Treatment for dementia

Learning from breakthroughs for other conditions

Jirka Taylor, Sonja Marjanovic, Ellen Nolte, Alex Pollitt and Jennifer Rubin
This report presents the findings of a study on medical breakthroughs in a series of conditions of ill health and the applicability of lessons from these breakthroughs for the field of dementia. The study has been funded by the UK Department of Health.

This document is divided into four parts. The first part presents the context and objectives of the study. The next part provides a synthesised overview of the main messages drawn from the case studies conducted for this study. The third part discusses the applicability of these messages for the context of dementia. The report concludes by suggesting a series of policy considerations with respect to potential future courses of action.

This report will be of interest to government, industry and civil society actors active or interested in the field of dementia. It will also be of interest to academic audiences interested in innovation policy.

RAND Europe is an independent not-for-profit policy research organisation that aims to improve policy and decisionmaking in the public interest through research and analysis. This report has been peer reviewed in accordance with RAND’s quality assurance standards. For more information about RAND Europe or this document, please contact Jirka Taylor (jirkat@rand.org) or Dr Sonja Marjanovic (smarjano@rand.org):

RAND Europe
Westbrook Centre, Milton Road
Cambridge CB4 1YG
United Kingdom
Tel. +44 1223 353 329
Executive summary

1) Study context and objectives

Over the past few decades, we have witnessed medical breakthroughs transform a range of diseases from being lethal to manageable conditions. Some examples include HIV, specific types of cancers and certain orphan diseases. In each case, successful breakthroughs have been enabled and supported by diverse social, institutional, scientific and technological factors.

Given the limited progress with dementia research and innovation efforts, the UK Department of Health (DH) commissioned RAND Europe to examine breakthroughs in the treatment of four conditions of ill health and to identify potentially transferable and adaptable lessons for the dementia context. This information could, in turn, help inform levers for supportive policy development.

In line with innovation systems thinking, our study built on a conceptualisation of breakthroughs as a process that is often gradual, and that rests on cumulative knowledge and repeated experimentation. Although sudden and unexpected advances can happen, they are more often an exception than the norm.

2) Study design and methods

The four conditions of ill health that this study focused on are HIV/AIDS, coronary heart disease, breast cancer and Parkinson’s disease. We recognise that there is no direct comparator to dementia (neither in terms of the nature of the scientific challenge, nor in terms of the wider social or financial context). Our selection of the four cases was influenced by a number of criteria. These include the existence of: (i) a clearly identifiable breakthrough; (ii) some shared features with dementia (e.g. extent to which aetiology is understood, existence of a lifestyle component); and (ii) some challenges held in common with dementia innovation efforts. We also aimed to achieve a balance in the types of challenges which our cases cover (e.g. scientific, regulatory, economic, social factors). An initial long-list of conditions was identified by the research team in discussion with health experts, and the final selection was determined in consultation with the Department of Health.

The study was primarily based on desk research and key informant interviews. For each case study, we first used desk research to identify the series of ‘events’ that contributed to a breakthrough, and to examine their nature. Examples include scientific advancements; regulatory approvals or new legislation, dedicated research funding or financing incentives; and lobbying and advocacy, among others. We aimed to capture the relationships among key events. We then conducted interviews with experts in each of the four disease areas to validate and enrich the insights from the desk research. Finally, we interviewed
leading experts in the field of dementia to discuss the perceived barriers to dementia treatment and the emerging insights from our case studies. We also discussed the implications of our case study findings for dementia research and innovation efforts.

It is important to note that it was outside the scope of our work to consider any counterfactuals. We focused on identifying factors which could potentially be useful for dementia breakthrough efforts and that were associated with breakthroughs in our case studies. We used triangulation across multiple informants, as well as desk research, to understand the contribution of specific events to the innovation process, as a proxy for exploring causation. We cannot claim that these factors would necessarily cause and ‘translate into’ a dementia breakthrough. Rather, we suggest that there are a number of areas for policy consideration worth reflecting on further, in light of our findings.

3) Key findings from the case studies of other health conditions

Our case studies identified four overarching factors which enabled breakthroughs in treatment. These were found to be associated with the innovation process across the four cases and included: (i) a commitment to tackling the science associated with a disease; (ii) an active and committed advocacy community; (iii) a flexible and responsive regulatory environment; and (iv) a coordinated strategic response and collaboration across sectors. The relative importance of each of these points varied across the conditions we examined. (Their applicability to dementia challenges is discussed in sections 4 and 5 of this executive summary.)

Commitment to tackling the science: The accumulation of scientific knowledge on various aspects of a disease was important across our cases. This included new basic science understandings (e.g. disease aetiology, nosology, pathophysiology), but also applied and clinical research on new compounds or drugs being considered for repurposing. Clinical research and experimentation often occurred in parallel to basic science activity (e.g. testing an existing drug in a new area, exploring the efficacy of a new compound). However, a relatively established basic science base was seen as a particularly important enabler for industry engagement (as was the existence of a clinical trials infrastructure which industry could feed compounds into). For example, understanding the fundamental science helped identify candidate molecules to use in drug development processes, as well as features of existing compounds which could potentially be useful for repurposing. Interdisciplinary collaboration and long-term sample studies were also central to addressing scientific bottlenecks across the research and innovation value chain.

An active and committed advocacy community: Our case studies highlighted the role that advocacy can play in prioritising a disease in policy agendas, ensuring political commitment and galvanising research and innovation investments. A strong social movement was sometimes associated with the ‘politicization’ of a disease. Advocacy efforts often included diverse stakeholder groups (especially so in the case of HIV). These spanned patient associations, celebrities, relatives, community leaders, the media, the scientific community, central and local government, NGOs and intergovernmental organisations (IGOs). They also tended to occur at multiple levels (locally, nationally, internationally). The personal leadership and the actions of high-profile individuals who could act as champions for a given cause were closely related to successful advocacy. This leadership took many forms – political, scientific or third sector–
based. Many philanthropic organisations active in disease research areas were linked to high-profile individuals.

A flexible and responsive regulatory environment: Collaborative and responsive regulatory authorities can play an important role in facilitating scientific breakthroughs and in incentivising the involvement of the pharmaceutical industry. The key regulatory provisions highlighted as important for research and innovation relate to accelerated review and drug approval processes. Some of the participants in this research emphasised that conducive regulatory interventions become important once there are tractable drug targets. However, our evidence suggests that paving the way for effective regulation can be done even when the scientific base is in the early stages of development. Some of the issues that are likely to be relevant can be foreseen a priori, and supportive regulation can also act as an incentive for innovation. In addition, some regulatory interventions (e.g. those associated with patent pools and drug repurposing efforts) might be important at earlier stages of breakthrough efforts than others (e.g. expedited approval). Regulation was part of a broader mix of factors that contributed towards scientific progress and to a breakthrough in treatment.

A coordinated strategic response and collaboration across sectors: Coordination is distinct from, but related to, collaboration. Our case studies highlight the importance of both coordination and collaboration for enabling breakthroughs in treatment. Coordination between national and international organisations at all levels, and across sectors and stakeholders, was important for the scale and pace of research and innovation activity. Collaboration between the public and private sectors was also crucial. Although overcoming research and innovation bottlenecks in the basic science underlying a disease was important for incentivizing the downstream engagement of industry, paving the way for this engagement could happen before the basic science was addressed. For example, a moral imperative associated with the scale of a public health burden, the visibility of a disease, and substantial public investment have encouraged pharmaceutical commitment in the past. The promise of supportive regulation also reduced barriers to industry engagement. Academic research institutions, clinical service providers and the pharmaceutical industry collaborated on diverse aspects of a breakthrough challenge and across various stages of innovation pathways. This included prompting and accelerating initial breakthroughs, sustaining innovation efforts over time (e.g. improved treatments, dealing with side effects, dosage issues), and ensuring access to treatments in post-breakthrough phases.

Applicability of case study insights to the dementia context

Our interviews with experts in the dementia field tested the applicability of insights from our case studies to the dementia context and led us to identify four key messages:

The lack of understanding of the ‘basic science’ behind dementia creates a major challenge for innovation, but supporting basic science should not occur at the expense of parallel efforts in applied and clinical research. Understanding the key biological mechanisms of dementia and its nosology (i.e. disease classification) was seen a key obstacle to achieving a medical breakthrough. The gap in basic science knowledge hampers prospects for identifying biomarkers for new drug development and challenges rational drug design models which have applied to other conditions, such as breakthroughs in
Parkinson’s disease. It also hampers industry prospects for selecting existing compounds to test for repurposing value. The challenge is compounded by the fact that many different types of dementia exist and that these may have different aetiologies. This implies there is a need for multiple and diverse treatments and combinations thereof. Evidence from both our case studies and our interviews with dementia experts highlight several potential strategies for tackling scientific bottlenecks. These include: (i) mobilisation of an interdisciplinary community of researchers, health and social care professionals who are committed to dementia research and are able to address the multiple facets of the disease; (ii) incentives to make dementia research more attractive to young scientists and/or to redirect the focus of established researchers towards a ‘critical mass’ of investigators; and (iii) dedicated funding committed by investors across the public, private and third sectors. In addition, and according to one key expert in the field, radical breakthroughs may also require explicit support of some experimentation with less scientifically validated potential solutions (e.g. through observational studies involving multiple treatments initially studied on a case-by-case basis).

Commitment to and support from an advocacy community is growing and could be prioritised further, potentially through a more nuanced advocacy approach. The case for enhanced advocacy in the dementia field is strong. A number of studies have highlighted the high economic burden associated with dementia and the fact that the number of people and families affected by dementia is considerable and is projected to rise substantially. Despite a recognised need, ensuring a stronger social movement around dementia is particularly challenging given the difficulties of engaging those affected by the disease, and it not being seen as an urgency in the same way that disease outbreaks are. There is also a need for the high level of political will to be sustained and matched by funding commitments. Evidence from both our case studies and our interviews with dementia experts identified a series of opportunities for strengthening advocacy for dementia research and innovation. These include: (i) establishing more coordinated efforts (nationally, regionally, internationally); (ii) recognising the diversity of goals in an advocacy agenda (e.g. highlighting the magnitude of the challenge, setting and sustaining dementia as a policy priority and communicating the economic case); (iii) considering who the most effective advocates might be and engaging champions of change; and (iv) improving the nature and degree of patient/carer involvement in dementia research.

There is also a need to better articulate what the aims of a treatment for dementia are and what would constitute a successful breakthrough. This could influence the direction of innovation efforts and of advocacy campaigns. A discrete diagnosis which recognises the diversity of diseases within dementia (as opposed to addressing dementia as one condition) may help with more targeted advocacy efforts. The innovation pathway for a solution that would alter the progression of disease might be different than that for innovation efforts targeted at improving the quality of care or preventing the onset of dementia. Similarly, the scope of what is meant by success merits attention. Efforts to find a breakthrough for one type of dementia (e.g. frontotemporal dementia) may have distinct features to efforts for breakthroughs in another dementia type (e.g. Alzheimer’s disease). While there are some commonalities, many of the scientific aspects of different types of dementias are unique (e.g., as suggested by a senior expert, those associated with risk factors or neurobiology). At present, the majority of investment support has been focused on Alzheimer’s disease (which is not surprising given its degree of
The scientific challenges related to breakthroughs for other types of dementia may call for more specific advocacy campaigns that rest on mobilising champions around a cause that is directly relevant to them.

**A flexible and responsive regulatory environment will be important to ensure innovation.** Although the ‘basic science’ behind dementia still needs to be tackled, foundations for supportive regulation can be put in place proactively so as to prevent delays in future translation efforts. Our interviewees highlighted several steps that could be worth considering. These include: (i) more staggered models of clinical trial design and such flexible arrangements as adaptive trials and conditional licensing; (ii) better streamlined clinical trial procedures (possibly drawing on lessons from the field of breast cancer, where combination therapy was successfully introduced); (iii) rapid review processes and fast tracking of approvals of promising drugs; and (iv) exploration of prospects for using existing infrastructure from other disease areas to facilitate R&D and trials in the dementia field. A responsive regulatory environment should be seen as an enabler of innovation efforts, within a wider policy mix. None of the interviewees suggested that legal and regulatory adjustments alone would be able to overcome fundamental challenges, such as the need for scientific advances and the availability of funding. Some regulatory interventions may be of more value once promising drug targets and compounds or combinations of compounds arise. However, other interventions – such as patent pools – may have been applicable even in the absence of immediate breakthroughs. Similarly, regulation around assistive technologies that could provide breakthroughs in the quality of care and quality of life for those afflicted with dementia are an important policy agenda.

**A coordinated strategic response and multi-sector, interdisciplinary collaboration are essential.** Overcoming the dementia challenge will strongly depend on successful cross-sectoral and cross-organisational collaboration and on a well-coordinated national and global effort. Initiatives such as the National Institute for Health Research’s (NIHR) Dementia Translational Research Collaboration and the Medical Research Council (MRC) Dementias Platform UK support this approach. Our evidence suggests that a national strategy, coordinating agency/agencies, and a monitoring and evaluation framework are central to well-coordinated national initiatives. There may be merit in mapping the ecosystem of dementia research activity, as a first step towards leveraging synergies between different initiatives and minimizing duplication of effort. In terms of the collaboration landscape, interviewees saw public–private partnerships (PPPs) as one important way of stimulating innovative solutions. However, a range of uncertainties associated with PPP design would need to be addressed. These relate to stakeholder incentives, network size, governance models, intellectual property (IP)/ownership arrangements, stakeholder influence on the direction of research, breadth of activity, legal arrangements and benefit distribution. The Structural Genomics Consortium model may offer relevant lessons for partnerships being considered in the dementia space, given its focus on pre-competitive R&D through a unique open access model, its scale and its multiple-stakeholder governance.

---

1 It is worth noting that charities represent an indispensable part of these efforts, as illustrated by the following two UK-based examples. Alzheimer’s Research UK recently launched a Drug Discovery Alliance, setting up new drug discovery centres (BBC News 2015). Similarly, Alzheimer’s Society UK has recently partnered with the Alzheimer’s Drug Discovery Foundation in a new research initiative (Alzheimer’s Drug Discovery Foundation n.d.).
Policy considerations and potential areas for action

Finally, we propose some ‘action areas’ for policy consideration (Table 1). These are based on the insights from this study and are informed further by our wider experience of the science, innovation and health policy issues raised in the report. These action areas aim to open discussion and encourage further constructive dialogue and exchange of ideas in order to make progress on the dementia challenge.

Table 1. Action areas for policy consideration

<table>
<thead>
<tr>
<th>Area for action</th>
<th>Policy consideration</th>
<th>Issues for policy dialogue and reflection</th>
</tr>
</thead>
</table>
| The science bottleneck and barriers to translation | The need for an interdisciplinary research community and associated consultation | 1. **Ensuring focus**: Would an interdisciplinary research community require redirecting the focus of existing researchers? Could they contribute ‘in parallel’ to dementia and other fields?  
2. **Understanding the competitive landscape**: What are the UK’s capacity strengths and gaps in dementia research?  
3. **Building capacity**: What should the training of future dementia researchers focus on (professional skills, disciplines)? How can a long-term career pipeline be supported?  
4. **Supporting diversity**: How can science policy support basic and clinical research without neglecting prevention, social care and health services research? What are some of the less ‘orthodox’ disciplines in which to support and strengthen capacity? Is there a need for a ‘high-risk’ fund to support out-of-the-box ideas and novel research and innovation approaches? |
| The need for a multi-pronged policy mix: support across the research and innovation value chain | 1. **A value chain approach and funding portfolios**: Basic science, applied research and clinical research occur in parallel as well as feeding into each other. What type of policy mix can support a dynamic research value chain? How can funders coordinate portfolios? Where do individual projects/programmes and larger national/international public–private collaborations sit in this value chain?  
2. **New compounds and new uses**: How can innovation policy support both new compound R&D efforts and drug repurposing efforts? For example, which incentives would address the risk–reward ratio that repurposing efforts entail (e.g. reputational and strategic implications of potential failure for industry)? What lessons can be drawn from existing repurposing initiatives? What is the public sector’s role in ensuring appropriate clinical trials infrastructure and supportive regulation for industry commitment to new compound R&D? |
| The role of collaborations | 1. **PPP models**: What lessons could we learn from public–private partnerships addressing similar challenges to those faced by the dementia field? Is there a role for an open-innovation PPP model to help support diversity and experimentation in pre-competitive dementia R&D? Are specialised PPPs needed for specific scientific challenges?  
2. **Facilitating collaboration**: Could such interventions as thematic networks, prize funds, staff exchanges and ‘mini-sabbaticals’ help facilitate interdisciplinary collaboration?  
3. **Coordination vs collaboration**: How can coordinating agencies support collaborative initiatives and minimise the unintended consequences of bureaucracy that can accompany coordination?  
4. **Monitoring and evaluation**: How can the UK evaluate and learn about the efficiency and effectiveness of its approach to the dementia challenge? |
## Treatment for dementia: Learning from breakthroughs for other conditions

### A strong and sustainable advocacy movement

Exploring the intricacies: Who is most feasible to engage and how?

1. **Champions**: Who are the individuals with the most credibility across the research, policy, industry, patient and public spheres? Do these differ across different types of dementia?

2. **The ‘borders’ of advocacy**: Should UK advocacy efforts target only UK individuals as champions, or is there merit in attempting to engage those outside the UK’s borders? Do potential new advocates need training on successful advocacy techniques?

3. **Individuals and institutions**: What types of contributions to the advocacy agenda could be made, respectively, by the wider public, individual champions (e.g. well-known individuals), and established charities?

4. **Social media**: What role could social media play in advocacy campaigns (e.g. widen the range of individuals who could contribute, help raise awareness, combat stigma, offer a peer support network)?

5. **Patient and public involvement**: How can patients/carers and the public best be involved in dementia research initiatives? Would engagement in research activity make them more likely to champion advocacy efforts? What can we learn from the PPI approaches being adopted by other initiatives?

### Paving the way for conducive regulation

Prioritisation and feasibility of various regulatory incentives

1. **Prioritising regulatory initiatives**: Would the DH and NIHR see value in a wider consultation on the relative importance of diverse regulatory enablers, and the trade-offs associated with each? (e.g. clinical trials governance processes, accelerated review, fast track approvals, conditional licensing?)

2. **Pooling IP**: How supportive and open to patent pools for dementia would industry be? What types of legal arrangements and commercial incentives would enable industry to jointly commit to searching for, identifying and sharing current compounds from other diseases?

