- Unhealthy diet
- Alcohol overuse
- Smoking
- Obesity
- Hypertension
- Dyslipidemia
- Diabetes
- Neuronal damage
- Vascular insults

Dementia

Protective factors

- Physical activity
- Cognitive reserve

Figure adapted from Sindi S, et al. F1000Prime Rep. 2015;7:50.
4-factor modelling

- RISKS
- DISEASE (Biomarkers)
- TIME (Changes in other 3 factors)
- DISEASE (Cognition et al)
The Vision

• That any given individual from birth onwards can be given an accurate ‘probability’ of a neurodegenerative ‘event’
  – Dementia
  – Cognitive decline
  – Biomarker change

• We will be making a ‘prognosis’ not a ‘diagnosis’
Secondary Prevention of Dementia

The three steps to achieve secondary prevention:

• **STEP 1: Identifying the ‘at risk’ person**
  – Risk factors (fixed and modifiable)
  – Cognitive profile (not ‘symptoms’)
  – Biomarker evidence of disease
  – Changes in these over time

Can we develop an accurate prediction algorithm/score?
Secondary Prevention of Dementia

The three steps to achieve secondary prevention:

• **STEP 2: Tailoring treatment**
  – Reducing modifiable risk factors
  – Enhancing resilience
  – Disease course modification through specific drug intervention(s)
Secondary Prevention of Dementia

The three steps to achieve secondary prevention:

**STEP 3: Measuring success**

– Individual’s probability status reduces

• Cognition improves
• Biomarkers normalise
• Risk of dementia decreases
Inadvertent Success?

A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II

F.E. Matthews\textsuperscript{1,2}, B.C.M. Stephan\textsuperscript{2}, L. Robinson\textsuperscript{2}, C. Jagger\textsuperscript{2}, L.E. Barnes\textsuperscript{3}, A. Arthur\textsuperscript{4}, & C. Brayne\textsuperscript{3}, Cognitive Function and Ageing Studies (CFAS) Collaboration\textsuperscript{8}

Figure 3 | Dementia incidence rates in men and women. (a) Incidence rate of dementia per 1,000 person years in men for CFAS I and CFAS II by age at baseline interview. (b) Incidence rate of dementia per 1,000 person years in women for CFAS I and CFAS II by age at baseline interview.
A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial


Table 2.
Risk of cognitive decline from baseline to 24 months

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention (n=554)</td>
<td>Control (n=565)</td>
</tr>
<tr>
<td>Overall cognitive decline</td>
<td>1 (reference)</td>
</tr>
</tbody>
</table>

| NTB total score | 1.23 (0.95–1.60) | 0.12 |
| Cognitive decline per domain | |
| NTB memory score | 1 (reference) | 1.29 (1.02–1.64) | 0.04 |
| NTB executive functioning score | 1 (reference) | 1.35 (1.06–1.71) | 0.01 |
| NTB processing speed score | |

In post-hoc analyses, we defined cognitive decline as decrease in NTB total score (overall decline) and NTB domain scores (decline per domain) between the assessments at baseline and at 24 months. Logistic regression analyses were used to assess risk of cognitive decline in the control group compared with the intervention group. Analyses are based on all participants with data available at both baseline and 24 months. NTB=neuropsychological test battery.
Ongoing clinical trials in Alzheimer disease (AD)

More than 200 drug development failures in the last 30 years
Schneider Mangialasche Kivipelto et al., JIM 2014

† Currently approved for AD treatment
Causation of Failure

- Disease Stage
- Restrictive Costs
  - Screen Failure
  - Non-adaptive design
- Accelerated or absent Phase 2
- Insensitive Outcomes

Conservatism
Solutions to Failure

EPAD

Disease Stage

Restrictive Costs
- Screen Failure
- Non-adaptive design

Sensitive Outcomes

Accelerated or absent Phase 2

www.ep-ad.org
SECONDARY PREVENTION

PRIMARY PREVENTION

Understand Biology

Deep and accurate clinical phenotyping

Develop and apply modeling strategies

Find Huge Numbers Participants

Communicate before, during & after ‘results’

Abnormal

- Aβ
- Tau-mediated neuronal injury and dysfunction
- Brain structure
- Memory
- Clinical function

Normal

Cognitively normal

MCI

Dementia

Clinical disease state

Biomarker magnitude

The Centre for Dementia Prevention
The EPAD Consortium

Academia

SMEs

Patient Organisation

Other industry

AMYPAD
UCL
GE
Piramal

www.ep-ad.org
EPAD Collaborating to prevent AD

Target identification and development

Trial ready cohorts and data

Clinical trials

www.ep-ad.org
How I Got Here
The EPAD Project Structure

**WP 5-8: Supporting Work Packages**
The EPAD Flow

EPAD trial “machine”

LOW probability, based on risk factors, disease evidence, symptoms

Enrichment Journey

Parent Cohorts
Virtual register
Research-Participants (RPs)
Identified by fingerprinting

Longitudinal Cohort Study-RPs phenotype & monitored

HIGH probability, based on risk factors, disease evidence, symptoms

Placebo arm
Shared across study

Proof of Concept Study
Single Sponsor

Study arm 1
Multiple Treatment arms

Study arm 2

Study arm 3

Continuous LCS recruitment

Adaptive design

www.ep-ad.org

https://www.youtube.com/watch?v=Ec5bei45ko4
Academic Progress to Date

Numerous Peer Reviewed Outputs
Supporting 32 EPAD Fellows
Two videos
1,732 Twitter Followers
EPAD Academy – Vision

To efficiently leverage EPAD resources to foster and develop academic research capacity and output in AD across Europe for maximum global impact.
3 initial pillars

People

Data

Output
EPAD Academy - Mission

To help create the next generation of AD researchers and thought leaders, by creating and facilitating opportunities for junior researchers’ career advancement.

To create fair and efficient procedures for EPAD and non-EPAD research teams to access EPAD data, samples and research participants with the objective of deepening the understanding of AD onset and progression, and the factors contributing to underlying processes.

To support the EPAD academic output in terms of scientific publications, participation in conferences and development of guidelines and studies, and to maximise their visibility and impact.
## Research Access Value

Data Access: Relatively straightforward (training and version control)
Participant Access: Most likely at a site/regional level

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>V500.0</td>
<td>V500.1</td>
<td>V500.2</td>
<td>V500.3</td>
<td>V500.4</td>
</tr>
<tr>
<td>1000</td>
<td>V1000.0</td>
<td>V1000.1</td>
<td>V1000.2</td>
<td>V1000.3</td>
<td>V1000.4</td>
</tr>
<tr>
<td>3000</td>
<td>V3000.0</td>
<td>V3000.1</td>
<td>V3000.2</td>
<td>V3000.3</td>
<td>V3000.4</td>
</tr>
</tbody>
</table>

*Exception is genetic analysis*
Summary

• **IMPORTANCE OF INTERNATIONAL COLLABORATION**
  – Knowledge, data and resource exchange
  – Operational know how
  – Internal learnings from a collaborative approach
  – Optimal resource use
  – Global perspective
Summary

• **CHALLENGES IN INTERNATIONAL COLLABORATION**
  
  – Leadership
    • Who is in charge?
    • What are the big questions – who agrees these and who delivers on them?
    • Cure by 2025 – really???
  
  – Sub-optimal resource use
  
  – Politics and politics
  
  – How do we share accolade, IP and academic output – what’s in it for me?
  
  – Continually feeding the early enthusiasm with victories
Summary

• SOLUTION

Clear Vision that always put the person with dementia or at risk of dementia in the heart of this vision, objectives and goals and make sure their voices are heard and listened to.
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115736, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.