Dementia research: progress and challenges

University of Birmingham College of Medicine: Challenging Dementia
September 6th 2013

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Alzheimer’s Research UK

• Independent, dedicated biomedical research charity

• Remit covers causes, preventions, diagnoses and treatments of Alzheimer’s disease and other dementias

• UK based; UK and international partnerships

• We have spent >£40million to fund >400 projects in the UK

• Our currently-active grants portfolio is ~130 projects worth £23m

• Leading UK charity funder and second largest charity funder of dementia research in the world
Outline

1. Overview of dementia research and its importance
2. Progress and challenges – the science of dementia
3. Progress and challenges – doing and enabling research
An overview of dementia research: ‘cause, cure, care’

- Epidemiology
- Disease pathologies
- Clinical features
- Living with dementia

Contexts: Social, economic, healthcare/service delivery

Best practices in care

Diagnoses

New treatments/preventions
100 years of biomedical Alzheimer's disease research

1906: Dr Alois Alzheimer describes the case of Auguste D: Clinical symptoms and post-mortem pathology

Plaques (amyloid beta)  Tangles (abnormal tau)
| **1910-1960/70s** | ‘Senile dementia’ seen as a normal part of ageing  
‘Alzheimer’s disease’ seen as rare, ‘non-senile’ dementia |
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<td><strong>1970s</strong></td>
<td>Levels of the neurotransmitter acetylcholine discovered to fall sharply in people with AD</td>
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| **1980s**      | Diagnostic criteria established for AD  
Genetic links to familial early onset AD appear  
Tau protein identified in tangles; amyloid beta plaques characterised |
| **1990s**      | 1st drugs approved: tacrine and donepizil (Arciept)  
1st transgenic animal model of AD developed  
First significant genetic risk factor found in late onset AD |
| **2000 - 2013**| New class of drug approved: memantine  
Development of sophisticated neuroimaging  
More genetic risk factors found for late onset AD  
Many clinical trial failures; concerns about Pharma withdrawing |
Pathologies and causes of dementia-causing diseases

• Alzheimer's, Parkinson's disease, Lewy Body Dementia, Prion disease, Frontotemporal dementias:
  - damage to and death of nerve cells in response to the build up of particular proteins

• Vascular dementia
  - damage to and death of nerve cells in response to reduced blood flow

• Mixed pathologies common; neuroinflammation

• Complex genetic and environmental causes

• Long pre-clinical phase is also likely to apply across these brain disorders

• We don’t understand enough about these processes
  – difficult to follow in people and to model expt’llly
Clinical features

• ‘Brain and mind’
  – neurology, psychiatry, clinical psychology:
  – cognitive and behavioural & psychological symptoms of dementia
  – common co-morbidities: other chronic diseases of ageing, depression (can appear similar at early stages)

• More accurate and more sensitive tools are needed for:
  – ‘timely’ and accurate diagnosis
  – prognosis
  – detection/stratification of pathologies
  – evaluating new treatments; surrogate end points in trials

Tools: cognitive & behavioural/functional markers, biomarkers
Biomarkers of direct pathology (AD only):

• Cerebrospinal fluid:
  - Tau, Phosphorylated Tau
  - Soluble amyloid beta

• Blood-based biomarkers?

• Positron Emission Tomography:
  - Tau: PET ligands being developed
  - Amyloid beta: Pittsburgh Compound B, Florbetapir (18F)
Biomarkers and signatures of the functional and structural consequences of dementia pathologies

- Electrical activity, Network activity: qEEG, functional MRI

- Metabolism: Fludeoxyglucose (18F) PET

- Cerebrovascular integrity/function: functional MRI, transcranial Doppler ultrasound

- Cell loss, atrophy: volumetric MRI
Treatments for Alzheimer’s

• 4 licensed treatments help with cognitive symptoms for a limited time

• Room for improved cognitive enhancers

• Large research effort into developing ‘disease modifying’ treatments to:
  - delay the onset of dementia and/or
  - slow its progressive course

