Looking into the future of dementia care

Cath Mummery
Dementia Research Centre, ION
Aiguille du Grepon

2015  850,000
2021  1,000,000
2050  2,000,000

£23bn
Cost of dementia to the UK

£8bn
Value to the UK of the work done by family carers
Current position dementia

Major improvements in recent years
  – Public Awareness
  – Diagnosis
  – Post-diagnostic care models

BUT

• Conceptually, disease of old age - untreatable, inevitable decline
• Limited symptomatic therapies

Current model

• Community based, predominantly psychiatric-led care focusing on supportive and palliative factors
Recent focus

- **G7 dementia summit 2013 – global initiative**
  
  "Ambition – a cure or DMT by 2025”

  -> Significant increase in funding to reach that goal

  - MRC/ARUK/Alz Soc 250 million DRI UK – translational research
  - NIH budget tripled 500 m 2013 – 1.4 b 2017

- **UK Prime minister’s 2020 challenge on dementia**

- **WHO Ministerial Conference on Global action against dementia 2015**
Delaying onset of symptoms by 5 years would halve prevalence.
Modifiable Risk Factors

- Low education
- Smoking
- Hypertension
- Diabetes
- Obesity
- Depression/isolation
- Physical inactivity

1/3 of AD might be Due to these risk factors
Reduce by 20% -> reduction in prevalence by 15%

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costa Freda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Lancet 2017; 390: 2673–734
Patient selection
Treat early
Robust outcome measures
Diagnosis and outcome: Biomarkers

Enable pathology specific diagnosis at an early stage

- **CSF Markers**
  - Tau and phospho-tau
  - Aβ 1–42
  - Ratio Ab42-tau

- **Neuroimaging**
  - Structural
  - Functional
Treat at the right time

PET amyloid in ADAD carriers vs non-carriers
Treat at the right time – motivation for prevention studies

<table>
<thead>
<tr>
<th>Prevention studies</th>
<th>Newer Phase II/III trials</th>
<th>Completing/Completed Phase III trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Biomarker Magnitude

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

Clinical Disease Stage

Cognitively normal

MCI

Dementia

http://adni.loni.ucla.edu/about/biomarkers/
Immunotherapy in AD

Dominant approach in AD since 2007

Monoclonal antibodies - Target the amyloid and help the body to clear it from the system

- ADUCANUMAB (BIIB037) (Biogen)
- BAN2401 (Eisai)
- GANTANERUMAB (Roche)
- N3pG (Lilly) – phase II w BACE I
Aducanumab 3 yr amyloid
Slowing of decline on CDR

Global trials ongoing in all 4 to determine efficacy
ARIA-E

Dose related
Increased risk in apo e4 carriers
Usually mild and reversible
? Immune mediated flux of amyloid in/out of vessels

-> high levels of vigilance in trials
Antisense Oligonucleotides (ASOs)

DNA

Pre-mRNA

mRNA

ASO

Protein

Disease-Causing Protein, e.g. misfolded tau
Clinical Experience with ASOs

Well-tolerated with no safety concerns to date

- **FIH Phase I MAD study in mild AD**
  - Targeting MAPT mRNA to reduce tau protein expression by 50%
- **In set-up phase I in MAPT FTD**

- **Huntington’s disease**
  - Targeting HTT mRNA to reduce huntingtin protein expression
  - Ph 1/2a multiple-ascending dose, safety & tolerability study in 36 pts
  - COMPLETED NOV 2017; initial news positive re safety and target engagement

- **Spinal Muscular Atrophy (SMA) (nusinersen)**
  - Altering SMN2 mRNA splicing to increase functional survival motor neuron protein
Consistent Change in HINE Motor Milestone Scores Across Multiple Studies

Finkel RS. (2017). Primary Efficacy and Safety Results From the Phase 3 ENDEAR Study of Nusinersen in Infants Diagnosed With Spinal Muscular Atrophy (SMA). Presented at the 43rd Congress of the BPNA, Cambridge, UK.

Improvement for SPINRAZA Populations: NURTURE (232SM201) = interim efficacy set, CS3A = all dosed infants; ENDEAR (CS3B) = interim efficacy set. For each study, visits with n<5 are not plotted.

Maximum total milestone score = 26. Median (range) age at first dose: 19.0 (8–42) days. Median (range) age at enrolment: = 155 (36–210) days. Median (range) age at first dose: 175.0 (30–262) days.
Significant issues we need to prepare for now

**DIAGNOSIS**

Major change in concept –> treatable mid life disease

Capacity

Need to diagnose earlier - mild cognitive symptoms or asymptomatic

Reliant on biomarker assessment – markers of amyloid +/- tau

Access to investigations limited eg LP/PET

Future blood biomarkers?
• TREATMENT

• Selection Criteria:
  stratify risk

  echo criteria used in trials?

• Outcome measures – criteria for success?

• Safety monitoring - MRI access

• SERVICE DELIVERY

• Implications for UK NHS service for dementia

• Cost of service
The shape of the future?

- **Lifelong brain health/predementia service**
  - Primary prevention and risk reduction
  - Optimising resilience
  - Molecular based diagnostics and monitoring – better access
  - Complex therapeutic interventions
  
  PREVENTATIVE

- **Individualised treatment programme**
  - Pharmacological
  - Nonpharmacological

- **Multispecialty and level collaboration**
  - to identify at risk individuals
  - selection criteria for DMT
  - To ensure seamless transition through
    - prevention, diagnosis and therapeutics
    - Preclinical, prodromal, dementia – different skill sets
Thank you!