3. **Open access approaches**: When and under what circumstances can open access approaches contribute to scientific advances?
Table of contents

Preface ......................................................................................................................................................iii
Executive summary ................................................................................................................................... v
Table of contents .................................................................................................................................... xiii
List of figures ........................................................................................................................................... xv
List of tables .......................................................................................................................................... xvii
List of boxes ........................................................................................................................................... xix
Acknowledgements ................................................................................................................................. xxii

1. Introduction ......................................................................................................................................... 1
   1.1. Objectives of this study ................................................................. 1
   1.2. Selection of case studies ................................................................. 2
   1.3. Methodology .................................................................................. 3

2. Medical breakthroughs in HIV/AIDS, coronary heart disease, breast cancer and Parkinson's disease: An overview of key observations from the case studies ............................................. 9
   2.1. Commitment to understanding the science associated with a condition is important ............ 9
   2.2. Commitment to and support from an advocacy community can establish and sustain
        momentum in innovation efforts .............................................................. 12
   2.3. A flexible and responsive regulatory environment is important for industry involvement .......... 15
   2.4. A coordinated strategic response and collaboration across sectors enables innovation .......... 16

3. Applicability of case study lessons to dementia................................................................................... 19
   3.1. Basic science should be supported, but not at the expense of applied and clinical research ...... 19
   3.2. Commitment to and support from the advocacy community is growing and could be
        prioritised further ..................................................................................... 21
   3.3. A flexible and responsive regulatory environment will be important to ensure innovation ...... 24
   3.4. A coordinated strategic response and multi-sector, interdisciplinary collaboration are
        essential ........................................................................................................ 27

4. On reflection: Potential areas for action and policy considerations ................................................. 31
   4.1. The science bottleneck and barriers to translation ................................................................... 31
4.2. The need for a strong and sustained social movement: Towards sustainable advocacy models........................................................................................................................................ 36
4.3. Paving the way for supportive regulation .................................................................................................................... 38
4.4. Concluding note .................................................................................................................................................... 38
List of references .................................................................................................................................................... 39
Appendix A: HIV/AIDS case study .......................................................................................................................... 57
Appendix B: Breast cancer case study ......................................................................................................................... 73
Appendix C: Coronary heart disease case study ....................................................................................................... 81
Appendix D: Parkinson’s disease case study .............................................................................................................. 93
Appendix E: Case study timelines ............................................................................................................................. 109
List of figures

Figure 1. Generic example of a case study timeline ................................................................. 6
Figure 2. HIV timeline ........................................................................................................... 109
Figure 3. Breast cancer timeline .......................................................................................... 114
Figure 4. Coronary heart disease timeline .......................................................................... 120
Figure 5. Parkinson’s disease timeline ............................................................................... 127
List of tables

Table 1. Action areas for policy consideration................................................................................................x
Table 2. Summary of considerations surrounding final case study selection .........................................................3
Table 3. Example questions for analysis of timeline factors ..................................................................................5
Table 4. Key insights on breakthrough dynamics in HIV .......................................................................................57
Table 5. Key scientific and technological trigger points of the HAART breakthrough.........................................59
Table 6. Key social influences on innovation in HIV ............................................................................................64
Table 7. Key political and economic drivers in innovation in HIV .................................................................66
Table 8. Key regulatory enablers in innovation in HIV .........................................................................................70
Table 9. Key insights on breakthrough dynamics in breast cancer .............................................................73
Table 10. Key scientific and technological trigger points of the tamoxifen breakthrough ...............................74
Table 11. Key social and political influences on innovation in breast cancer ....................................................77
Table 12. Key economic and regulatory drivers in innovation in breast cancer .................................................79
Table 13. Key insights on breakthrough dynamics in coronary heart disease .....................................................82
Table 14. Key scientific and technological trigger points of the statins breakthrough ........................................84
Table 15. Key social influences on innovation in coronary heart disease .............................................................88
Table 16. Key political and economic drivers in innovation in coronary heart disease ....................................90
Table 17. Key insights on breakthrough dynamics in Parkinson’s disease .........................................................93
Table 18. Key scientific and technological trigger points of the levodopa breakthrough ........................................94
Table 19. Key scientific and technological trigger points of the deep brain stimulation breakthrough .......95
Table 20. Key scientific and technological trigger points of the cell therapy breakthrough ............................95
Table 21. Key social influences on innovation in Parkinson’s disease ..............................................................101
Table 22. Key political and economic drivers in innovation in Parkinson’s disease ........................................104
List of boxes

Box 1. Ongoing initiatives in the field of dementia ................................................................. 22
Box 2. Ebola and the regulatory environment ........................................................................ 25
Box 3. Structural Genomics Consortium ................................................................................. 28
Box 4. Dementia Translational Research Collaboration ......................................................... 29
Box 5. Medical Research Council Dementias Platform UK ..................................................... 30
Box 6. Existing examples of repurposing platforms ................................................................ 33
Acknowledgements

The authors would like to thank the Department of Health for commissioning this research project and enabling the research team to conduct this study.

We would also like to thank Suzanne Clabby, Becky Farren, Zoltan Bozoky and Michael Brown of the Department of Health for their helpful and constructive feedback on earlier versions of this report and for their careful reading of interim materials and progress updates.

We are grateful to all those who contributed to the research efforts leading to this publication – Jacopo Bellasio, Veronika Horvath, Anne Kirtley, Catie Lichten, Calum MacLure, Joanna Miler, and Megan Sim.

In addition, we are indebted to the experts interviewed in the course of the study, who kindly shared their views with the research team and commented on the emerging findings.

We would also like to express our thanks to our quality assurance reviewers, Dr Jo Chataway and Dr Sue Guthrie, for their thoughtful comments and suggestions on earlier versions of the draft.

Last but not least, we would like to thank anonymous external peer reviewers for their comments and reflections on the draft final version of the research report. Their observations and suggestions have been taken into consideration by the research team and are reflected in the final text.
1. Introduction

The past few decades have seen a series of medical breakthroughs that enable the treatment, if not cure, of a range of diseases, transforming them from fatal to manageable conditions. Examples include certain cancers, HIV and some orphan diseases. More recently, new treatments have been developed for hepatitis C, with the potential to cure the disease (Pawlotsky 2014), and for melanoma (U.S. Food and Drug Administration [U.S. FDA] 2014a). In many of these cases, diverse factors have contributed to successes.

By contrast, progress on dementia has been limited (Specification for Research 2014). There are currently no treatments available that will cure or even alter the progressive course of dementia, despite ongoing research investigating new therapies and recommendations for supporting people with dementia (National Institute for Care and Health Excellence [NICE] 2006). Health and care systems have so far been able to offer only support for those affected by dementia and their caregivers and families. This has largely been through services aimed at early diagnosis; the optimisation of physical health, cognition, activity and well-being; the identification and treatment of behavioural and psychological symptoms; and the provision of information and long-term support to caregivers (World Health Organization [WHO] 2012).

Tracing the particular social, economic, political, regulatory and scientific contexts associated with specific diseases and their associated breakthroughs has the potential to identify factors which may be relevant for the dementia innovation context. For example, research into the history of Alzheimer’s disease and senile dementia has uncovered various economic, social and political factors that may have affected the understanding of their nosology (Amaducci et al. 1986).

1.1. Objectives of this study

Against this backdrop, the UK Department of Health (DH) commissioned RAND Europe to examine medical breakthroughs in selected areas of ill health and to explore the extent to which lessons from these areas may be transferable to dementia innovation efforts. More specifically, the study sought to identify and examine the range of factors that have enabled medical breakthroughs in those areas to occur and to help identify factors and actions which could support policy development in dementia.

The general understanding of the term breakthrough (particularly in medical fields) is a ‘sudden advance, especially in knowledge or technique’ (Merriam-Webster n.d.). In reality, the process of innovation is often gradual, and rests on cumulative knowledge and repeated experimentation. Although sudden and unexpected advances can happen (and although serendipity sometimes plays a role), they occur more as an exception than as a rule (de Rond & Thietart 2007; Runde & de Rond 2010).
The types of factors associated with breakthroughs can be diverse. For example, they may include economic drivers (such as investment in research, tax relief incentives, the use of patenting to attract investment, and sharing of investment risk), research collaborations and mechanisms of attracting research talent, infrastructure for the translation and commercialisation of academic research (e.g. incubators, technology transfer offices, enterprise offices), regulatory changes (such as fast tracking clinical trial requirements, facilitating testing of multiple-drug use) and infrastructure facilitating data-sharing for research purposes (e.g. genetic databanks). Other contextual factors such as public perceptions of a health condition and its prioritisation on the policy agenda, or adverse events following introduction of a treatment into the population, can also influence the prospects for a breakthrough and its success over time. The notion of a breakthrough, as we conceptualise it in this study, should take into account the processual and dynamic nature of science and innovation pathways. Ultimately, it is necessary to recognize that the processes surrounding breakthroughs are often messy and rarely linear in their trajectories.

The objective of this study was to inform dementia research and innovation efforts and to help identify levers for supportive policy development through lessons derived from breakthroughs observed in four other health research areas. In order to do so, the study aimed to:

- Analyse breakthroughs in the treatment of four selected conditions of ill health
- Consider a wide range of contextual factors associated with those breakthroughs
- Identify potentially transferable lessons for the dementia context

Our report is structured as follows. The remainder of this chapter explains the rationale behind the selection of the four case study areas covered by this study and includes a brief overview of the research team’s methodological approach. Chapter 2 presents the findings from the case studies, synthesised in the form of four overarching takeaway messages. Chapter 3 builds on these findings and discusses the applicability of lessons derived from the case studies to the context of dementia. We use a combination of evidence from case study desk research and interviews, as well as evidence from interviews with experts from the dementia field. Finally, Chapter 4 concludes by bringing together the main points from our research and wider experience in science and innovation policy, and discusses the implications for next steps and future courses of action in dementia innovation efforts.

1.2. Selection of case studies

To understand the conditions that give rise to breakthroughs and identify lessons which might be transferable to the dementia context, we selected four conditions of ill health to examine as case studies. In selecting these cases, we sought examples of conditions that (i) are associated with a clearly identifiable breakthrough, irrespective of its form, and (ii) share some common features with dementia, acknowledging that a direct comparator is not possible (more detail on the methods can be found in Section 1.3 below). We aimed to cover a range of features of interest to dementia innovation efforts, including scientific challenges, and also features of the wider context, relating to advocacy, regulatory, political and economic factors. We made an initial long-list of conditions through discussions with health experts, and the final selection was made in consultation with the Department of Health (DH). We aimed
to include a neurological condition in the case study set, but to not be limited by neurological disorders only, because there are few neurological conditions that share the same challenges as dementia and that have witnessed breakthroughs. Some of the challenges dementia innovation efforts face can benefit from learning about how such challenges were tackled in other disease areas.

The four conditions of ill health we selected are HIV/AIDS, coronary heart disease (CHD), breast cancer and Parkinson’s disease (PD). Treatments associated with these conditions can be viewed as different types of medical breakthroughs. For instance, a breakthrough may revolve around the development of a medical intervention that will treat (but not necessarily eliminate) the causal agent for a given condition. Antiviral treatment is an example of such a breakthrough. Other breakthroughs, such as antihypertensive treatment, may reduce the impact of a given condition by reducing the likelihood of complications occurring. A further example of a breakthrough is the discovery that an existing medical treatment used for one condition can be used to treat another condition.

Table 2 captures the main considerations employed for our selection of case studies, and how these apply to each of them.

### Table 2. Summary of considerations surrounding final case study selection

<table>
<thead>
<tr>
<th>Condition</th>
<th>Associated breakthrough</th>
<th>Features of interest</th>
</tr>
</thead>
</table>
| HIV/AIDS             | Highly active antiretroviral therapy (HAART) | • Inability to fully cure the condition  
• Associated with strong advocacy  
• Affects subset of population |
| Breast cancer        | Tamoxifen               | • Aetiology not fully understood  
• Affects subset of population  
• Associated with strong advocacy |
| Coronary heart disease | Statins                | • Strong lifestyle component to causation  
• Very strong commercial case |
| Parkinson’s disease  | Levodopa                | • Neurodegenerative condition with unclear aetiology  
• Inability to fully cure  
• Primarily affects older people |

### 1.3. Methodology

We carried out an evidence review and key informant interviews. The evidence review sought to identify, for each case study, the series of events that contributed to a given breakthrough and the key milestones that were involved in the development of a treatment. We classified these events into five broad categories: scientific/technological advancement, regulation or legislation-related, economic factors, social movements and advocacy, and political influences. We aimed to capture the temporal and, to the extent possible, causal relationships between events identified as ‘notable’. This classification aimed to inform an understanding of the breakthrough pathway, as well as cross-case comparisons. Examples of the types of factors we sought to identify within each specific category of factors are presented in
It is important to state up front the limitations of this approach. First and foremost, we are aware that any selection of case studies is open to discussion about their suitability, as it would be impossible to find an exact comparator to dementia (neither in terms of scientific and technological challenges, nor in terms of the wider social and financial investment context). As will be discussed in greater detail in the main body of the report, we also recognise that dementia is not a single disease but rather a term for an array of specific conditions, all of which might have different aetiology and could be an object of study in their own right. However, given the scope of the study, this level of analysis was not feasible. Furthermore, the nosology of dementia is still poorly understood, and that itself is a field in development. We selected a range of health conditions which – across them – covered some of the challenges to innovation and breakthroughs that we know apply to dementia, and which we hoped to learn from.

Our study also does not have a counterfactual. In other words, within the scope of this work, we could not ascertain whether a breakthrough would not have happened had it not been for the factors and events observed as important steps on the way to the breakthrough. Within each case study, we aimed to assess the contribution and impact of specific factors by triangulating insights from diverse experts involved with either the breakthrough itself in some way (e.g. as a member of the policy, scientific, drug development or advocacy stakeholders) or with the wider disease field. Broad agreement between interviewees for specific case studies lends confidence to our interpretations. However, we did not identify and examine within the scope of this work potential cases that might have featured similar factors and yet have not had any breakthroughs. Nor were we able to assess whether the breakthroughs we examined could have occurred in the absence of factors and events we identify as important. By looking only at successful cases with demonstrable breakthroughs, we build in an implicit assumption that at least some factors and elements of past drug development models are applicable to the context of dementia (another possibility may be that a completely new paradigm of drug development would need to be established). Despite these limitations, our approach begins to draw out diverse insights on how breakthroughs happened across diverse conditions, offering potentially useful lessons adaptable to the dementia context.

Finally, while many factors aside from levels of investment influence prospects for innovation and for breakthroughs, it is worth keeping in mind that levels of investment differ, both within the four disease areas and between them and dementia.

As a result of these limitations, we do not claim that a particular course of action will lead to breakthroughs, but rather that it appears to be associated with breakthroughs. In such instances, we believe there is enough evidence to build a persuasive case that the actions in question could help facilitate a breakthrough in the field of dementia, if adapted and tailored to the dementia context.
Table 3. Example questions for analysis of timeline factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Example questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Political</td>
<td>Evidence of political will/focus?</td>
</tr>
<tr>
<td></td>
<td>Any key intergovernmental agreements?</td>
</tr>
<tr>
<td></td>
<td>Any notable national position papers/white papers?</td>
</tr>
<tr>
<td>Social</td>
<td>Demographic factors (e.g. age group affected) implicated in the disease and influencing the breakthrough effort?</td>
</tr>
<tr>
<td></td>
<td>What was the public health context (prevalence of disease, degree of burden)?</td>
</tr>
<tr>
<td></td>
<td>Any notable cultural issues (e.g. stigma, advocacy, activism)?</td>
</tr>
<tr>
<td>Scientific and technological</td>
<td>Maturity of knowledge base?</td>
</tr>
<tr>
<td></td>
<td>Key research advances (including their associated publications)?</td>
</tr>
<tr>
<td></td>
<td>Key technology and/or product developments, trials, patents, etc.?</td>
</tr>
<tr>
<td></td>
<td>Was focus on mitigation/prevention, treatment or cure?</td>
</tr>
<tr>
<td></td>
<td>Was focus on basic or applied R&amp;D?</td>
</tr>
<tr>
<td>Economic</td>
<td>How were R&amp;D and associated innovative activity funded (e.g. public awareness and education campaigns)?</td>
</tr>
<tr>
<td></td>
<td>Where there particular favourable financial incentives?</td>
</tr>
<tr>
<td></td>
<td>What impact did the potential market (size, viability) have on the innovation environment?</td>
</tr>
<tr>
<td>Legal and regulatory</td>
<td>Key related policies/regulatory incentives (e.g. related to trials, reimbursement, provider coverage)?</td>
</tr>
<tr>
<td></td>
<td>Push and pull mechanisms for incentivising innovation?</td>
</tr>
<tr>
<td></td>
<td>Ethical issues related to the breakthrough pathway?</td>
</tr>
<tr>
<td></td>
<td>What type of organisational forms were involved (e.g. collaborations, PPPs, joint ventures (JVs), integrated research centres, other, private sector)?</td>
</tr>
<tr>
<td></td>
<td>What types of collaborations were involved?</td>
</tr>
<tr>
<td></td>
<td>What were the perceived key risks and enablers associated with the event/environment at the time?</td>
</tr>
</tbody>
</table>

We considered a broad evidence base to understand the key drivers behind breakthroughs in the four cases considered in the study. For each case study, we searched academic databases and grey literature for key publications on the breakthroughs in question and expanded the initial list of reviewed literature through hand searching the bibliographies of identified studies, where appropriate, and through recommendations of key informants we interviewed.

Based on the review of the published evidence, we developed a timeline for each of the case studies, depicting key events over time. Guided by a PESTLE analysis framework, we classified these according to the six categories of factors, as described above, and marked them accordingly with different colours. A generic version of the timeline is depicted below in Figure 1.

---

2 For a brief description, see, for instance, Chartered Institute of Personnel and Development (2013).
In a second step, we conducted interviews with experts in each of the four areas of ill health. These interviews enabled us to validate the emerging insights from the evidence reviews, the draft timelines and our understanding of the breakthrough in question. We further aimed to solicit views on the relative importance of individual contextual factors we identified and also to consider transferability of the contextual factors to dementia.

In a final step, we conducted a second set of interviews with experts in the field of dementia. During these second interviews, we first explored the perceived barriers to dementia treatment breakthroughs and potential solutions to overcome these barriers. We then discussed with each interviewee the extent to which emergent findings from the four case studies could be transferred to the dementia context. Finally, we also solicited their views on any other contextual factors that may be specific to the dementia field.

Study participants were identified through a combination of purposive and ‘snowball’ strategies using the published literature, official websites, the authors’ professional networks and recommendations from other study participants. We focused on a range of stakeholders representing academic researchers, clinicians, industry representatives and policy officers. Potential study participants were sent an invitation by email. This invitation included an explanation of the background to the study. Interviews explored broad themes along the lines of the categories of contextual factors presented above. In addition, experts in the field of dementia were invited to comment on the emerging messages formulated based on evidence review.

The majority of interviews were carried out by telephone, and all followed ethical principles of conducting research involving human subjects. This means that key informants were approached in their professional role only and that no sensitive personal information was collected. Data protection measures were put in place to maintain confidentiality of interview participants from whom consent for participation in the interview was obtained. Interviews were usually undertaken by two researchers to allow for reflexive questioning in response to any unanticipated emerging themes. Interviews were conducted in English; they lasted 45 to 60 minutes and were audio-recorded following consent to record being given. Notes taken throughout the interviews were subsequently verified and complemented using the interview recordings.

Analyses of interviews were informed by the key themes summarised in
Table 3, which served as guidance for the interviews. Additional emerging themes were also sought. We interviewed a total of 15 key informants representing different stakeholder groups. Eleven informants were selected based on their expertise in one of the case study areas, while four interviewees were selected based on their expertise in the field of dementia.

In addition to the evidence review and interviews, a member of the research team attended the Second Global Dementia Legacy Event, co-hosted by Canada and France and held in Ottawa in September 2014. He held a small number of informal discussions with participants on the sides of the main event’s programme. Also, members of the research team presented and discussed emerging findings at a Dementia Steering Group meeting in October 2014 in London and to the World Dementia Council, also in October 2014. Insights from all these events also contributed to the formulation and refining of the findings presented in this report.

The research team held three internal workshops to cross-analyse and synthesise findings from the case studies, formulate key observations and discuss implications for dementia innovation efforts. As part of this process, the researchers identified common enablers and barriers across the selected cases and reflected on unique factors.

The cross-analysis identified four overarching factors associated with case study breakthroughs. These are: (1) understanding of basic science, (2) advocacy, (3) regulatory environment, and (4) coordination and collaboration. Within each category, distinct enablers and barriers played out in a mix of similar and unique ways across the four cases.
There are a range of political, social, economic, scientific and technological, and regulatory/legal factors which contributed to innovation breakthroughs in the disease conditions we investigated. These can broadly be categorized into four overarching categories of enablers:

- Commitment to tackling the science: a good understanding of the underpinning science behind a particular condition and/or success with applied/clinical research efforts and experiments to repurpose existing drugs
- A strong commitment on the part of civil society
- A flexible and responsive regulatory environment
- A coordinated strategic response and strong partnership among academic institutions, the pharmaceutical industry, and health and social care service providers

We discuss these enablers in more detail below, highlighting how they applied across the case studies. As will be made clear, the relative importance of each of these points varied across the four conditions. We recognise that there may be alternative routes to breakthroughs and impact outside of the issues our case studies identified as being the most important. Overall, however, the key factors we identify represent those which evidence highlighted as having the strongest impact on the breakthroughs.