• Most ‘disease modifying’ AD drugs have been targeting amyloid – all have failed so far

• Concern about Pharma sector abandoning this area
A simplified model of cognitive decline in Alzheimer’s disease

Cognitive function DECREASING

Normal ageing
Mild Cognitive Impairment
Dementia CARE NEED

Time (years)

Adapted from Sperling et al (2011) Alzheimer’s & Dementia 280-292
Current symptomatic treatments for AD
‘Disease-modifying’ drugs

The previous six Phase 3 clinical studies in AD have sought this type of effect – but all have failed.
Trials of anti-amyloid drugs – wrong targets, wrong drugs, or tested too late?

Pre-symptomatic phase

- Amyloid β Accumulation (CSF/PET)
- Synaptic Dysfunction (FDG-PET/fMRI)
- Tau-mediated Neuronal injury (CSF)
- Brain structure (vMRI)

Cognitive function

Time (years)

Mild Cognitive Impairment

Dementia

Trials

Adapted from Sperling et al (2011) Alzheimer's & Dementia 280-292
Prevention in pre-symptomatic phase – The best chance of success against amyloid? Other approaches needed…

- Pre-symptomatic phase
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  - Brain structure (vMRI)

- Cognitive function
- Mild Cognitive Impairment
- Dementia

Intervention/treatment

Time (years)
A lifelong view of preventative risk reduction

Education, diet, exercise...

Pre-symptomatic phase
Living with dementia

Research is needed to inform care delivery and practice in care homes, hospitals, in the community:

• Ensuring that people with dementia are able to benefit from care and support services

• Management of pain or co-morbidities

• End of life care

• Effective ways of supporting carers
What is needed to ensure that dementia research can happen and deliver for patients in the short and long term?

• People

• **Resources, infrastructure:**
  equipment, access to patients, samples, reagents, tools

• Funding
• **People** with ideas, knowledge of the field, methodologies

• Established researchers and ‘new blood’

• The UK and worldwide dementia research communities are small.

• For every dementia researcher in the UK, 8 work on cancer.

• Few research clinicians in dementia – a worry for the future in an area where UK has some world leaders.

  Why – *dementia seen as difficult, poorly funded? Changes in medical training? Lack of opportunities, too few mentors?*
• Tackling dementia requires researchers from a wide variety of disciplines/backgrounds:

  *Medicine, biology, physics, chemistry* ……..

  *Academia and industry*

  who need to interact and collaborate

• Research which seeks to address the direct requirements of patients and carers needs their direct input

• *How to achieve this?*

  *Networks of researchers, conferences, funding calls for multi-disciplinary approaches*
Research into dementia has been underfunded in relation to the scale of the challenge it presents.

UK research funding by disease (2007-8): government and charity

Disease cost/research spend ratio (2007-8)

DEMENTIA 2010
The prevalence, economic cost and research funding of dementia compared with other major diseases
Funding avenues for UK dementia research:
Charity and statutory funders,
Publication analysis Sep 2011-Aug 2012

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<tr>
<th>Funding Agency</th>
<th>No. publications</th>
<th>Research Areas</th>
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<td>Economic and Social Research Council</td>
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<td>Care, Social</td>
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Thomson Reuters Web of Science database
The profile of dementia research in the UK has never been higher
The Prime Minister’s Challenge on Dementia (March 2012)

3 components:

1. Driving improvements in health and care
2. Creating Dementia Friendly Communities
3. Better research:
   • Overseen by ‘Research Champions Group
   • Further pledges of funding for dementia research – doubling to £66m by 2015.
   • Much investment in clinical research – projects, networks/infrastructure, cohorts

What will happen beyond 2015?
Some closing thoughts

• At all levels of healthcare provision, there is a vital need for a good understanding of:
  - dementia and the issues surrounding it
  - the particular needs of people with dementia and their carers

• The research effort against dementia needs:
  - Clinician scientists to be research leaders and to keep non-clinical researchers informed about the diseases they are working on
  - Non-research clinicians to be ‘research-friendly’

Dementia research funders would like to hear from you!
Thank you