For a detailed narrative of each case study, please refer to the appendices.

2.1. Commitment to understanding the science associated with a condition is important

In all four of our case studies, notable scientific breakthroughs were preceded by an accumulation of scientific knowledge on various aspects of the given condition of ill health. This knowledge included not just new basic science understandings (e.g. disease aetiology, nosology, pathophysiology), but also new applied and clinical research insights (e.g. on clinical endpoints, safety and efficacy data from clinical trials of new compounds or of drugs which were being examined for repurposing).

The boundaries between basic and applied or clinical research can be blurred, and there is no single universally accepted definition of these terms. In this study, we build on the definitions presented in Wooding et al. (2011), where basic biomedical research is understood to ‘focus on normal or abnormal
function at the molecular, cellular, organ or whole body level’ and where clinical research focuses on ‘patients, better diagnostics or treatments and increasing quality of life’. We consider clinical trials of new compounds and trials of existing compounds for new purposes to be part of the latter category. This approach is in line with the definitions used in the Organisation for Economic Co-operation and Development (OECD) Frascati manual on the measurement of scientific and technological activities, which sees basic research as ‘experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view’ and applied research as ‘directed primarily towards a specific practical aim or objective’ (OECD 2002). While basic and clinical research are often considered as quite separate areas of work, there is evidence to suggest that not considering them in isolation from one another may have advantages for the translation of research into practice. For example, previous studies have shown that research carried out by basic researchers who have a clear clinical motivation or by researchers who work across different stages of the translation pathway tends to have a higher impact in terms of health and social benefits (Wooding et al. 2011).

In some cases, such as HIV and CHD, demystifying the basic science underlying the disease was particularly challenging and seen as a major breakthrough. For example, our interviewees emphasised the importance of understanding the (retro)viral cause of HIV for targeting clinical research efforts. In the field of CHD, the development of statins was enabled by a growing understanding that atherosclerosis was associated with elevated levels of one type of cholesterol, low-density lipoprotein (LDL), and low levels of another, high-density lipoprotein (HDL).

Interdisciplinary collaboration was central to addressing scientific bottlenecks, including efforts to understand the basic science of the diseases in question, an issue we return to in Section 2.4. Understanding the causal mechanisms associated with a disease typically involved insights from diverse fields, including epidemiology, pathophysiology, molecular biology, microbiology and immunology. In the case of HIV, in addition to a large and sustained public funding drive, a concerted effort to encourage researchers from different fields to direct their attention to AIDS research was important, and it helped create an interdisciplinary AIDS research community. A factor that enabled relatively swift fundraising and a rapid, coordinated research response was the ‘outbreak’ nature of the disease.

Interdisciplinary collaboration continued to be important in more downstream research efforts. In the case of breast cancer, the publically funded research infrastructure enabled interdisciplinary research on tamoxifen to continue during a period where there was little commercial interest on the part of its manufacturer, ICI Pharmaceuticals (today part of AstraZeneca). Academics and clinical researchers alike were able to make use of the research facilities which, in the words of one interviewee, ‘allowed a critical mass of people to be in the same place at the same time’.

With respect to the relationship between basic and clinical research, the fact that there was a simultaneous pursuit of both types of research across the four diseases we examined reinforces the importance of approaching breakthrough efforts with an awareness of the dynamic and non-linear nature of scientific discovery and innovation processes:

- Often, efforts to tackle the basic science bottleneck occurred in parallel with clinical research and experimentation. Given the scale of the scientific challenge and the degree of public
health burden, industry also committed to clinical research activity in parallel, such as testing compounds it had developed for other diseases for safety and efficacy in HIV (e.g. AZT). AZT was a previously failed cancer drug, but it was also a compound which industry had been testing for efficacy with other viruses.

- At the same time, basic science advancements gradually fed into other applied and downstream R&D efforts.\(^3\) For instance, the introduction of levodopa for the treatment of Parkinson’s disease built on evidence of the role of dopamine as a neurotransmitter in the brain (i.e. a basic understanding of molecular function), the relationships of PD to dopamine in the brain (Carlsson 1959; Carlsson et al. 1958) and the demonstration of striatal dopamine deficiency in PD (Ehringer & Hornykiewicz 1960).

In three instances (HIV, breast cancer, CHD), interviewees with experience of working in the pharmaceutical industry stressed the importance of an established overall science base and a growing body of knowledge for the industry’s ability to engage in innovation processes – or example, to identify candidate molecules to use in the drug development process.\(^4\) To illustrate, in the case of coronary heart disease, one interviewee explained that the discovery of the pacemaker enzyme caused pharmaceutical companies to start thinking about the possibility of developing a treatment that would target cholesterol biosynthesis, thus paving the way to the discovery of statins. In HIV/AIDS, the discovery of viral load as a marker for treatment effectiveness was also a key scientific development for pharmaceutical contributions to antiretroviral innovation.

The case studies highlighted a range of mechanisms which proved important for building a scientific base with which industry could engage and which industry found attractive. In addition to directed funding for an interdisciplinary research community, these mechanisms included long-term, large-sample studies and public funding of clinical trials infrastructure.

Long-term, large-sample studies enabled the research community to improve its understanding of how a population is affected by particular conditions. Two notable examples of studies that contributed to the understanding of coronary heart disease are the Framingham Heart Study (Castelli 1984) and the Seven Countries Study (Keys ed. 1970). The former started in the late 1940s, when it became apparent that heart disease was the biggest cause of mortality in the United States. It aimed to find new approaches to prevention. The latter ran in the late 1960s and showed that the incidence of heart attacks (in 15,000 middle-aged men followed for 10 years) was linearly proportional to the level of cholesterol in the blood.

Examples from the case studies also suggest that large-scale studies may improve the understanding of the science underlying a given condition even after a treatment breakthrough. In the context of breast cancer,

---

\(^3\) This is not to say that other applied and clinical research efforts – such as on repurposing existing compounds – were not going on in parallel.

\(^4\) Critical mass in research is hard to define (although it is comparatively easier to recognise its absence). One way to see conceive it is as the minimum capacity (e.g. staff, research units, equipment, money, management and governance systems and practices) that is needed to compete effectively at an international level in a given area of research. Needless to say, the concrete volume of what constitutes a ‘critical’ mass will vary from one area to another (Marjanovic et al. 2012).
the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) provided definitive evidence that tamoxifen saves lives in early breast cancer (EBCTCG 1998). Similarly, the Scandinavian Simvastatin Survival Study (4S) is generally credited with effectively ending the cholesterol debate following the introduction of statins (Scandinavian Simvastatin Survival Study Group 1994). In the context of Parkinson’s, the ELLDOPA trial attempted to answer a question on when the appropriate time to start L-dopa treatment is, although it did not produce any conclusive result (Fahn & Parkinson Study Group 2005).

Another way to help tackle the scientific bottlenecks and pave the road for industry engagement that was pointed out by our interviewees is public funding of clinical trials infrastructure. In the case of HIV, the National Institutes of Health (NIH) drove the effort to develop the clinical trials infrastructure needed for testing potential new treatments. Industry found this attractive, because it meant that the infrastructure would already be in place when they were ready to feed in novel, emerging compounds.

It is worth noting that advances in the scientific base underlying conditions of ill health can translate into breakthroughs in other ways than new drugs. The HIV/AIDS, breast cancer and Parkinson’s case studies illustrate breakthroughs which were achieved through ‘repurposing’ existing compounds and/or modifying the mode of their usage. However, across all four of our case studies, it was an improved understanding of the basic science that helped fuel a concerted scientific push to tackle the diseases and that helped identify features of existing compounds which could be useful for repurposing.

Finally, the development of the scientific base in general should not be understood only in the narrow sense of identifying suitable candidates for new drug development or achieving better outcomes through drug development. Using the example of coronary heart disease, one interviewee stressed that long before statins became available for widespread use, the roles of smoking and high blood pressure as etiological factors in cardiovascular disease had been well established. In fact, before statins were developed, intervention plans had already existed for tackling smoking and high blood pressure, and these interventions had resulted in significant decreases in deaths from heart disease. This example illustrates how targeted research and innovation processes occur in a wider historical and prior-knowledge context, which inputs into avenues of research that are pursued and into the framing of scientific enquiries. It also highlights the importance of interplay between basic, applied, biomedical and non-biomedical science.

2.2. Commitment to and support from an advocacy community can establish and sustain momentum in innovation efforts

Social advocacy, including grass roots activism, can have a strong influence on the scale and nature of research investments into a disease area. Advocacy can often influence the degree of political commitment

---

5 While the focus of our HIV/AIDS case study was on HAART, it is worth mentioning that AZT was originally developed as a cancer drug (Broder 2010).

6 Levodopa had been the object of study before its use as Parkinson’s treatment by Cotzias in 1967. Cotzias’s substantial contribution lay in the demonstration of how one could safely use high enough doses of L-dopa to be effective (Cotzias et al. 1967).
to helping improve outcomes for a disease. Our case studies highlighted that a high degree of political will can be a strong enabler of scientific advancement and innovation in challenging health fields, but that it is not necessarily a prerequisite for a breakthrough.

Of the four case studies covered in this project, the role of advocacy was perhaps best exemplified by the case of HIV. Advocacy efforts by gay activists and other allied interest groups, predominantly in the United States but also in some other countries, have been credited with being one of the driving forces of progress towards effective treatment options. Many of those living with the condition in the developed world were educated and had links and access to the media and politics, which helped to establish an effective advocacy community early on. Some of these advocates trained others, which grew the base of effective advocates for HIV, helping to develop a critical mass of civil society support.\(^7\) This was highlighted as a significant contribution by experts interviewed for this study, a point which is supported by evidence in the published literature (Kaiser Family Foundation n.d.). The social movement surrounding AIDS was so successful, in part, because:

- It made AIDS a political issue and spoke to the political priorities transcending public health concerns, such as outbreak management, the treatment of minorities (ethnic, sexual preferences), and anti-discrimination laws
- The sheer scale and scope of advocacy efforts was an enabling factor
- The social movement took place at multiple levels (national, state, international)
- Advocacy work has been sustained over time

Advocacy efforts played a role in our other case study diseases as well, although perhaps not always quite as prominently as in the case of HIV. Social activism in the area of breast cancer, particularly in the 1980s and 1990s, has been well documented and has been credited with contributing towards a range benefits, such as increased research funding, public awareness or psychological benefits to patients and their families (Anglin 1997). An analysis of the relationship of disease advocacy and its effect on US federal medical research priority setting (Best 2012) found breast cancer (together with HIV/AIDS) an example of an ‘unusually large and successful’ campaign.\(^8\) Indeed, the magnitude of the successes of HIV/AIDS and breast cancer advocacy efforts contributed to the mobilisation of activists in other diseases areas who were concerned about the disproportionate attention paid to a narrow group of conditions (Johnson 1998, cited in Dresser 1999).

\(^7\) An example from the UK context that may be applicable to the dementia context is the Long Term Conditions Alliance, a UK-based International Alliance of Patients’ Organisations, which provides training and support to other advocacy organisations.

\(^8\) This is not to suggest that there were no differences between HIV/AIDS and breast cancer. In absolute terms, in the 1980s HIV/AIDS funding was bigger than that of any other disease, prompting concerns of other areas being underfunded. For instance, a breast cancer researcher observed in 1984 that US spending per patient was about US$11,000 for HIV/AIDS, compared with only slightly in excess of US$400 for breast cancer (U.S. House of Representatives 1984). Of course, spending per patient is only one of many possible metrics. Mortality gained greater prominence in the 1990s as a method of commensurating individual disease areas (Best 2012).
In the field of coronary heart disease, according to one interviewee, ‘profession-led’ advocacy has played a role as well. The establishment of the physician- and social worker–led not-for-profit American Heart Association (AHA) (originally founded in 1915 as the Association for the Prevention and Relief of Heart Disease) preceded the discovery of statins by more than 60 years. During this period, AHA’s activities went hand in hand with major scientific discoveries. For example, reflecting the increasing focus on the association between diet and blood cholesterol, AHA issued endorsements of ‘prudent diet’ as early as the early 1960s (AHA 1961). In addition, one interviewee highlighted the importance of the American College of Cardiology, founded in the late 1940s, which served as a ‘powerful voice in advocacy for heart disease research, standards of care, practice guidelines, etc.’

It is worth emphasising that, across all case studies, albeit to a varying degree and with HIV being the strongest example, advocacy efforts often included a cross-section of groups and interests. These comprised patient groups and associations, celebrities, relatives, community leaders, media, the scientific community, NGOs and IGOs (e.g. WHO, UN/Joint UN Programme on HIV/AIDS [UNAIDS], G8, the World Trade Organization [WTO]). This provides support for the conclusion that a multi-pronged advocacy approach can be highly effective and that both national- and international-level advocacy campaigns are desirable, as is coordination between them.

Our case studies suggest that personal leadership and the actions of high-profile individuals who could act as champions for a given cause were closely related to successful advocacy. This leadership took many forms – political, scientific or third sector–based. To illustrate, several experts we interviewed for this study credited the political leadership of US President Nixon and his launch of the ‘war on cancer’ with helping to set up scientific infrastructure that would contribute to breakthroughs in breast cancer over the course of the subsequent decade. The passage of the National Cancer Act (NCA) in 1971 resulted in a substantial increase in investment in cancer research, by quadrupling the budget of the National Cancer Institute (NCI) over the next 6 years, in addition to other actions (Rettig 1978). One interviewee observed that this funding led to the creation of an infrastructure of cancer centres where laboratory scientists and clinicians had offices in the same place. One of these centres was the University of Wisconsin Clinical Cancer Center, where parts of the research into tamoxifen took place.9

The case of breast cancer also demonstrates the importance of individual champions in the research community. Arthur Walpole’s interest in tamoxifen while working for ICI Pharmaceuticals (currently AstraZeneca), followed by the work of Craig Jordan as principal investigator into tamoxifen as a cancer drug, have both been billed as instrumental in enabling the repurposing of the drug. Tamoxifen had become a failed contraceptive after the original manufacturer lost commercial interest in the drug (Jordan & Brodie 2007).

Lastly, one of our interviewees (with familiarity across the set of case studies) commented on the role of champions in galvanising civil society efforts. This interviewee observed that the most effective philanthropic organisations active in the field of medical research and care have frequently been associated

---

9 We also note the role of women’s groups in advocacy efforts in the area of breast cancer, though collected evidence suggests that their contribution became prominent in the aftermath of tamoxifen’s repurposing.
with high-profile individuals. The Michael J. Fox Foundation, active in the field of Parkinson’s, and the Susan G. Komen Foundation, active in the field of breast cancer, are among notable examples.

2.3. A flexible and responsive regulatory environment is important for industry involvement

A consistent message emerging from the four case studies is that active, collaborative and responsive regulatory authorities appear to play an effective role in facilitating scientific breakthroughs and in incentivising the involvement of the pharmaceutical industry. As such, they may contribute to accelerating the pace of innovation. It is possible to pave the way for effective regulation even when the scientific base is in early stages of development, as some of the issues that are likely to be relevant can be foreseen a priori.

In the case of HIV, the US drug regulator (U.S. Food and Drug Administration [FDA]) collaborated closely with pharmaceutical companies and adopted a set of regulations that enabled industry engagement with HIV/AIDS R&D. These included procedures for expedited reviews and accelerated drug approvals (U.S. FDA 2014b). For example, in 1987, the FDA created a drug class called ‘treatment investigational drugs’, which allowed for fast track approvals. The FDA also created a new ‘AA’ priority category in the classification of all new approval applications to ensure prompt review. Regulation also allowed for the importation of promising but unapproved drugs for treating people with life-threatening conditions, such as HIV. In 1989, the National Institute of Allergy and Infectious Diseases (NIAID) endorsed a ‘parallel track’ policy enabling access to experimental treatments for those who did not qualify for clinical trials. In 1992, the FDA introduced accelerated approval regulations, under which the clinical benefit of the drug in question, which has to be reasonably predicted, is fully confirmed through additional human studies that are completed after the drug has obtained marketing approval. This change enabled the agency to prioritise approval for drugs that were emerging as the most promising candidates, and it was seen as a managed risk. Regulation during the HIV epidemic was both proactive and responsive. For example, once the ACTG 5059 study showed the superiority of a new treatment (Gulick et al. 2004), global guidelines were changed within months. In addition, actions by national regulatory agencies were complemented by coordination at the international level. For instance, the 2001 WTO Doha Declaration and patent pools helped to create viable markets and to address issues of drug access and affordability (WTO 2001).

In the context of coronary heart disease, close collaboration between the pharmaceutical industry and regulators also contributed to research progress. The FDA cooperated with a drug developer and consented to a small scale, pre-approval trial use of lovastatin by a group of high-profile US clinicians, who were looking for treatment options with patients with severe hypercholesterolemia that was unresponsive to then-available agents. The trial was successful, with substantial decreases in LDL cholesterol and total cholesterol in the blood of the patients (Bilheimer et al. 1983; Illingworth & Sexton 1984). This helped the development of this class of drugs to continue during a period in which there were unconfirmed concerns about its links to cancer.10 One key informant stressed that in this particular

---

10 These concerns have never been substantiated (Vagelos 1991).
instance, Merck had a very good and open working relationship with the FDA, which helped elicit a constructive response on the part of the regulators.

Conversely, regulatory factors may also constitute a barrier to innovation. For example, one interviewee suggested that the European Union’s [EU] decision not to allow human cells to be patented may hamper the EU’s ability to attracting funding to take stem cell treatments to the clinical level. Although the impacts of the legislation are subject to much debate, according to this interviewee, the legislation may put European Parkinson’s disease research at a disadvantage relative to the rest of the world. In this instance, the EU’s position is a reflection of a particular ethical stance. Nevertheless, this serves to illustrate the potential for legal and regulatory factors to impede research efforts, given the wider competitive landscape of research and innovation and of prevailing governance models. In addition, the expert felt that EU guidelines on stem cell research are interpreted differently across different countries, which may make it difficult to conduct a consistent trial across Europe.

Ultimately, the evidence we collected for our case studies suggests that regulatory interventions should not be seen as a solution that would, on their own, lead to substantial breakthroughs. Rather, based on the collected evidence and expert views, regulatory factors appear to be a part of a mix of factors that may contribute towards and enable scientific and medical progress. None of the interviewees who explicitly commented on the relative importance of contextual factors suggested that legal and regulatory adjustments would be able to overcome such fundamental challenges as the need for scientific advances and the availability of funding. Similarly, the case studies and key informant interviews found no evidence of regulatory and legal challenges that would have been insurmountable in the process of innovation.

2.4. A coordinated strategic response and collaboration across sectors enables innovation

A consistent message that emerged from all four case studies and the interviews with key dementia experts is that coordination between national and international organisations at all levels, and across sectors, can support the pace and scale of research and innovation activity. Experts noted that coordination efforts may need to involve a range of stakeholders. These may include national-level health and finance ministries, IGOs, NGOs, patient associations and physician societies.

The HIV/AIDS case study highlighted the importance of both national- and international-level coordination. National coordinating agencies were important not only for governance and oversight of research, innovation, treatment and care initiatives, but also because their existence lent credibility to funders considering investments in a region. At the same time, national efforts needed to be compatible with and complementary to those of international initiatives, such as those led by the WHO, UNAIDS, WTO, Global Fund to Fight AIDS, Tuberculosis and Malaria (shortened here to Global Fund) and others. It is important to balance the benefits of coordinated, efficient resource distribution with the risks of excessive bureaucracy.

It is worth noting that public authorities do not always have to be the driving force in coordinating innovation. One key informant offered the example of deep brain stimulation for treatment of
Parkinson’s disease, the development and advancement of which was to a large extent supported by strong leadership by the manufacturer of the technology that could be used in such procedures.

Coordination is distinct from, but closely related to, collaboration. At the practical level, collaborative partnerships among the pharmaceutical industry, research and clinical institutions were important for various stages of innovation in our case studies. These partnerships made important impacts by:

- Prompting and accelerating initial breakthroughs
- Sustaining innovation efforts over time (e.g. improved treatments, dealing with side effects, dosage issues)
- Ensuring access to treatments in post-breakthrough phases

Across our case studies, collaboration between the public and private sectors was crucial. Although overcoming research and innovation bottlenecks in the basic science underlying a disease was important for incentivising the downstream engagement of industry, it was possible to pave the way for this engagement before the basic science was ‘cracked’. For example, a moral imperative associated with the scale of a public health burden or the visibility of a disease encouraged the pharmaceutical industry to commit to addressing it. In the case of HIV, a strong and sustained public funding commitment (i.e. publically funded research labs and clinical trial infrastructure) helped promote industry involvement and collaboration with academics. The promise of supportive regulation also reduced barriers to industry engagement. We elaborate on the theme of collaborative innovation models in Section 3.4.

Finally, partnerships have an important role even in the period following a notable breakthrough. For instance, one interviewee pointed out that the manufacturer of lovastatin (Merck) leveraged strong existing partnerships with clinicians in Scandinavian countries, established through previous collaboration on a different project. Several years after the approval of lovastatin, these partnerships were made use of to conduct a large-scale study on the effect of the drug on patients at risk of CHD. That study played an instrumental role in strengthening the evidence base and addressing existing reservations about the use of lovastatin that emerged following the drug’s introduction in the previous decade – effectively, in the words of one interviewee ‘starting the statin revolution’ (Scandinavian Simvastatin Survival Study Group 1994).

Partnerships also proved crucial in widening access to HIV/AIDS treatments and ensuring affordable pricing in developing countries in post-breakthrough phases. Regulations such as the UN-supported Medicines Patent Pool (MPP, established in 2011) also helped create licensing agreements with seven pharmaceutical companies to allow for reduced prices for HIV drugs.
3. Applicability of case study lessons to dementia

Based on an assessment of the applicability of findings from the four case studies to dementia breakthrough efforts, we identify four propositions:

- The lack of understanding of the ‘basic science’ behind dementia (and indeed behind different types of dementias) creates a major challenge for innovation. At the same time, there is a need to sustain applied and clinical research on potentially promising new treatments, the repurposing of existing compounds, and research into prevention and care.

- Commitment to and support from civil society is growing and should be prioritised further, perhaps with more bespoke advocacy campaigns.

- A flexible and responsive regulatory environment will be important to ensure innovation, and the foundations for effective regulation can be set proactively even in the absence of a tractable drug. Some areas of regulation may have more relevance in the near term (e.g. patent pool prospects), whereas others may have more relevance once the basic science is more advanced.

- A coordinated strategic response is essential.

We elaborate on these propositions in greater detail in this chapter. The observations presented here draw exclusively on evidence collected as part of our case studies and in interviews with key experts in the field of dementia.

3.1. Basic science should be supported, but not at the expense of applied and clinical research

Most key informants confirmed the importance of a robust knowledge base to help understand the key biological mechanisms underlying dementia and noted that the pharmaceutical industry currently does not appear to have sufficiently promising molecular targets to focus on. All four key informants with expertise in the field of dementia explicitly stated this lack of targets as the biggest obstacle to achieving a medical breakthrough in dementia. As one interviewee put it, past failed drugs did not fail because of regulatory or other reasons, but because, on the whole, they were simply targeting the wrong molecules. A perceived lack of highly promising compounds at present makes the risk–reward ratio unattractive for industry. As one interviewee stated, ‘if you have money to invest, you’d invest in cardio or cancer, not dementia, based on return on investment’.
The gaps in understanding of the basic science of dementia (including nosology) hamper the identification of adequate biomarkers needed for the development of new drugs and the potential repurposing of drugs developed for treatment of other diseases. They are also an obstacle to the early detection of symptoms that might help to develop support mechanisms early on.

In contrast with some of the conditions covered in the case studies, the challenge of basic science in dementia is compounded by the fact that there exist multiple types of dementia, all of which may have different aetiologies and may require different types of treatment and care solutions. Multiple approaches can be used to classify individual types of dementia. Classification efforts can be based on such aspects as symptom complexes or topographical involvement (Emre 2009) and have been evolving with historical shifts in the cultural and social context of dementia (George et al. 2011). Some forms of dementia are considered more common than others. For instance, the Alzheimer’s Association (n.d. a) estimates that Alzheimer’s disease accounts for approximately 60–80% of all dementia cases. This relatively high prevalence of Alzheimer’s may have contributed to the fact that the disease was long seen as interchangeable with dementia (Hachinski & Munoz 2000; Willis & Hakim 2013), with greater distinction between specific dementia conditions made more commonly only recently (George et al. 2011; Sosa-Ortiz et al. 2012). Even within individual types of dementia (e.g. Alzheimer’s disease) there exists substantial variation between subtypes (e.g. early onset, late onset disease) (Whitehouse 2013; Whitehouse & George 2008).

Therefore, given the heterogeneity of dementia, successful drug therapies may need different compounds, or combinations thereof, for different types of dementia as well as for different population groups. A first step towards tackling this challenge is to better understand disease classification and aetiology associated with dementia(s). Other possible strategies that our interviewees identified for tackling these challenges take the form of parallel efforts in the applied and clinical science spaces. One approach is the search for innovative clinical endpoints (which recognise the typically long gap between the onset of dementia and its diagnosis, and which aim to consider at-risk groups). Interviewees also highlighted the need to focus on stratifying patients in clinical studies to better reflect the multitude of dementia types. In addition, any policy mix may need to consider vehicles for supporting experimentation and high-risk experimental research approaches, perhaps, as suggested in a solicited expert opinion, including approaches which differ from conventional rational drug design paradigms.

There is also a need to articulate what a successful breakthrough would constitute – and to acknowledge that this could vary by stakeholder or by types of dementia disease. It may be that interventions that do not slow disease progression or help patients return to the starting point before the disease onset are regarded as successful as well (Rockwood et al. 2003). Example could be interventions that improve the

---

11 For a historical account of the evolving understanding of and attitude towards dementia, see, for example, Boller and Forbes (1998).

12 The interpretation of some features of dementia may also differ among researchers in the field. Portacolone et al. (2013) describe two contrasting perspectives – that of viewing dementia as a disease and that which interprets dementia as a part of the ageing process.
quality of life (e.g. assistive technologies) or quality of care. This strengthens the case for a multi-pronged approach.

In addition to the above, and based on lessons from case studies and complementary evidence from experts in the dementia field, several overarching strategies can be applied to try to address the dementia science bottleneck and to enhance a cumulative body of knowledge. These include:

- **An interdisciplinary community of researchers, health and social care professionals committed to dementia research.** This community would require careful coordination, as well as time and effort invested at the outset to establish a ‘common’ language between disciplines that do not necessarily have a history of working together (further issues concerning innovation coordination are discussed in greater detail in Section 3.4).

- **Incentives to make dementia research more attractive to young scientists and/or to redirect the focus of established researchers.** As one interviewee observed, if researchers self-select by continually proving themselves to be at the cutting edge of research, they would be able to act as champions for addressing the challenge of dementia and contribute to further raising its profile.

- **Dedicated funding for dementia research – across different disease types.** Substantial and sustainable funding is needed to make dementia research more attractive to young scientists and to potentially redirect or channel the focus of some of the more established research communities. Despite recent increases in the focus on dementia, funding available for dementia research remains limited, particularly taking into account the size of the challenge and its potential long-term costs. According to our interviewees, it is likely that multiple sectors and agencies will need to be involved in plugging the funding gap. This includes governments, the philanthropic/charitable sector, public–private partnerships (PPPs) and industry. Several interviewees stressed that an increasing share of the funding might need to be provided by philanthropic organisations, as public sources may not be available to the extent needed or may not be as flexible as is desirable. There may be scope for considering funding programmes to support particularly ‘non-orthodox’ and experimental research and innovation ideas.

### 3.2. Commitment to and support from the advocacy community is growing and could be prioritised further

The case for enhanced advocacy in the field of dementia is strong. A number of studies in Europe and, more recently, the United States have highlighted the high economic burden associated with dementia, therefore providing a strong ‘business case’ for advancing research (Hurd et al. 2013). The number of

---

13 For instance, one key informant opined that philanthropy is more amenable to enabling a quick pace of innovation, as opposed to government processes of filling out grant applications and waiting for approval, which delays progress.
people and families affected by dementia is considerable, and it is projected to rise substantially in the future, particularly in low and middle income countries (Wimo & Prince 2010). At the political level, there is currently an unprecedented amount of attention and a strong global push to advance research into dementia. A central role has been played by the United Kingdom and the British prime minister, which has manifested itself in an array of ongoing initiatives (see Box 1). Sustaining the current level of political commitment will be important, and social movements and advocacy groups as well as industry and regulatory stakeholders are likely to be in a position to influence political commitments.

It is worth recalling that, as discussed in the previous chapter, while the way in which social and political advocacy has translated into increased levels of financial support varies substantially across disease areas, positive advocacy effects have been well documented. For instance, a historical analysis of US federal research funding (Best 2012) found two types of effects. First, advocacy had a redistributive effect, in that disease areas with high levels of patient organisation had been able to secure increases in resource allocation. Second, advocacy efforts were found to have a systemic effect, in that they influenced the decisionmaking process by encouraging policymakers to think of patients as the primary beneficiaries of medical research, as opposed to research institutions.

**Box 1. Ongoing initiatives in the field of dementia**

An overview of recent events, summits and conferences lends support to the observation that the profile of dementia as a global political issue has been on the rise. For instance, in contrast with HIV/AIDS (having featured as a topic in G8 summits before, in 2000, 2003, 2004 and 2005) (AIDS.gov n.d.), until the G8 Summit on Dementia on 11 December 2013, there had been no significant global collaborative expression of concern over the growing threat of dementia. However, in 2014, the first meeting of the World Dementia Council was held in London (Department of Health 2014a), followed by the Global Dementia Legacy Events in London and Ottawa. To illustrate further, there have been several high-profile international interactions between the UK and China in China, and between the United Kingdom and the United States in London, on the issue of the dementia challenge. The fact that additional meetings were planned for 2014, in addition to the G8 Summit, which is to take place in the United States in February 2015 (Department of Health & Prime Minister’s Office 2013), further demonstrates the existing international political momentum.

Several recent UK-specific developments can serve as additional testimony to the current high profile of dementia as a political and policy issue across a wide range of stakeholders. First, the project to

---

14 These discrepancies continue even today. For instance, current NIH funding for HIV/AIDS research amounts to approximately US$3 billion, while FY2014 dementia funding was about US$700 million, of which Alzheimer’s disease alone was US$562 million, i.e. approximately 80% of the total (NIH 2015).

15 See, for instance, Foreign and Commonwealth Office (2014).

16 See, for instance, Department of Health (2014).
While the importance of advocacy and social activism was acknowledged by most of our interviewees, several reasons were noted why it may be more difficult to build a strong advocacy movement in the field of dementia, as compared with other disease areas (e.g. HIV, as discussed in Section 2.2).

- First, the population of people with dementia does not tend to be as organised as the population in the other studies cases we examined. Dementia is also more heterogeneous than some of the other case studies we investigated – especially in terms of the diversity of disease types it includes, and possibly also in terms of the diversity of population groups it affects. This can make a coordinated advocacy effort more challenging to secure.
- Second, the nature of the condition itself is a serious obstacle. This is especially true at moderate and advanced stages of the disease, at which point people are less able to campaign on their own behalf and to articulate their preferences. The limited amount of early diagnosis exacerbates this dynamic.
- Third, dementia is not one but many diseases, and more bespoke targeting of advocacy efforts might be needed to support more neglected areas within dementia itself (currently the majority of funding has gone towards Alzheimer’s disease), and to recognise some unique scientific challenges (e.g. related to risk factors).
- Several experts pointed out that it may be harder to generate a sense of urgency with dementia than was the case with some other diseases. The reasons for this were said to include: (i) dementia not being an infectious disease (and hence it is not treated as an outbreak in the way HIV was or Ebola currently is); (ii) people are expected to continue to live for a prolonged period of time after they have been diagnosed; (iii) there may be some discrimination (consciously or otherwise) associated with the fact that dementia generally affects older age groups (Genoe 2010).

17 It was eventually outvoted by antibiotics (Department for Business, Innovation & Skills 2014).
On a related note, while this was not necessarily an observation shared by interviewed experts, the literature highlights the issue of stigma associated with dementia, which may need to be overcome in order to further strengthen advocacy efforts.\(^{18}\)

Similarly, multiple challenges persist from the political point of view. The current high level of political will does not appear to be matched by the volume of dementia-focused funding (see discussion in Section 3.1).

In addition, several key informants expressed concerns about the sustainability of the current level of political focus on dementia, particularly in the absence of a significant breakthrough prospect in the near future. Sustaining this focus may be important in ensuring that dementia is treated as a priority in upcoming policy and research budget cycles.

To address these challenges, advocacy needs to be strengthened. Building on lessons from the case studies and on recommendations from interviewed experts, we have identified several opportunities for action that may help facilitate an effective advocacy agenda:

- There are possibilities for more coordinated efforts that take place at multiple levels (nationally, regionally and internationally).
- There is a need to recognise the multitude of goals of advocacy movements, including highlighting the magnitude of the challenge, placing and sustaining dementia as a policy priority and communicating the economic case for strategies to tackle the dementia challenge.
- There may be value in considering who the most effective advocates might be. To an extent, this process is already gaining momentum, exemplified by a growing focus on carers,\(^{19}\) but the process may need to gain stronger support in order to effect change.
- There is scope for improvements in the nature and degree of patient involvement in dementia research, particularly in clinical trials. Although this point was not made directly by our interviewees, from what we have found in this study it seems plausible that this could also have a reinforcing effect on the ability of patients to act as social advocates.
- It may also be worthwhile to identify and support champions of change with experience and credibility across stakeholder communities (research, professional practice, policy).

### 3.3. A flexible and responsive regulatory environment will be important to ensure innovation

Although the ‘basic science’ behind dementia still needs to be tackled, foundations for supportive regulation can be put in place proactively so as to prevent delays in future translation efforts. Confidence in a conducive regulatory landscape can also act as an incentive for innovation.

---

\(^{18}\) This is in line with an observation made by Best (2012), who found that ‘once patients were viewed as beneficiaries of medical research funding, stigmatized diseases were at a growing disadvantage.’ For literature on dementia and stigma, see, for instance, Batsch and Mittelman (2012), Benbow and Jolley (2012), and Mukadam and Livingston (2012).

\(^{19}\) See, for instance, Newbronner et al. (2013).
In that regard, our interviewees highlighted several steps that could be worth considering as part of a regulatory agenda for dementia, and especially for enabling industry engagement:

- In an effort to reduce the costs associated with clinical trials and to increase the chance of a successful outcome, it may be worth exploring departure from a traditional binary (yes/no) approach in favour of more staggered models of clinical trial design, which would enable piecemeal progress. Flexible arrangements, such as adaptive trials and conditional licensing, might be considered, and these could spur scientific efforts.
- Because of the likely need for combination therapy in treating dementia, standard clinical trial requirements may be very burdensome and lengthy. Streamlining the procedure, possibly drawing on lessons and approaches from the field of breast cancer, where combination therapy has been successfully introduced, may be a way to remove unnecessary barriers to new drug introduction.
- There may be scope to use existing infrastructure from other disease areas to facilitate R&D and possibly clinical trials in the field of dementia (while still also maintaining its original purpose). This would require identifying both the physical resources that are in place in some other disease areas and any spare capacity or scope for accessing them (e.g. from clinical research networks, laboratories, data systems infrastructure).

With respect to other legal and regulatory arrangements, prospects for rapid review processes and fast track approvals of promising drugs were considered particularly attractive, once prospects for a potential treatment become more apparent. Extending patent exclusivity protection was identified as potentially attractive for the pharmaceutical industry. But the implications of such regulation on downstream innovation would need to be considered because extending patents could have negative effects on encouraging further innovation through ‘blocking effects’ (i.e. through preventing freely available access to ‘prior art’ needed for R&D efforts and by impact on market availability and attractiveness).

Two interviewees highlighted that regulatory changes can be brought about by political and societal pressure stemming from the perceived seriousness of a given public health challenge. To illustrate this, they used the example of Ebola to flag the existing possibilities of a flexible regulatory environment (see Box 2). One key informant drew explicit parallels with dementia in that both can be relatively well predicted and modelled. The difference is that in the case of Ebola, its burden was made much clearer to key stakeholders and it has been treated as an outbreak.

**Box 2. Ebola and the regulatory environment**

The World Health Organization (WHO) has promoted a fast tracking of the development of drugs and vaccines to tackle Ebola. It announced that they were hopeful that they could ‘accomplish, within a matter of months, work that normally takes from two to four years, without compromising international standards for safety and efficacy’ (Sifferlin 2014). More significantly, a WHO panel which convened on the issue of Ebola concluded that ‘it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention’ given the severity and extent of the
Ultimately, however, it is worth reiterating that, based on observations from other disease areas and expert interviews, it appears that regulatory interventions are unlikely to lead to substantial breakthroughs on their own. This point is related to the fundamental challenge of gaps in the existing scientific base in the field of dementia and its current state of development.

Rather, regulation can be seen as part of a wider mix of policy interventions to encourage research and innovation investments, and to speed up research activity and translation into the clinic and the market. The fact that regulation and regulatory science are increasingly seen as part of the industrial and innovation policy mix can be evinced from existing regulatory strategic documents and related ongoing debates. As such, the presence of a responsive regulatory environment should be seen as an enabler of innovative efforts, while its absence can be understood as a barrier to the advancements of breakthroughs.

20 See, for instance, FDA (2011).
Some of the participants in this research emphasised that conducive regulatory interventions become important once there are tractable drug targets. However, our evidence suggests that paving the way for effective regulation can be done even when the scientific base is in early stages of development: some of the issues that are likely to be relevant can be foreseen a priori, and supportive regulation can also act as an incentive for innovation. In addition, some regulatory interventions (e.g. those associated with patent pools and drug repurposing efforts) might be more important at earlier stages of breakthrough effort than others (e.g. expedited review).

3.4. A coordinated strategic response and multi-sector, interdisciplinary collaboration are essential

Most experts who commented on this issue felt that our ability to overcome the dementia challenge will strongly depend on successful cross-sectoral and cross-organisational collaboration and on a well-coordinated national and global effort. In terms of coordination, our evidence suggests the importance of a national strategy, coordinating agencies, and a monitoring and evaluation framework. It could be important to try map the ecosystem of dementia research activity, as a first step towards leveraging synergies between different initiatives and minimizing duplication of effort.

In terms of the collaboration landscape, interviewees saw public–private partnerships as one important way of stimulating innovative solutions. However, a range of uncertainties associated with PPP design would need to be addressed. First, different stakeholders may have varying incentives guiding their activities that are not always compatible with each other. Reconciling these incentives may be a precondition for successful collaboration. Other uncertainties relate to governance models and issues such as intellectual property (IP)/ownership arrangements, influence on the direction of research, a broad or narrow focus, legal arrangements and benefit distribution, as well as the scale of inter-industry collaboration. According to our interviewees, agreeing on a set of principles that could streamline the preparation of legal contracts might help reduce the costs of collaborating. This simultaneously represents a coordination issue. One interviewee also stressed the importance of setting the legal parameters of the relationship between industry and clinicians, to ensure transparent allocation of resources and equitable distribution of benefits.

According to some of the people we spoke to, and in line with evidence collected through our desk research, the Structural Genomics Consortium (SGC) PPP model may offer relevant lessons for

21 For instance, besides aims to contribute to improved clinical/health outcomes through their research, the nature of academic research is such that researchers need to sustain their careers and research funding by publishing papers – though we note that funders are also increasingly pushing the importance of societal impact and that researchers are often now required to report on it. By contrast, industry is driven to a greater extent by commercial interests (returns on investment). There are also challenges to collaboration associated with benefit distribution and attributing value to the respective contributions of partners. For example, industry may be interested in tax breaks as an incentive for supporting and engaging with public-sector precompetitive research in dementia.

22 In fact, two industry representatives shared that the preparation of legal contracts requires substantial investment, to the tune of several person-months. This is not only costly for all parties involved, but can substantially delay the onset of collaborative efforts.
partnerships being considered in the dementia space, given its focus on pre-competitive R&D and its being a large scale global effort. The key features of the SGC model that could be relevant are summarized in Box 3.

**Box 3. Structural Genomics Consortium**

The Structural Genomics Consortium (SGC) was established in 2004 as a public–private, not-for-profit, open access initiative. The aim of this partnership is to accelerate the progress and productivity of pre-competitive structural biology research, through an open-innovation model. The SGC is funded by nine pharmaceutical companies and public sector funders from the UK and Canada. Its model has three distinguishing features:

1. All research outputs are publically available and IP restrictions on the use of research outputs are excluded until later phase clinical trials.
2. For a specific level of investment, the funders can influence the direction of SGC research, have members represented on the SGC Board and place their own scientists in SGC laboratories.
3. The model is a multi-funder effort, and it aims for long-term sustainability because long-termism would offer a degree of stability and certainty to the wider research agenda.

RAND Europe evaluated the SGC (Morgan Jones et al. 2014) and found that the following key aspects of its model contribute to successful function and performance:

- The opportunity for funders to influence the direction of research, including which potential drug targets to investigate. This is attractive, as it gives funders a level of control while at the same time de-risking emergent areas of research for which they have very little in-house expertise (by virtue of the open-innovation and open access model).
- Industry involvement brings considerable technical expertise and industrial management models, which contributes to the speed and efficiency with which research can be done. What seems to differentiate SGC research from much university-based research, and what is highly valued by investors, is that the studies are entirely reproducible.
- The model allows for a wide range of collaborations between multiple stakeholders to be established quickly and efficiently (e.g. no need for lengthy material transfer agreements). This includes collaborations between SGC scientists in two labs (one in Toronto and one in Oxford, 20 research groups within the labs overall) with collaborators across academia and industry. Coupled with the open access nature of the initiative, the breadth and number of collaborations influences the scale and productivity of research activity.
- The scale of the network – the number of organisations involved– is also attractive because it lends visibility to the research efforts. Participants liked being seen as part of a wider global effort and as having access to a global network.
Evidence from our interviews suggests that the United Kingdom may be particularly well positioned to assume a leadership role in dementia research as part of a wider, collaborative global effort. In addition to the strong political commitment to dementia, enablers of leadership in these areas were said to include high-quality academic institutions; well-developed infrastructure for social care; and the fact that the UK, in comparison with other countries, already collects good quality data on population health outcomes. Several examples of existing UK-based collaborative platforms may serve as examples; these are described in greater detail in Box 4 and Box 5 below.

### Box 4. Dementia Translational Research Collaboration

The National Institute for Health Research (NIHR) Dementia Translational Research Collaboration (TRC) was established by the UK government following the prime minister’s 2012 call for improved research and care in dementia (NIHR n.d.). The TRC is made up of four new NIHR Dementia Biomedical Research Units (BRU) and six NIHR Biomedical Research Centres (BRC) with dementia-related research themes (NIHR Office for Clinical Research Infrastructure n.d. b). The BRUs and BRCs are based in Cambridge, South London and Maudsley, Newcastle, University College London, Imperial, and Oxford (NIHR n.d.). The key aspects of the collaboration are as follows (NIHR n.d.):

- Its major focus is to improve the partnerships among academia, the National Health Service (NHS) and industry in order to tackle the development of new treatments in dementia.
- It has established work streams to develop shared resources and consistent experimental procedures to address the main questions in dementia research across the research and innovation pipeline, including early diagnosis, patient stratification, phase 1 and phase 2 experimental medicine and proof-of-concept trials.
- Its combined resources and technologies are infrastructure (including imaging capabilities and informatics expertise), tissue (including biobanks and brainbanks) and patients (including electronic medical records and patient recruitment support) (NIHR Office for Clinical Research Infrastructure n.d. a).

The TRC’s projects have thus far included a feasibility study for intensive phenotyping of early Alzheimer’s disease patients (NIHR n.d.), a first-in-man gene therapy trial for Parkinson’s disease,
Box 5. Medical Research Council Dementias Platform UK

The MRC Dementias Platform UK (DPUK) is a public–private partnership developed and led by the Medical Research Council (MRC) with support from the NIHR and other partners (NIHR n.d.). The DPUK was formed to address the prime minister’s 2012 ‘challenge on dementia’. The MRC has provided £12m funding over an initial period of 5 years, supplemented by a total of £4 million from six partner companies, which includes cash contributions and company resources (MRC 2014). The DPUK is directed by Dr. John Gallacher at the University of Cardiff, together with an executive team of investigators from seven universities (Cambridge, Edinburgh, Imperial College London, Oxford, Newcastle, University College London and Swansea). Industry partners include Araclon, MedImmune, GSK, Ixico, Janssen Research & Development in collaboration with Johnson & Johnson Innovation, and SomaLogic (MRC 2014).

The DPUK aims to accelerate progress in research and to develop knowledge leading to new drug treatments and other therapies that could prevent or delay the onset and progression of dementia. To do so, the DPUK is creating the world’s largest population study in dementia research by bringing together 2 million participants, aged 50 and over, from 22 existing study groups in the UK (MRC 2014). The DPUK uses a novel approach that considers the overall health of a person (examining the brain as well as the brain within the context of the whole body). The DPUK hopes to identify cognitive, genetic, physiological and imaging measures (biomarkers) to understand the risk factors and variable progression of dementia (MRC 2014).

The largest contributing study to DPUK’s big data initiative is the UK Biobank, which aims to collect brain, heart, blood vessel and bone scans from 100,000 people, making it the world’s most ambitious research imaging programme. Eventually, the UK Biobank hopes to collect a range of health data from 500,000 people (Davenport 2014).

We reflect and expand on the theme of collaboration, and what this means for future dementia policy and areas of action, in Chapter 4.
4. On reflection: Potential areas for action and policy considerations

The insights we obtained through the work presented in this report lead us to propose a number of areas for action. For some of these, the evidence base raises important questions related to prioritisation and implementation. In this concluding chapter, we further elaborate on these questions. We also draw on our wider experience of science, innovation and health policy issues to present additional options for consideration, as food for thought. As such, unlike the key messages discussed in the preceding chapters, the points below do not build exclusively on evidence collected in the course of this study, but take into account considerations from wider innovation policy areas. They do not represent concrete recommendations and should not be understood as definitive conclusions. Rather, they constitute policy considerations, which are presented with the aim to encourage further constructive dialogue and the exchange of ideas on ways forward in the dementia challenge.

4.1. The science bottleneck and barriers to translation

As discussed in Chapters 2 and 3, the need to address the science underlying dementia remains a major challenge. However, it is also important to enhance momentum with applied and clinical research efforts focused on identifying new clinical end points and on doing clinical trials of new compounds and drugs which could potentially be repurposed from other disease areas. There is also a range of scientific challenges associated specifically with translation of existing insights and research developments. For example, we have witnessed limited levels of success in moving scientific advancements and promising interventions that seem to work in animals into humans. Finally, our evidence and wider experience with science policy suggests that supporting health services research, implementation science and social care research are also important and should not be neglected.

A number of areas for policy consideration are suggested as a result of these observations. They include the roles of consultation, institutions and individuals as enablers of progress, as well as wider issues related to ways of managing risks and encouraging interdisciplinarity, diversity and experimentation. These points are elaborated on in the next three sections.

4.1.1. The need for interdisciplinarity

Our study made a case for the need to mobilise an interdisciplinary community of scientists and health and social care professionals, as well as other stakeholders (patient and public involvement groups,
industry, regulators), who would be committed to understanding the science of dementia from multiple perspectives. This resonates with the insights from RAND and other studies on research and innovation pathways, which traced how impacts were generated. For example, our studies on the benefits and economic returns from research in the cardiovascular and mental health fields (Wooding et al. 2011, 2013) found that the engagement of non-academic stakeholders (for example, regulators, funders, clinicians, patients and the media) was found to be important in the research translation process. This finding is supported by the wider innovation policy literature on the importance of university–industry–government relations in innovation processes (e.g. Leydesdorff & Etzkowitz 1998). Van Rijnsoever and Hessels (2011) examined factors that facilitate interdisciplinary collaboration and found that experience of working in firms or government organisations represents one enabler. They highlighted that interdisciplinary collaboration tends to occur more frequently in applied disciplines than in basic research.23

4.1.2. The role of consultation

How an interdisciplinary research and innovation community can be established and sustained merits further consideration. This issue raises a number of questions related to prioritisation and implementation. For example, there is a need to identify key research priorities and to engage individuals from the relevant disciplines, the health and social care professions, industry and patient representative groups in the process. To this end, it may be useful to reflect on the scope for a multi-stakeholder consultation on the key scientific challenges and funding priorities for dementia. Such a consultation could be led by such bodies as the DH, NIHR, MRC or Wellcome Trust and potentially facilitated by an independent institution active in dementia research and science policy. It could address a number of questions:

- Would establishing a dementia research community require redirecting the attention of existing researchers/scientists in some functional areas to dementia, or could researchers do work on dementia in parallel to their core current research activities?
- What are the capacity strengths and gaps in the UK dementia research landscape? What are the gaps in existing knowledge about dementia?
- In which areas do we need to focus the training of a future critical mass of researchers in the dementia field (in academia and in industry)?
- What are some of the less ‘orthodox’ disciplines that should be engaged in the dementia challenge? For example, computational models and advances in computer science may be relevant in understanding and modelling brain responses.
- What type of science policy mix could support basic science priorities while ensuring that they are carried out with a clinical focus and without neglecting the potential for impact from research in the prevention, social care and health services space?

23 Interestingly, they also found that female scientists are more likely to engage in interdisciplinary work. In addition to financial instruments for encouraging interdisciplinarity, van Rijnsoever and Hessels (2011) highlight the importance of a favourable reward structure for individual academic performance.
4.1.3. A multi-pronged policy-mix: The role of collaborations, individuals and institutions

As introduced earlier in this report, innovation and the search for breakthroughs are not linear processes. A multi-pronged approach to policy could focus on both research aimed at developing new drug candidates and the repurposing of existing compounds from other diseases simultaneously, and this may be a strategy worth exploring. This would still require incentivising industry, given the risk–reward considerations that repurposing efforts can entail (such as the reputational and strategic repercussions of potential failure of existing compounds in new areas). Stakeholders in dementia policy may wish to examine the incentives and governance models of existing repurposing initiatives and what lessons can be learnt from them for the dementia context. Box 6 below outlines selected examples of initiatives and platforms already active in the repurposing space.

Box 6. Existing examples of repurposing platforms

| Discovering New Therapeutic Uses for Existing Molecules (National Center for Advancing Translational Sciences n.d. a) | A programme launched by the NIH’s National Center for Advancing Translational Sciences to explore new ways to repurpose partially developed candidates for use in new indications. It invites academic investigators to apply for NIH funding to investigate the use of existing agents in a specific disease area. To date, 26 agents previously deprioritised for business reasons have been made available by five pharmaceutical companies. Industry will have the first option to license from the academic research partners any new intellectual property potentially resulting from the research, while retaining the protection stemming from any already existing patents (National Center for Advancing Translational Sciences n.d. b). In line with a point raised earlier in this report, the programme has developed standard template agreements for use by all parties in the process, with the aim to streamline and facilitate cross-sectoral and cross-organisational collaboration. |
| In parallel, in the UK, the MRC partnered in 2012 with AstraZeneca to give academic researchers access to 22 compounds, the development of which had been put on hold by the pharmaceutical company (MRC 2012). UK-based academic institutions can apply for MRC funding to investigate the possibility to use these compounds in different contexts. As for the NIH programme, the IP generated by the new research would belong to the academic institution, with AstraZeneca retaining any existing rights. In 2014, the model was expanded to include six more pharmaceutical companies, which have each committed a range of deprioritised molecules for the scheme (MRC 2014). |
| It should be stressed that the two initiatives described above are public-driven and are therefore of particular relevance for policy makers. However, as such they represent only one possible model of drug repurposing efforts. Other existing types are private-sector driven (e.g. Bayer Healthcare’s Common Mechanism Research and Pfizer’s Indications Discovery Unit) (Agres 2011) and not-for-profit driven (e.g. WIPO Re:Search consortium and the Johns Hopkins Clinical Compound Screening Initiative) (Allarakhia 2013). |
Identifying ways to engage industry in the development of new treatments for dementia is equally important. Although our interviews suggest that this will be easier to achieve once the more basic science of dementia is better understood, a proactive approach by public authorities may be needed to understand how pharmaceutical companies can best contribute and to ensure industry readiness to engage. This is another area where consultation with industry stakeholders may be beneficial.

Several considerations may be suggested for engaging industry. First, regulation and supportive clinical trials infrastructure (state-of-the-art facilities, access to patient populations, responsiveness to emerging science) are likely to be important. Second, drawing on insights from our wider work in science and innovation policy, thematic networks, prize funds and other interventions could help create a vibrant and sustainable dementia research landscape in the UK and globally. Further, public–private partnerships are at the core of a set of new life sciences policies in the UK (Chataway et al. 2012).

There is diversity in focus areas across different public–private collaborations – from more specialized initiatives to those with broader remits, that is, covering a range of activities across the biomedical R&D and healthcare sector value chain (e.g. research, diagnostics, drug development, collaboration with regulators, public engagement, and care delivery). Alongside diversity in focus areas there is a diversity in network size and structures. In some cases, the partnership arrangements are worked out at the outset, whereas in others the network structure is more emergent and evolving. As highlighted in our recent review of public–private partnerships in the personalized medicine space (Chataway et al. 2012), there are many different incentives for collaborating. For instance, through these partnerships, members may be better able to access funding, complementary skills, resources infrastructure and business support from the coordinating bodies. Other incentives for collaboration are the potential for coordination and avoiding duplication of effort, favourable commercial exploitation rights and the ability to influence the direction of pre-competitive research. Partnerships may also provide support for technology validation and coordination of efforts to influence policy.

Collaborations, such as the NIHR Dementia Translational Research Collaboration and the MRC Dementias Platform UK initiatives, are likely to be important for dementia innovation efforts.

There is also scope to consider open-innovation business models for public–private partnerships, such as that pursued by the Structural Genomics Consortium. It would be important to consider what role partnerships of this type might play in supporting and de-risking precompetitive R&D, as well as in encouraging experimentation and risk. IP arrangements, legal issues surrounding benefit distribution, and ways of determining the direction of research and coordinating research activity are all important factors to consider in these types of institutional arrangements.

In addition, interventions such as ‘mini-sabbaticals’, staff exchanges and visits may be a way of enabling researchers from diverse disciplines, including those who have not focused on dementia as their core research activity, to contribute interdisciplinary perspectives and out-of-the-box thinking to dementia research and innovation priorities. As discussed below, ensuring that these interactions can take place in person may be particularly important.

---

24 For a discussion of prizes see, for instance, Brutscher et al. (2009).
It is also important to keep the role of individuals as research and collaboration champions at the forefront of a multi-pronged approach to policy. Previous studies (Wooding et al. 2011) have explored the impacts that arise from biomedical and health research. By looking at the development of the work over a 10–20 year time period, they have identified a number of factors associated with the successful translation of research. These include the role of individuals who are able to work across boundaries (be they disciplinary boundaries or stages of the research translation process); the importance of individuals who are motivated by a clear patient need and who effectively champion research agendas and transition into clinical practice; the importance of personal interactions between researchers; and the role of non-academic stakeholders in research and the adoption of new ideas. These factors are described further below.

Working across boundaries

There is evidence from the mental health field that research carried out by researchers who work across boundaries has a greater impact in terms of both academic outcomes and wider societal benefits (Wooding et al. 2013). This was found to be true both for researchers working across different scientific disciplines and for researchers working at different stages of the research-to-practice continuum (for example, in both basic and applied science or also in the policy domain). This finding resonates with previous work carried out in the cardiovascular field, which demonstrated higher societal impact from clinical research in which the principal investigator showed clear evidence of thinking strategically about how the research findings could be translated (Wooding et al. 2011).

Outside the realm of health research, a broader body of management literature concerning the role of ‘boundary spanners’ exists, dating from the 1970s. The term was initially used to describe a role which connects organisations to their external environment, serving as a source of new knowledge regarding environmental contingencies and conditions. It has since been applied to biomedical and health research in relation to the brokering of relationships across networks and the facilitation of the transfer of knowledge across contexts (Swan et al. 2007). This more active conceptualisation of boundary spanning was demonstrated by, for example, Lander and Atkinson-Grosjean (2011), who showed the importance of collaboration between basic and applied research in a Canadian network of clinical scientists studying immunological disorders.

Individuals who champion research agendas or translation

In a series of cases looking at the history and development of interventions in mental health, the role of key individuals and groups has been highlighted in driving particular research agendas and advocating promising lines of treatment (Wooding et al. 2013). For example, the development of clozapine (the first of the ‘second-generation’ antipsychotics to be developed) was found to have been facilitated by a small number of advocates – including researchers and clinicians who saw benefits for their patients, a key industry representative who had championed the development of the drug, and patient advocates. The importance of committed individuals resonates with the wider innovation literature around such concepts as product champions and innovation gatekeepers (see, e.g. Howell & Higgins 1990). The motivation of these ‘champions’ to address a clearly identified clinical need, rather than to pursue curiosity-driven research, has also been suggested to be important (Wooding et al. 2011).
Personal interactions

While there is an extensive literature on the benefits of formal research collaboration (see, for example, Kraut et al.’s [1988] study of patterns of contact in communication in scientific research), it is more difficult to conceptualise the informal interactions which can help shape research (e.g. Katz & Martin 1997). It has, however, been suggested that conferences, visits and informal networks of researchers were important in moving forward the research agenda in the development of a number of mental health interventions (Wooding et al. 2013). This was particularly the case in the sharing of experience between researchers based in different countries.

In light of the need to consider how policy might support high-risk and experimental research, it could be helpful to examine institutional forms that could help identify and broker links between individuals and groups whose research activities may be relevant for dementia, whether or not they are working in a discipline that has an obvious link to dementia. In addition to considering the role of public–private partnerships in enabling collaboration and networking, it is worth considering the potential merits of an ‘information broker for dementia’ – a centralised scouting and brokerage agency – that could take stock of the current state of dementia research and ‘headhunt’ interesting ideas from non-traditional disciplines. This broker could also maintain oversight (and perhaps have a monitoring and evaluation [M&E] remit) of progress and share learning. Agencies of institutions of this type have been explored in global health and neglected disease contexts (Kettler & Marjanovic 2004). Such an agency would work within the context of a national strategy and M&E framework.

Finally, there may be lessons to learn from initiatives which focus specifically on high-risk R&D, such as the NIH high-risk/high-reward initiative or private sector efforts. One example of a private initiative is British Petroleum’s Venture Research Unit (1980–1990), which funded researchers who questioned current thinking and aimed to conduct transformative research. Although these models may not be directly transplantable to dementia, they may offer interesting ideas on how high-risk research can be pursued within a wider policy mix.

Laudel and Gläser (2014) also explore how research funding can support unconventional projects across disciplines. They identify the need for large and flexible budgets, long time horizons and risk-tolerant selection processes. Their findings resonate with the Structural Genomics Consortium’s funding approach, which has been shown to result in more diverse research portfolios and outputs than does traditional grant funding (Morgan Jones et al. 2014).

4.2. The need for a strong and sustained social movement: Towards sustainable advocacy models

Our case studies highlight the importance of advocacy in raising the profile of a disease area, mobilising investments and helping sustain research and innovation activity. As discussed in Chapter 3, multiple approaches to effective advocacy exist, but their relevance to dementia is varied. Dementia is also many diseases, which all may require tailored advocacy strategies and distinct advocates.
In this context, a number of policy issues and areas for action arise. These, in turn, prompt a number of questions about implementation that need to be tackled to establish a sustainable and vibrant dementia advocacy community. The questions are:

- **Who is it most feasible to engage? In particular,**
  - Which individuals have the most credibility across the research, policy, industry, patient and public spheres?
  - Should UK advocacy efforts target only UK individuals as champions, or is there merit in attempting to engage individuals from outside the UK as well?
  - Whereas patients with dementia are unlikely to drive advocacy campaigns, there may be scope to further enhance the involvement of individuals with early stage dementia or their family members, as well as well-known individuals who could champion the case.
  - Related to this, it may be worth considering what types of contributions to the advocacy agenda the wider public and well-known individual champions could make.

- **What is the best way to mobilise the engagement of advocates? In particular,**
  - What role could social media play in advocacy campaigns, in addition to more ‘orthodox’ media channels? Could it widen the range of individuals who could contribute to an advocacy effort and form an organising structure? Could it help raise awareness of the scale of the challenge and communicate a sense of urgency (given that dementia is not seen as an outbreak, like HIV was or Ebola is)? Social media may simultaneously offer a peer support network akin to that enabled by leading dementia charities and societies, and may help combat stigma by ‘normalising’ the topic.
  - How can patients and the public best be involved in dementia research initiatives, and would engagement in research activity make them more likely to champion advocacy efforts? Many NIHR initiatives are experimenting with novel ways of PPI involvement, and there may be lessons relevant to the dementia context emerging from initiatives such as the Collaboration for Leadership in Applied Health Research and Care (CLAHRC).
    - For example, the South West Peninsula CLAHRC pursued an engagement by design model, where patients and the public could nominate research questions and where they were trained to specify them in a research-friendly manner (Soper et al. 2013). Whereas this may be more readily applicable to health services research, it could potentially also identify new and experimental areas of more basic science research, for example, within the field of cognitive neuroscience.

- **It is also important to reflect on the role of stigma as a barrier to creating a vibrant advocacy community. In addition, many families who have gone through the experience of caring for individuals with dementia need time to recover from the experience before they are willing and able to channel their energy into an advocacy campaign.**
In this context, it may be that efforts to engage family members in dementia advocacy need to consider what other types of support (such as psychological support) these individuals may benefit from.

Tackling the barriers to a productive advocacy landscape is likely to require a concerted national effort to, first, identify the right individuals to involve and, second, explore incentives for their engagement. A multi-faceted approach which aims to involve both individuals and existing charities and societies is likely to be needed. It may also be worth examining how those who have most successfully championed the cause operate and whether there is value in sharing their knowledge, methods and experiences with a wider potential advocacy pool and thus help replicate their achievements. Such a ‘train the trainer’ style approach was applied in the case of HIV.

4.3. Paving the way for supportive regulation

Our case studies identified a number of regulatory issues which would need to be addressed in order to enhance industry commitment to dementia R&D. These range from push mechanisms that aim to create physical infrastructure conducive to industry involvement,25 to pull mechanisms focused on viable markets and rapid access to them and on new institutional arrangements to support innovation, potentially through public–private partnerships. The incentives that are seen as important by our interviewees include rapid review processes and accelerated approval mechanisms, as well as conditional licensing prospects and, potentially, patent extensions.

In terms of policy actions, the DH and the NIHR may wish to engage in a wider consultation on the relative importance of diverse regulatory enablers, and on the trade-offs associated with each. It could also be useful to bring industry stakeholders together to discuss whether such options as patent pools might be viable in the dementia context. Related considerations revolve around the types of legal arrangements and commercial incentives which would enable industry to jointly commit to searching for, identifying and sharing current compounds from other disease areas which may have value for the dementia context.

4.4. Concluding note

To conclude, this report presents a set of findings on breakthroughs in four areas and on how lessons learned from examining the contexts in which these breakthroughs occurred may be applicable to dementia. As much as this approach has identified areas of action that are likely to be important in addressing the dementia challenge, it also raises questions about implementing and prioritising the next steps to be taken. We hope that this study will provide a useful ‘living document’ and encourage further dialogue on how best to harness the opportunities which each of the areas for action that we have identified presents.

25 For example, ensuring that the requisite clinical trials infrastructure into which industry is to feed promising molecules is in place, reducing bureaucracy and the time within which trials could begin.


doi:10.1038/478441a

Cancer Research UK (homepage) (2014). As of 6 November 2014:

http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/cancerstats-key-facts-on-breast-cancer


Rand Europe


42


Medical Research Council (2014). Seven pharma companies offer up compounds to UK researchers news release]. As of 6 November 2014: http://www.mrc.ac.uk/news-events/news/seven-pharma-companies-offer-up-compounds-to-uk-researchers/


National Center for Advancing Translational Sciences (n.d.a). Discovering New Therapeutic Uses for Existing Molecules. As of 6 November 2014:


Appendix A: HIV/AIDS case study

The story of breakthroughs in Highly Active Antiretroviral Therapy (HAART)

Background and Context

Since the first reported case of AIDS in 1981, medical advances and innovation in HIV/AIDS treatment have transformed the disease from a fatal infection to a manageable chronic condition. Efforts to manage the disease have been targeted at prevention, treatment and a cure. Although there have been important developments before and after (e.g. AZT and other antiretroviral [ARV] treatments as prevention strategies), highly active antiretroviral therapy (HAART) is widely accepted as one of the biggest breakthroughs in the global fight against HIV/AIDS. Since its introduction in the mid-1990s, mortality rates have dropped dramatically (79% in the United States) (Augustyn et al. 2012) and the quality of life for people with AIDS has improved, although we have witnessed gradual increases in the number of people living with AIDS globally (estimates range from 31.4 to 35.9 million people at present [AVERT 2014]).

Key learning and messages

Table 4. Key insights on breakthrough dynamics in HIV

<table>
<thead>
<tr>
<th>Understanding the science and the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Understanding the basic science (disease causes, pathogenesis) was essential for any further breakthroughs related to efforts to identify drug targets and develop treatments.</td>
</tr>
<tr>
<td>2. Scientific progress was underpinned by the mobilisation of a global, interdisciplinary community of researchers, including both clinical and non-clinical specialists. Creating this community was an important milestone, as it required redirecting the attention of existing scientists towards HIV/AIDS, as well as continued training and capacity building over time.</td>
</tr>
</tbody>
</table>

A multi-stakeholder, interdisciplinary approach

| 3. Much of the early research advances took place in large government-funded research institutes and universities, with industry contributing compounds for testing and later stage clinical trials. Industry had a large role to play in the development of HAART treatments, bringing drug development skills and expertise. This was enabled by the enormity of the scientific challenge, the scale of disease burden, the moral imperative and the prospects of a viable market. A large public-funding push helped attract investment from industry in addition to the abovementioned incentives. Inter-industry collaboration supported by careful legal management helped identify markers of treatment effectiveness. |
| 4. Improved diagnostic capacities further enabled the increasing of investments into treatment R&D. |
| 5. AIDS treatment clinical trials were prospective, randomised and controlled, but not double-blinded. They were |
highly innovative in that they:

- Actively engaged patients in the R&D process. The user experience results were immensely valuable for industry, e.g. in determining dosing regimens and understanding side effects. AIDS research also left a lasting legacy in the governance context. For instance, the European Medicines Agency Committee on Proprietary Medicinal Products has patient representatives as an outcome of the experience with AIDS treatment clinical trials.

- The NIH established a clinical infrastructure into which the industry could feed novel compounds as they emerged. Establishing the infrastructure needed for requisite clinical trials underpinned innovation in treatments throughout the 1990s and 2000s (e.g. oversight groups, networks, protocols, legislation) and was received very favourably by the private sector.

6. The scale of the challenge drove inter-industry collaboration. With careful legal scrutiny, pharmaceutical company consortia formed to tackle the treatment challenge. These consortia were behind major breakthroughs, such as identifying viral load as a surrogate marker and pooling drugs to establish more effective treatment combinations.

7. Although work in the HIV domain was characterised by a high level of investment risk, the fact that the pipeline of the pharmaceutical industry provided ample resources in the same period enabled the engagement of pharmaceutical companies in the area.

The need for continued innovation

8. The clinical and commercial side effects of first-generation drugs, issues related to drug resistance, and cost considerations were drivers of continuous innovation and search for improved treatments.

9. Context emerged as an important factor: development of treatments had to account for the fact that the characteristics of the epidemic differed across countries, including such aspects as the groups of the population at risk and variants of the disease. This underlined the need for diversity in treatment innovations, as different groups of patients could have differential responses to the same treatment.

The role of a social movement

10. Social, grassroots activism had an extremely powerful influence on innovation in HIV/AIDS treatment. It exerted influence though pressure on political powers, regulators and industry. The movement contributed to a rapidly growing political will and focus on the disease as well as a favourable funding, commercial and regulatory environment.

11. The most influential advocates and organisations were able to train others on effective advocacy mechanisms, helping their movements to reach critical mass.

12. The social movement surrounding AIDS was successful due to multiple factors:

- It made AIDS a political issue and spoke to the political priorities transcending public health concerns, such as outbreak management, the treatment of minorities (ethnic, sexual preferences), and anti-discrimination laws.

- The sheer scale and scope of advocacy efforts was also an enabling factor: advocates were active at the state (US), national and international levels.

- The movement has been sustained through time.

13. In the United States, key advocates included patient groups and associations, celebrities, relatives of those affected by AIDS, as well as influential community leaders. The media and the scientific community also played an important role.

14. Internationally, intergovernmental organisations (e.g. WHO, UN/UNAIDS, G8, WTO) were key actors of awareness raising and of focalising commitments from the global political community as well as academia, the NGO sector and industry.

15. In the UK the centralised nature of the national health system facilitated lobbying efforts towards government more so than in the United States. However, in the United States more funds were available.

16. Key individuals with experience and credibility across stakeholder communities (including the communities in research, professional practice, policy and regulation) acted as champions for coordinated, strategic responses and as central nodes in a network.

The importance of a coordinated and strategic response

17. The 'outbreak' nature of the disease helped ensure a coordinated and strategic response, and helped
overcome any potential barriers to rapidly mobilising public funding as well as private sector engagement for research. This was particularly the case in the United States, and to a more limited extent also internationally.

18. It also contributed to an integrated approach, which included simultaneously:

- Targeting research and innovation in the treatment space primarily, but also prevention and education
- Targeting health systems and strengthening services to ensure accessibility and affordability of treatments.

19. A strategic response helped with efficient coordination between national and international organisations at all levels (e.g. national-level health and finance ministries, IGOs, NGOs, patient associations, physician societies). UNAIDS recommended that every country should have a central coordinating agency, a national AIDS strategic plan, and an M&E framework. Having a national coordinating agency also ensured that international funding agencies had confidence that the money would be appropriately allocated in-country.

Regulatory and legislative scope and efficiency

20. Shortened timelines in access to patients represented an important incentive for the pharmaceutical industry. Rapid response of regulation to new scientific developments was key in making innovations in treatment quickly accessible to patients, including:

- Regulation to create viable markets (WTO Doha Declaration, patent pools)
- Expedited /fast approval
- Rapid review processes

21. Visible, large public investment and regulatory commitments to HIV treatment were also important to incentivise industry investment in R&D in turn. Public investment into areas that were attractive for industry (e.g. clinical trials infrastructure) were also important in this context.

22. Anti-discrimination policies were important in reducing stigma related to the disease.

Other

23. Support for collaborative organisational forms (e.g. pharmaceutical consortia with careful legal scrutiny, joint international initiatives bringing together different stakeholders, International AIDS Vaccine Initiative [IAVI]) was important for bringing together public and private sector strengths and resources. However, official PPPs as an organisational form were more present in efforts for vaccine development than in HAART innovation efforts.

In this case study, we examine the diverse contextual factors which have enabled innovation in HIV/AIDS disease management, with a specific focus on the HAART breakthrough. We are interested in the confluence of scientific and technological, social, political, economic (funding-related), regulatory and legal drivers of innovation, how bottlenecks were overcome, the key associated actors and major events, and potential implications for other innovation efforts and disease areas.

Table 5 below highlights key learning points. The subsequent section discusses developments and the relationships and reasoning behind them in more detail. This is followed by a section that identifies some implications and questions relevant for the dementia context and for dementia innovation policy. In places, direct quotes from interviewees are presented, without any attribution, as agreed on with the interviewed experts. These quotes are set in italics.

Table 5. Key scientific and technological trigger points of the HAART breakthrough

<table>
<thead>
<tr>
<th>Scientific and technological advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HIV identified as the cause of disease, 1984</td>
</tr>
<tr>
<td>- Antiretroviral drug zidovudine/azidothymidine (AZT) discovered, 1986</td>
</tr>
<tr>
<td>- Supportive clinical trials infrastructure established, key milestones in late 1980s to mid-1990s</td>
</tr>
</tbody>
</table>
Highly active antiretroviral therapy (HAART) discovered
  - First clinical trial of multi-drug therapy, 1992
  - First protease inhibitor approved by the FDA, 1995
  - HAART becomes standard of care, 1997

Innovation in how clinical trials are done: NIH establishes a comprehensive infrastructure into which the pharmaceutical industry can readily feed developments; viral load as a surrogate marker rather than a clinical endpoint; trials are prospective, randomised and controlled, but not double-blinded; outcome analysed for up to 1 year (from mid-1990s onwards); patients engaged in the research process, as collaborators of scientists and academics – provide a user perspective

Intercompany Collaboration for AIDS Drug Development (ICC) pharmaceutical company consortium formed, 1993

Incremental improvements in HAART therapies: innovations in potency/efficacy, safety and side effects, as well as costs (mid- to late 1990s and 2000s)
  - ACTG 5059 study shows important differences between different compound combinations, 2003
  - U.S. FDA, with President’s Emergency Plan for AIDS Relief (PEPFAR), approves the 100th AIDS drug, 2009

Rapid regulatory responses, making better treatments accessible quickly:
  - ACTG 5059 shows that a popular treatment regimen is inferior to efavirenz-based HAART; changes in global guidelines follow within months, 2004
  - FDA commits to expedited approval (median time of 5 months in 1996–2006 period)
  - FDA releases a guidance document for expedited approval for low-cost, safe, effective, co-packaged, low-dose therapies, 2004
  - Atripla, first once-a-day, single pill approved by FDA, 2006

Affordable treatment
  - UN-supported Medicines Patent Pool (MPP) established: licensing agreements with pharmaceutical companies to allow for production of low-cost versions of pharmaceutical HIV drugs, 2011
  - Advances in ARVs as prevention: the journal Science names HPTN 052 study (prevention trials network) as breakthrough of the year, 2011
  - The first pre-exposure prophylaxis treatment (Truvada) approved by FDA, 2012

The science and the evidence: Understanding HIV/AIDS

Developments in identifying and characterising HIV were a prerequisite for all further innovation efforts. The first official reporting of the disease was in gay men in the United States, in 1981. Soon after, in 1982, Robert Gallo (NIH) suggested a retroviral cause (and grew the virus in cells) and Luc Montagnier (Institut Pasteur) identified Lymphadenopathy Associated Virus (LAV) as a potential cause. The viruses they had independently isolated were shown to be one and the same, confirmed to cause AIDS in 1984, and renamed Human Immunodeficiency Virus, or HIV.

By 1983, all major routes to HIV transmission were known. The US Centers for Disease Control and Prevention (CDC) confirmed that these excluded casual contact, food, water, air and surfaces, which was an important contribution for managing public misconceptions and attitudes towards infected individuals.
Once the basic science became better understood, innovation, at least in the context of diagnostics and drugs, happened relatively quickly. As discussed below, this momentum was underpinned by a very strong social movement and advocacy campaigns; rapidly growing political will and focus on the disease; and a favourable funding, commercial and regulatory environment.

In both the scientific and policy communities, the late 1980s and early 1990s were characterised by a growing recognition of the need to create a global, interdisciplinary community of researchers with a commitment to tackling AIDS. This community needed to include various disciplines – biochemists, immunologists, virologists, medicinal chemists, public health specialists as well as non-clinical professionals (e.g. in the fields of social care, social science looking at stigma), among others. Building this community was extremely challenging, and it required a concerted effort to ‘direct the energy’ of researchers from different fields to AIDS. An enabling aspect was the ‘outbreak’ nature of the disease, meaning ‘money had to be thrown at it’ and enabling a rapid, coordinated response approach. Once that was achieved, as one interviewee put it, ‘We had never seen such rapid expansion of knowledge on a disease’.

Much of the earliest research advances took place in large, government-funded research institutes and universities, (e.g. NIH labs, Institut Pasteur and others) with industry contributing compounds for testing and later stage clinical trials. It was clear that all of the needed expertise could not be brought into one place, and that virtual, multi-sectoral, multinational networks would in this context be essential. In a time where internet connectivity wasn’t as widely available as today, this meant providing for more regular telephone and face-to-face meetings of a very diverse community of experts, one example of which would be the International AIDS Conference.

**Early treatment breakthroughs**

**Industry collaboration**

Once the pathophysiology was better understood, industry played a very big role in the development of treatment breakthroughs. Mobilising industry engagement was relatively straightforward given the enormity of the scientific challenge and the moral imperative, as well as the existence of a market (especially in developed countries, but also in developing countries with a longer-term perspective and regulatory incentives in mind). A large NIH budget also helped attract complementary pharmaceutical investment. ‘Industry had very specific skillset that academics and NIH did not have – knew how to develop drugs’. According to one interviewee, ‘money was never the issue with AIDS, never the barrier to moving things along as quickly as possible’, although if money was needed from industry, ‘it had to be in exchange for something’. ‘The difficulty was the actual science’. At the time, industry could also afford to take more risk than it can today, given a consistent pipeline of innovation in products and revenue sources largely driven by ‘blockbusters’ in the cardiovascular sphere. All major pharmaceutical companies were involved in HIV/AIDS innovation, and they even had inter-company collaboration initiatives. For example, the heads of research labs put together the Intercompany Collaboration for AIDS Drug Development (ICC, essentially a pharmaceutical consortium) in 1993. The consortium met every two months, developed and shared pre-competitive knowledge with careful legal scrutiny and legal representation at meetings. These meetings helped discover viral load as a marker of HIV treatment effectiveness, among others. Treatment
information patient groups also played an active role in the research process, collaborating with industry and academic scientists in clinical trials. The user perspective was very valuable for determining dosing regimens and understanding side effects. The search for AIDS treatment left a lasting legacy in this context: ‘Because of HIV, European Medicines Agency Committee on Proprietary Medicinal Products has patient representatives’.

**Improvements in diagnostic testing**

In the late 1980s, a series of diagnostic tests were developed and approved by the FDA, each showing gradual improvements over the previous in terms of specificity, sensitivity, speed of detection, or user-friendliness (e.g. oral diagnostic, 1984; ELISA-based, 1985; Western Blot–based, 1987; HIV-1 10 minute kit, 1992), with further innovation on this front happening in the mid-1990s through to early 2000s (e.g. home testing and collection kit, 1996; rapid diagnostic kit with 99.6% accuracy, 2002). Better and easier diagnosis prospects were accompanied by increased investment into the discovery and development of drugs which could treat HIV. Although there was a growing understanding of the importance of targeting prevention (e.g. through education campaigns and awareness raising), the majority of advocacy attention was focused on the need for a treatment or cure.

**Treatment with zidovudine/azidothymidine (AZT)**

The first major breakthrough came with the discovery of antiretroviral drug zidovudine/azidothymidine (AZT, commercial name Retrovir) in 1986, by GlaxoSmithKline (then Burroughs Wellcome) and collaborators from the US National Cancer Institute. While Burroughs Wellcome had been testing AZT against viruses in mice, it had not focused on HIV specifically. Collaborators at NCI successfully tested these compounds against HIV in one of their assays, and soon after they started a phase 1 trial with Burroughs Wellcome and Duke University. Further trial phases were conducted by Burroughs Wellcome. The patent for AZT was granted in 1985, and the FDA approved it for use in HIV treatment in 1987, at a cost of US$10,000/year. This was the shortest time span between demonstration of a compound’s effectiveness in the lab and its approval in history (just over 2 years). AIDS activists embraced it, even though it was toxic, because they ‘viewed it as the only hope’, and even though it really only promised ‘an additional year of life, rather than long-term improvement’. Concerns related to side effects and drug resistance soon emerged, and these concerns were associated with the search for newer, more effective, safer and more affordable therapies.

**Developments in the field of clinical trials**

Throughout the HAART era, major advances also occurred in terms of how clinical trials were done, particularly in relation to the involvement of patients (user perspective on dosage, side effects) and in the development of viral load as a surrogate marker, rather than using progression (a clinical endpoint) as a marker. This made clinical trials easier and cheaper to conduct. In the late 1980s and early 1990s, the NIH also drove the effort to develop the clinical trials infrastructure needed for the testing potential new feeds into the innovation pipeline (e.g. NIH established office of AIDS research and AIDS Clinical Trials Group in 1988, and the Terry Beirn Community-based Clinical Trials Act established a trials network in 1991). Industry found the clinical trials infrastructure particularly helpful, given the complexity of the
Multi-drug therapies and the introduction of HAART

The first clinical trial of multi-drug therapy happened in 1992, and the first protease inhibitor was approved by the FDA in 1995. This marked the beginning of a new era of highly active antiretroviral therapy (HAART), which relies on the use of multiple drugs that act on different viral targets. After scientist David Ho (Aaron Diamond AIDS Research Center, Rockefeller University, NY) advocated for a ‘hit early, hit hard’ multi-drug treatment strategy at the 11th international AIDS conference in Vancouver (1996), HAART became the new standard of care (1997). ‘Once it became obvious that triple-drug combination therapy could transform AIDS from a deadly to a chronic condition, political will, advocacy and research money coalesced around this clear solution’. In addition to 11th international AIDS conference, publications in the New England Journal of Medicine (Gulick et al. 1997; Hammer et al. 1997) – which showed the benefits of a combination of particular types of compounds in triple-drug therapy – were among the most important scientific ‘events’ associated with HAART.26

HAART was – and continues to be – hailed as the major breakthrough in the fight against AIDS to date. Very soon after its introduction, however, resistance to protease inhibitors (one of the common compounds) began to emerge. By 2002, side effects had also become a growing concern. Throughout the mid- and late 1990s and 2000s, innovation efforts focused on examining new drug combinations and formulations; different dosages; boosters; and, in general, incremental innovations in HAART potency/efficacy, safety and side effects, as well as costs. For example, in 2003, the ACTG study showed important differences between nucleoside reverse transcriptase inhibitors (NRTI) pairings. Part of this effort resulted from what had been learnt from innovation in cancer, where experimentation with multiple-drug combinations had already happened. It was also important to realise that the epidemic was not necessarily the same in each country (e.g. different population groups can be at risk, which meant that different groups could have differential responses to the same treatment and which called for continued innovation and experimentation in the types of treatments that were available).

The role of industry and markets in developing HAART

Most of the drugs were patented and developed by large pharmaceutical companies (GSK, Abbott, Gilead Sciences) or by partnerships between them (e.g. Gilead with Tibotec, Gilead with Bristol-Myers Squibb).

26 Based on two nucleoside analogue reverse transcriptase inhibitors with a protease inhibitor.
Further innovations came in the discovery of single-pill formulations (the first being from Gilead) and the first once-a-day, single tablet regimens (Atripla, approved by FDA in 2006, combined drugs from Gilead, Bristol-Myers Squibb and Merck).

Although the United States led the effort behind HAART, European investigators, universities and organisations also played substantial roles. For example, Janssen Pharmaceuticals (now part of Johnson & Johnson) was heavily involved in the development of early protease inhibitors.

After patents on some of the key therapeutic compounds expired, generic manufacturers in developing countries (Indian, Thai, Brazilian and South African companies) also entered the landscape, reducing costs and improving access while often finding innovative and creative ways of driving down costs. Since 2000, the cost of AIDS drugs in India has dropped by 99% (from US$10,000 to US$70). Regulation such as the UN-supported Medicines Patent Pool (MPP, established in 2011) also helped create licensing agreements with seven pharmaceutical companies to allow for reduced prices for HIV drugs.

In more recent times, more and more attention is being placed on the role ARVs can play in prevention in addition to a cure. For example, in 2011, the journal *Science* announced the HIV Prevention Trials Network (HPTN) 052 study as breakthrough of the year. The first pre-exposure prophylaxis treatment (Truvada) for reducing risk of infection in individuals at high risk was approved by the FDA in 2012.

### Table 6. Key social influences on innovation in HIV

<table>
<thead>
<tr>
<th>Social advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Social, grassroots activism has an extremely powerful influence on innovation in HIV/AIDS treatment</td>
</tr>
<tr>
<td>• A series of high-profile deaths or disclosures, 1980s–2000s</td>
</tr>
<tr>
<td>• The Denver Principles for treating people with AIDS with dignity, 1983</td>
</tr>
<tr>
<td>• The first AIDS discrimination lawsuit, 1983</td>
</tr>
<tr>
<td>• National Association of Patients Living with AIDS (NAMWA) formed in United States, 1983</td>
</tr>
<tr>
<td>• AIDS Action formed, 1984</td>
</tr>
<tr>
<td>• AIDS Coalition to Unleash Power (ACT UP) international advocacy group formed, 1987</td>
</tr>
<tr>
<td>• Institute of Medicine Report in United States calls for national education campaign and formation of a national AIDS commission, 1986</td>
</tr>
<tr>
<td>• Tombstone campaign launched, representing the first national HIV/AIDS campaign in the UK, 1987</td>
</tr>
<tr>
<td>• WHO declares 1 December World AIDS Day, 1988</td>
</tr>
<tr>
<td>• Protests throughout 1980s and early 1990s – impetus for increased investment, e.g.</td>
</tr>
<tr>
<td>• ACT UP protests about FDA drug approval process, 1988, and for more treatments and expansion of clinical trials to include more women and people of colour, 1990</td>
</tr>
<tr>
<td>• major HIV/AIDS protests in San Francisco, in New York and at US headquarters of Burroughs Wellcome, 1989</td>
</tr>
<tr>
<td>• NAPWA convenes first national AIDS watch: people across United States lobby Congress to increase funding, 1995</td>
</tr>
<tr>
<td>• The International AIDS Conference (ongoing, organised biannually since 1985): key gathering for the international community (researchers, policymakers, patient associations, advocacy organisations, funders)</td>
</tr>
<tr>
<td>• Minority group AIDS awareness days introduced in United States, 2000s</td>
</tr>
<tr>
<td>• Efforts of WHO, UNAIDS, G8 and WTO escalate from the late 1980s and then again in the mid-late 1990s, once prospects for treatment become clearer and issues of access and affordability come to the forefront</td>
</tr>
</tbody>
</table>
The importance of social movements for HIV/AIDS advocacy in developing treatments

In brief, within 5 years of the first case of HIV/AIDS being reported, a drug able to treat the disease was on the market (AZT), and within 15 years since this first report, a safer and more effective HAART-based treatment had been discovered and approved. The impact of social influences on this process cannot be underestimated, not in the least in terms of the impact of advocacy and activism on political authorities. These authorities, in turn, played a key role in mobilising sufficient funding from public sector sources, as well as private sector contributions in kind, or by securing government access to products for large scale trials. ‘The AIDS advocacy community was able to mobilise patients, caregivers, physicians and other healthcare professionals – politicians couldn’t ignore this.’ At the same time, policymakers ‘wanted to get advocacy community on the inside contributing to development, instead of on the outside causing trouble.’

Advocacy in the United States

Much of the initial voice behind the AIDS movement came from the gay community in the United States. ‘The strength of patient activation was vital, and it came from grassroots rather than from governments.’ Celebrities, too, had a big role to play, and over time ethnic minority groups gained increasing influence. The scientific community and the media, too, helped to raise the profile and importance of HIV/AIDS in powerful decisionmaking circles. The key behind this impact was a huge and sustained national momentum and the ability to channel activism and lobbying activities in a way that ‘spoke to’ political agendas and public health priorities. The most vocal and influential advocates and organisations were also able to train others on effective ways of lobbying.

Some of the most illustrative cases are:

- A series of high-profile deaths or HIV disclosures, reported on vocally by the media, helped keep the spotlight on the disease throughout the 1980s, 1990s and 2000s (e.g. Rock Hudson, Liberace, Ryan White, Freddie Mercury and Greg Louganis disclosing their HIV-positive status). The advocacy community also included powerful support from HIV-negative celebrities, such as Elizabeth Taylor. There were numerous instances of discrimination in the early period following the identification of the disease, including refusing access to school to children with HIV acquired through contaminated blood. The first AIDS discrimination lawsuit was related to a doctor threatened with eviction for treating an AIDS patient (1983). Influential patient associations/lobby groups with a focus on combating discrimination were also formed early on. Examples include the Denver Principles (1983), which advocated for treating people with AIDS with dignity and formed the charter for the founding of the National Association of People with AIDS, or NAPWA (1993). AIDS Action (a US national advocacy campaign) was established, 1994

- In 1986, the Institute of Medicine called for a national education campaign and a national AIDS commission; a national Academy of Science report criticised the US government for insufficient response to the crisis
In the late 1980s and early 1990s, a series of protests provided impetus for increased investment (e.g. ACT UP protests about FDA drug approval process in 1988 and for more treatments and expansion of clinical trials to include more women and people of colour in 1990; major HIV/AIDS protests in San Francisco and New York and at the US headquarters of Burroughs Wellcome in 1989); NAPWA convened first national AIDS watch: people across United States lobbied Congress to increase funding, 1995

Although later in time, minority groups (e.g. the Black, Latino, Caribbean, Asian, Pacific, and gay communities) also began campaigning and raising awareness about HIV/AIDS prevention strategies and treatment needs and options. They introduced HIV and AIDS awareness days starting in the 2000s

The International AIDS Conference (held biannually since 1985) is a key gathering for the international community, bringing together stakeholders from across different groups – researchers, policymakers, patient associations, advocacy organisations, funders. As part of awareness-raising efforts, WHO declared 1 December World AIDS Day, 1988

Advocacy in Europe

In the United States, advocacy had multiple points of influence (Congressional agencies, federal agencies and drug companies). This was different to the situation in Europe, where most funding comes from a national health organisation (e.g. the in the UK, NHS) and some charities (e.g. in the UK, the Terrence Higgins Trust lobbied the Department of Health and the NHS on the HIV issue). Although, given the centralisation of the national health system, lobbying can be easier in the UK than the US context, once decisions were taken, in the United States a higher amount of overall resources was mobilised than in the UK. In the UK, the Tombstone campaign was the first national HIV/AIDS campaign (1987), and it pre-dated most of the bigger national US efforts.

Table 7. Key political and economic drivers in innovation in HIV
Political response to the HIV/AIDS pandemic

In response to the intense social momentum and the growing burden of disease, accompanied by initial scientific progress, the political response to HIV/AIDS escalated rapidly, particularly in the United States. This was accompanied by substantial and incrementally expanding financial investments, which, in the early phases of the pandemic, came principally from public bodies. The US government AIDS budget grew quickly. Although international public and intergovernmental investment efforts lagged behind...
somewhat, they gained pace in the early 2000s, once the prospects of affordable treatment became a reality. Below we highlight some of the key events related to the political and economic environment (for the complete list of milestones, see Table 6).

In the United States, political effort can be traced back to the first US Congressional hearing on HIV/AIDS (1982). In the same year, legislation was passed to allocate US$5 million to the CDC for surveillance, and US$10 million to the National Institutes of Health for HIV research. According to one interviewee, the head of NIAID at the time (Anthony Fauci) was the ‘architect of how the US government addressed the AIDS issue’. He is an individual with huge reach and credibility and he had a central role in managing and governing the direction of funding and research. In 1983, Congress introduced a bill for US$12 million of funding targeted specifically at AIDS research and treatment. It allocated another US$70 million in 1985, US$30 million in emergency funding for AZT access in 1987, and US$80 million for AIDS research. Soon after (1989), the Health Resources and Services Agency (HRSA) granted US$20 million for home- and community-based care (for some states this was their first involvement with HIV care/treatment), and an CDC/HRC initiative provides US$11 million for seven community health centres. In 1989, the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act came into being. This US$220.5 million federal funding initiative for community-based care was managed by the HRSA.

Social activism also played a role in pricing, particularly by pressing for the pharmaceutical industry to make more medicines available at affordable prices.

In the early stages of the disease, public policy was largely focused on availability and distribution of AZT; the science community was trying, at the same time, to shift the focus to both prevention and innovation for longer-term and better treatments.

US HIV/AIDS policy from Reagan to Obama

In the late 1980s, President Reagan established the Presidential Commission on HIV (1987) and Congress the National Commission on AIDS (1989). Subsequent presidents all reaffirmed their commitment to the HIV/AIDS agenda. For example, President Clinton established the White House National AIDS Policy Office, in 1993; the HIV/AIDS Presidential Advisory Council, in 1995; a special package of initiatives to reduce the impact on racial and ethnic minorities (including a US$156 million Minority AIDS Initiative), in 1998; and the Millennium Vaccine Initiative, in 2000.

In ‘phase 2 of the HIV response, Congress devoted millions to the NIH. This spurred rapid scientific development, stimulated whole new industries, drove companies to come on board and take opportunities to partner with NIH and CDC for trials in order to move drugs forward’. At the same time, advocacy groups were pressing the FDA to make drugs available faster (after they had been identified as effective). Overall, we witnessed between the mid-1980s and mid-1990s ‘a confluence of money coming in, the regulatory framework changing and PPPs developing’. The pharmaceutical industry also contributed in different ways, namely, in-kind contributions, donations of compounds to test, managing some phases of R&D, and funding R&D efforts focused on drug development internally.

In early 2000, the United States began focusing more intensively on the international HIV/AIDS landscape, partially from a national and global security standpoint. President Clinton declared HIV/AIDS
a threat to national security and created a Presidential Envoy for AIDS Cooperation. This was in part related to the UN Security Council identifying AIDS as a security issue (2000), which was ‘viewed as a major victory in getting AIDS on the [global] agenda’. That same year, the UN Security Council met to discuss the impact of the AIDS pandemic on peace and security in Africa, which presented the first time that a health issue had been discussed in the international security context. Two years later, the US National Intelligence Council reported on AIDS in India, China, Russia, Nigeria and Ethiopia.

George W. Bush sustained the political commitment of his predecessor. In 2003, he established PEPFAR (President’s Emergency Plan for AIDS Relief), which some say was Anthony Fauci’s idea. PEPFAR was a US$15 billion, 5 year plan. In 2008, PEPFAR was renewed, with a commitment of up to US$48 billion over 5 years. In a similar light, in 2009, President Obama launched the Global Health Initiative, a 6 year, US$63 billion commitment encompassing PEPFAR. He also signed the Patient Protection and Affordable Care Act, in 2010, which contains provisions for special protection of people living with HIV, and lifted the longstanding immigration and travel ban on people with HIV. In 2011, President Obama announced accelerated efforts to increase access to treatment, as well as new funding for the AIDS Drug Assistance Programme.

**International initiatives**

Internationally, at the intergovernmental level, the key players in the fight against AIDS were the WHO, UNAIDS, G8 and WTO. The first WHO meeting on HIV/AIDS was held in 1982, and the WHO launched its Global Programme on AIDS in 1987. In that same year, AIDS was the first disease ever to be debated in the UN General Assembly. Nearly 10 years later, in 1996, UNAIDS (the Joint UN programme on HIV/AIDS) began, which became an important vehicle for global action and coordination of efforts. That same year IAVI was established as a public–private partnership, to speed up the search for a vaccine. This occurred partially in response to a growing understanding of the disease and a general view of vaccines as a more effective response to public health crises. In 2000, the G8 Summit issued a statement on need for more HIV/AIDS resources.

At the 1998 International AIDS Conference in Geneva, the HIV/AIDS community began placing focus on what could be done to tackle AIDS in developing countries, as the disease had become more manageable in high-income countries. In terms of political impact on pricing, President Clinton issued an executive order to assist developing countries in importing and producing generic HIV treatments, in 2000. Also in 2000, UNAIDS and WHO, together with other groups, announced an initiative of five pharmaceutical companies to negotiate reduced prices for HIV/AIDS drugs in developing countries. This initiative was in line with the Drug Access Initiative jointly established two years before, in 1998, by the pharmaceutical industry and the WHO to ensure progress towards treatment affordability.

A year later, in 2001, the WTO Doha Declaration affirmed the rights of developing countries to manufacture or buy generic treatments to deal with public health crises. A number of international initiatives and national efforts emerged to increase access and affordability of treatment, as well as address other aspects of the pandemic. For example, in 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria was formed as a major international financing institution, with impact across a range of activities spanning prevention, treatment, the strengthening of health systems, collaborative activity, infrastructure,
monitoring and evaluation. In 2003, the Clinton Foundation secured further reduced prices for developing countries, and the South African government announced a new ARV treatment programme. In that same year, the WHO launched their ‘3 by 5’ initiative, with the aim of treating 3 million people by 2005. In 2005, WHO, UNAIDS and Global Fund announced the results of joint efforts to help 700,000 people access drugs, which, although it constituted some progress, remained far behind the targets of the initiative. In 2010, WHO, UNAIDS and UNICEF jointly published a Universal Access Report, celebrating progress in access to innovations produced over the past two decades.

A key enabler of progress was the alignment of governments at all levels and a well-orchestrated and coordinated strategic response. Within these initiatives, intergovernmental organisations such as the WHO and UNAIDS worked together with national-level health/finance ministries, physician societies and working patient groups. As advocated by the head of UNAIDS at the time, Peter Piot, the recommendation was that ‘every country should have a strategic plan for AIDS, one coordinating agency, and a monitoring and evaluation framework’. These coordinating agencies at the country level would work with organisations at the global level to ensure compatible data and evidence to inform policy (e.g. treatment guidelines). Having a national coordinating agency also ensured that international funding agencies such as PEPFAR and the Global Fund had confidence that the money would be appropriately allocated in-country.

Table 8. Key regulatory enablers in innovation in HIV

<table>
<thead>
<tr>
<th>Regulatory developments – key advances by US and international organisations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Accelerated regulatory approval and accelerated review processes</td>
</tr>
<tr>
<td>o FDA creates treatment investigational drugs class, enabling fast track approval, 1987</td>
</tr>
<tr>
<td>o FDA guidance on expedited approval, 2004</td>
</tr>
<tr>
<td>o ACTG 5059 shows superiority of a new treatment; changes in global guidelines follow within months, 2004</td>
</tr>
<tr>
<td>o Rapid (protocol) review incentives</td>
</tr>
<tr>
<td>• Enabling access to treatment and affordability:</td>
</tr>
<tr>
<td>o Regulation by FDA allows importation of unapproved drugs, 1987</td>
</tr>
<tr>
<td>o National Institute of Allergy and Infectious Diseases (NIAID) ‘parallel track’ policy enables access to experimental treatments for those who do not qualify for clinical trials, 1989</td>
</tr>
<tr>
<td>o FDA recommendations for treatment of particular groups, 1998</td>
</tr>
<tr>
<td>o First national treatment guidelines, 1998</td>
</tr>
<tr>
<td>o WTO Doha Declaration affirms the rights of developing countries to manufacture or buy generic treatments, 2001</td>
</tr>
<tr>
<td>o UNITAID Medicines Patent Pool negotiates licensing agreements with pharmaceutical companies for low-cost versions of HIV drugs, 2011</td>
</tr>
<tr>
<td>• Anti-discrimination legislation (e.g. Denver Principles, 1983; Americans with Disabilities Act, 1990)</td>
</tr>
<tr>
<td>• Various guidelines to minimise risks of infection, late 1980s</td>
</tr>
</tbody>
</table>
An evolving regulatory context to support development of and access to treatment

According to one interviewee, a lot of the innovations in HIV/AIDS would not have happened had it not been for a changing regulatory environment.

The first enabling feature was an adaptive regulatory landscape. Regulation in the United States responded quite quickly to new scientific knowledge. For example, in 2004, the ACTG 5059 study showed that a popular triple-nucleoside regimen (zidovudine/lamivudine/abacavir) was inferior to efavirenz-based HAART, and within months there were changes in global guidelines.

Incentives to accelerate regulatory approvals of promising treatments were particularly attractive for industry. As early as 1987, the FDA created a new class of drugs (treatment investigational drugs), which allowed for fast track approval. In 2004, the FDA released a guidance document for expedited approval for low-cost, safe, effective, co-packaged, low-dose therapies. By 2009, the FDA with PEPFAR approved the 100th AIDS drug.

Regulations targeting access and affordability were also important; these included not only various drug approvals, but also supporting acts. For instance, in 1987, the FDA allowed the importation of unapproved drugs for treating life-threatening conditions, such as HIV. In 1989, NIAID endorsed a ‘parallel track’ policy enabling access to experimental treatments for those who did not qualify for clinical trials. Over time the FDA adopted various recommendations for treatment of particular groups (e.g. pregnant women, children), while the CDC produced the first national treatment guidelines for the United States in 1998. At the international level, WTO Doha Declarations and Patent Pools and related initiatives were crucial in addressing pricing bottlenecks for developing countries.

Other regulations and legislation focused on fair treatment of individuals affected by HIV/AIDS (anti-discrimination legislation). These included the above-mentioned Denver Principles (1983) and the Americans with Disabilities Act (1990). Some provisions aimed at minimising risks to infection, such as the CDC guidelines for counselling and antibody testing to prevent HIV infection and AIDS, were adopted in 1987. The controversial mandates for testing for HIV on all visa applications to the United States date from the same year. Guidelines for the prevention of transmission for healthcare workers were adopted in 1989. The 1993 Revitalisation Act, making US HIV immigration exclusion policy law, was lifted in 2011 by President Obama.

Despite the presence of novel treatment options, incidence rates remain constant

The rapid increase in HIV/AIDS infection and mortality rates was a further motivation for investments in research, innovation and education. By 1985, at least one case of HIV was reported globally. By the early and mid-1990s, AIDS became the leading cause of death for US men aged 25–44 and for all Americans aged 25–44. By 1995, 500,000 cases had been reported in the United States. UNAIDS estimated in 1997 that 30 million people were living with HIV globally and that 16000 are infected daily. In 1999, the WHO announced AIDS to be fourth biggest killer worldwide (33 million living with the disease, 14 million deaths).
And despite a rapid decline in mortality rates in the late 1990s and 2000s in the developed world, as treatments became available and improved, the infection rates in the United States did not change dramatically. In 2009, for example, Washington, DC, still had a higher HIV prevalence rate than West Africa. However, the disease has become more manageable over time.
Appendix B: Breast cancer case study

The story of using tamoxifen to treat and prevent breast cancer

Background and Context

Breast cancer is the most common cancer in the UK, with more than 49,900 people diagnosed in 2010 (Cancer Research UK website 2014). Worldwide, it is estimated that more than 1.38 million women were diagnosed with breast cancer in 2008 (Ferlay et al. 2010). Survival rates in the UK have been improving, largely as a result of faster diagnosis due to improvements in treatment, raised awareness, and the NHS screening program. This is reflected in UK five-year survival rates, which increased by 33 percentage points between 1971–1975 and 2005–2009 (Cancer Research UK website 2014). One important treatment which was rolled out over that time period is the drug tamoxifen, which is now widely used in the treatment of breast cancer.

Key learning and messages

Table 9. Key insights on breakthrough dynamics in breast cancer

<table>
<thead>
<tr>
<th>Understanding the science and the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the point at which tamoxifen was being investigated as a treatment for cancer, it was known that the growth of some breast cancers was stimulated by oestrogen. These cancers were termed oestrogen receptor positive. Tamoxifen, an oestrogen receptor blocker, was initially developed to be a contraceptive. When it was shown not to be an effective contraceptive, tamoxifen was investigated as a potential treatment for oestrogen receptor-positive breast cancer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A multi-stakeholder, interdisciplinary approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>The complete story of tamoxifen involves input from industry, academia and philanthropy, combined with the persistence of the scientists involved, in particular Arthur Walpole from Imperial Chemistry Industry pharmaceuticals (ICI) and V. Craig Jordan from academia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The need for continued innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>While the tamoxifen story started as ‘failed’ contraceptive drug at ICI, it was only because of Walpole’s championing of its potential that continued innovation took place.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The role of a social movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>The cancer taboo was challenged by Mary Lasker starting in the mid-1940s through creating awareness in the public domain, and this led to increased research funding for cancer research. Awareness was increased further still in the ‘war on cancer’, initiated by Mary Lasker in 1969. It was only in the 1970s that awareness of breast cancer began to be noticeable through the publishing of survivor personal narratives and self-help books. The following decades led to much more awareness as many breast cancer–related charities were set up.</td>
</tr>
</tbody>
</table>
While tamoxifen was patented in the UK in 1965 and eventually in the United States in 1985, the lack of a US patent did not slow progress of the development of tamoxifen because it was felt that other pharmaceutical companies were not interested in the drug and so the drug would have no competition. Tamoxifen was even marketed in the United States before a patent had been secured, after it had received FDA approval in 1977.

Table 10. Key scientific and technological trigger points of the tamoxifen breakthrough

<table>
<thead>
<tr>
<th>Scientific and technological advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Beatson discovers that removal of the ovaries extends the lives of women with breast cancer, 1896</td>
</tr>
<tr>
<td>• Non-steroidal anti-oestrogens developed and intended for use as contraceptives but discontinued due to safety concerns</td>
</tr>
<tr>
<td>• Tamoxifen developed as a potentially safer anti-fertility agent; however, it is found to induce ovulation rather than reduce fertility in humans</td>
</tr>
<tr>
<td>• Tamoxifen trialled as a breast cancer treatment</td>
</tr>
<tr>
<td>• Tamoxifen approved for clinical use in the UK in the treatment of breast cancer, 1973</td>
</tr>
<tr>
<td>• Initially, tamoxifen used only in cases of advanced breast cancer, but later used as an adjuvant treatment in early breast cancer</td>
</tr>
<tr>
<td>• A preventative action of tamoxifen is investigated from as early as 1976, with large trials in high-risk women in 1998, 2005 and 2007 leading to the recommendation for the use of tamoxifen as a preventative treatment in women who have a family history of breast cancer</td>
</tr>
</tbody>
</table>

The science and the evidence: Treating breast cancer with tamoxifen

Tamoxifen is an anti-hormone therapy for breast cancer that acts by blocking the action of the hormone oestrogen. Many breast cancers are termed hormone receptor positive, meaning that they are stimulated by the hormones oestrogen and progesterone to grow. Cancers which are oestrogen receptor (ER) positive are most commonly treated with tamoxifen. Tamoxifen blocks the oestrogen receptor, preventing the oestrogen molecule from locking onto the cancer cells and preventing oestrogen from stimulating the cancer to grow. This means that treatment with tamoxifen can reduce the risk of cancer recurring after surgery or of cancer developing in the other breast. Around three quarters of breast cancers are ER positive and hence can benefit from this kind of anti-hormone therapy.

Early development of the drug

The first clue to the role of oestrogen in breast cancer came in the late 1800’s, when Dr George Beatson found that he could extend the lives of women with breast cancer by surgically removing their ovaries (Beatson 1896). However, the development of anti-oestrogens, such as tamoxifen, did not commence until over 50 years later. Interestingly, this drug was not developed in a cancer research program. Instead, the first non-steroidal anti-oestrogens were developed and tested in 1957 as part of the Merrell cardiovascular program and were intended for use as contraceptives. Research in Merrell was discontinued shortly afterwards due to safety concerns, but this area was explored subsequently by Arthur Walpole, then head of the fertility control program for ICI Pharmaceuticals, and his colleagues. In 1962, ICI filed a patent for tamoxifen, developed as a potentially safer anti-fertility agent. However, although tamoxifen
was an effective postcoital contraceptive in rats, it was found to induce ovulation rather than to reduce fertility in humans. Following this discovery, because of the link between oestrogens and breast cancer growth, Arthur Walpole went on to investigate whether tamoxifen was an oestrogen or an anti-oestrogen in humans. In 1973, he convinced ICI to market tamoxifen in the UK for breast cancer treatment, and it was approved for clinical use in the UK in that year (Jordan 2003).

**Clinical trials and use of tamoxifen as adjuvant**

Initially, tamoxifen was only used in cases of advanced breast cancer. However, a number of clinical trials were conducted in Europe and the United States to investigate its wider use in breast cancer (for example, Baum et al. 1983; Ingle et al. 1981). Many studies demonstrated that tamoxifen could be used as an adjuvant treatment in early breast cancer, and by 1984, tamoxifen was the adjuvant endocrine treatment of choice for breast cancer according to the US National Cancer Institute (Jordan 2003). Its use as an adjuvant treatment for breast cancer was similarly widespread in the UK. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) was initiated in 1983 to collect data for hormonal and cytotoxic therapy in 1985. The EBCTCG played an important role in demonstrating the effectiveness of tamoxifen, publishing a meta-analysis of the evidence for its use in early breast cancer in 1988 (EBCTCG 1988) and, later, in 1998, showing that tamoxifen was effective in the treatment of premenopausal women, thus widening its usage even further (EBCTCG 1998).

**Concerns about side effects**

Initially, tamoxifen was typically given for a period of 1 year after primary treatment, because it was known to be effective over that time period in advanced breast cancer (Ingle et al. 1981) and it was feared that longer use could lead to drug resistance (Jordan 2003). There were also concerns that, since tamoxifen was classified as an anti-oestrogen, long-term therapy would increase the risk of osteoporosis and CHD. Although initial concerns around these side effects were addressed (Jordan et al. 1987; Love et al. 1991, 1992), further concerns emerged in the mid-1980s, when tamoxifen was found to enhance the growth of endometrial cancer in the laboratory (Gottardis et al. 1988; Satyaswaroop 1984). This was shown to be replicated in humans, with tamoxifen causing a fourfold increase in the (small) risk of endometrial cancer in post-menopausal women (Fisher et al. 1994; Fornander et al. 1989). In 1990, tamoxifen was also found to produce liver tumours in rats (Greaves et al. 1993), but this was not found to be replicated in humans. It is interesting to note that, according to Jordan (1995), ‘if rat liver tumours had been noted in the early 1970s, drug development in this area would have stopped, as there was no successor to tamoxifen’.

**Introducing tamoxifen in preventative care**

The suggestion that tamoxifen not only could be used to treat cancer, but also could act as a preventative came as early as 1976 (Jordan 1976), with further support on the basis of existing research and clinical experience of the use of tamoxifen in 1991 (Nayfield et al. 1991). These findings were reinforced in 1998.

---

27 Adjuvant treatments are additional treatments given to support the primary therapy (e.g. surgery or chemotherapy). The term typically refers to treatments that are given once the primary therapy has proved effective to remove any remaining cancer cells and to reduce the risk of relapse.
by a US trial of 13,388 high-risk women, which found a 50% reduction in invasive breast cancer (Fisher et al. 1998). However, it was not until 2013 that NICE recommended the use of tamoxifen as a preventive treatment in women who have a family history of breast cancer (NICE 2013). This was largely based on evidence from two high-quality randomised controlled trials (RCT) (Cuzick et al. 2007; Fisher et al. 2005). The first of these was conducted in the United States and the second in Australia and the UK (with Cancer Research UK funding).

In summary, tamoxifen was first a failed drug for fertility treatment. Continued research on the drug but now in the field of breast cancer research lead to the discovery that it was a good treatment for oestrogen receptor–positive breast cancer. Successive studies found that tamoxifen could be an effective adjuvant therapy and, finally, it was shown to be effective as a preventative drug for oestrogen receptor–positive breast cancer. This illustrates the change in fortunes for a drug with no clear application at the outset, which subsequently evolved into a pioneering targeted anti–breast cancer drug during the 1970s.

**Key champions of the tamoxifen breakthrough**

The two key champions of the tamoxifen breakthrough were the scientific researchers Arthur Walpole and Virgil Craig Jordan. The discovery and development of tamoxifen was not a planned effort by ICI Pharmaceuticals Division to establish themselves as a major player in oncology, but instead a story of independent interpersonal relationships (Jordan 2003). The story starts with research led by Walpole in the 1960s and then moves on to research conducted by what Jordan called ‘tamoxifen teams’ that he established across six places around the world over a period of 40 years, starting in the 1970s. Other individuals involved in the discovery and development of tamoxifen as a treatment for breast cancer include Mike Barett, Mike Harper, Dora Richardson, Roy Cotton and Louis Trench (Jordan 2014).

**Arthur Walpole**

Arthur Walpole was the person who first investigated whether tamoxifen might be effective in treating breast cancer. He was head of the fertility control program for ICI when tamoxifen was being developed as a contraceptive. When it failed clinical trials as a contraceptive, ICI lost interest in investing in tamoxifen any further. However, prior to his work in the fertility research field, Walpole had worked in the field of breast cancer research, and he believed that tamoxifen had promise as a treatment for breast cancer. He therefore wanted to conduct further experiments to prove this, and he threatened ICI that he would take early retirement should they not let him do so. In 1971, the first clinical trial of tamoxifen as breast cancer treatment was carried out, and it was found that tamoxifen had equivalent efficacy to previous endocrine therapies, but with fewer side effects (Cole et al. 1971). Ultimately, Arthur Walpole was instrumental in convincing ICI to market tamoxifen in the UK for breast cancer treatment in 1973 (Jordan 2003).

**Virgil Craig Jordan**

V. Craig Jordan first met Walpole in 1963, during his summer break from school, when he was working as a technician in organic synthesis at ICI (Jordan 2003). Subsequently, Jordan graduated with a degree in biochemistry in 1969 and a PhD in 1972 from the University of Leeds. His PhD work was aimed at crystallizing the oestrogen receptor with an oestrogen or an anti-oestrogen to discover how ‘failed
contraceptives’ worked. When it came to defending his thesis, the university called in Arthur Walpole to be an examiner, as they lacked the expertise in the field. As a result of this introduction, Walpole helped Jordan get a postdoctoral position at the Worcester Foundation for Experimental Biology in the United States, where he was meant to work with Michael Harper to develop new contraceptive methods. However, by the time of Jordan’s arrival, Harper had accepted another job, and so the Worcester Foundation told him to set up his own laboratory for 2 years. Jordan contacted Walpole to discuss potential research goals. As Walpole was unable to pursue his interest in investigating tamoxifen as a treatment for breast cancer to the extent that he wished at ICI, he handed this project over to Jordan. In 1974, after he had been in America for 2 years, Jordan returned to work at the University of Leeds (Gupta 2011). His first key paper, in 1976, presented evidence to suggest that tamoxifen could be used as a preventative drug (Jordan 1976). Subsequently, he published on the use of tamoxifen in the clinic with long-term adjuvant therapy, chemoprevention with tamoxifen, the selective ER modulators, the warning about an ‘association between tamoxifen and endometrial cancer, raloxifene to prevent osteoporosis and prevent breast cancer at the same time, the evolution of acquired resistance to tamoxifen, and the new biology of oestrogen-induced apoptosis’ (Jordan 2014). Jordan attributed this succession of findings to the resolve and persistence by the researchers involved and to a supportive environment from academia, industry and comprehensive cancer centres (Jordan 2014).

Table 11. Key social and political influences on innovation in breast cancer

<table>
<thead>
<tr>
<th>Social and political advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The taboo on discussing cancer is challenged by Mary Lasker starting in the mid-1940s</td>
</tr>
<tr>
<td>• The first step Mary Lasker takes is to reform the American Society for the Control of Cancer, renamed the American Cancer Society in 1944, to increase the scale on which it raises awareness using modern publicity and advertising techniques</td>
</tr>
<tr>
<td>• Mary Lasker secures substantial philanthropic donations that stimulated cancer research from the late 1940s onwards</td>
</tr>
<tr>
<td>• In the United States, the National Cancer Act (NCA) is passed, but there is no discussion on different types of cancers, 1971</td>
</tr>
<tr>
<td>• Awareness of breast cancer as opposed to cancer in general is low until the 1970s, when awareness increases as a result of survivor narratives and self-help guides</td>
</tr>
<tr>
<td>• Now there are many organizations and charities championing breast cancer research, both by increasing awareness, e.g. use of the pink ribbon, and by raising funds to support research</td>
</tr>
</tbody>
</table>

The origins of breast cancer advocacy in the public sphere

Up until the 1970s breast cancer was at the margins of public consciousness. This period overlapped with the initial stages of research on tamoxifen as a potential treatment for breast cancer in the 1950s and 1960s. Literature on breast cancer was primarily restricted to medical journals and histories. The low profile of breast cancer could have been due to breast cancer not being perceived as much of a threat to society, as it was not contagious and affected mainly women past their childbearing years. Another contributing factor may have been the historic inequality between men and women, particularly with
regard to the majority of physicians being male and the majority of patients being female (Leopold 1999). Additionally, the complexity of the biology underlying breast cancer has made it difficult for the public to grasp what it actually is and therefore the realistic probability of surviving or preventing it. With time, however, as evidence accrued, tamoxifen gained exposure and raised its profile. Thanks to the persistence of the key scientists responsible for its discovery, Arthur Walpole and V. Craig Jordan, the breakthrough in breast cancer treatment could be made even in a public climate that did not recognise breast cancer as a pressing emergency.

Mary Lasker and advocacy in the United States
The initial investigations into tamoxifen as a treatment for breast cancer took place approximately a decade after a large, concerted effort to raise awareness about cancer in general started in the United States. Even though breast cancer was not high profile at this time, the changing of the climate in relation to cancer research in general will have had a positive impact on breast cancer research and awareness in the long run.

The transformation of cancer from being a low-profile subject to a widely discussed and highly funded field of research was largely a result the work of health activist Mary Lasker. In the mid-1940s, she set out to raise cancer awareness and create a world-leading institutional base for cancer research. The first step Lasker took to achieve her goals was to reform the operations of the American Society for the Control of Cancer, which had been established in 1914. Her work used modern advertising and publicity techniques in order to increase the funds raised, strengthen the public’s faith in medical science and promote the idea that research could provide a ‘cure’ for cancer. The society was renamed the American Cancer Society in 1944, and, by 1948, US$3.5 million was being channelled into cancer research grants. She helped integrate discussion of cancer into the public dialogue via radio advertisements and through articles in widely read publications. Lasker successfully lobbied Congress to increase the funds it allocated to the National Cancer Institute. As a result of her efforts, the NCI received US$14 million in 1947, compared with US$1.75 million in 1946 (National Library of Medicine [NLM] report on the Mary Lasker papers).

By the late 1960’s and early 1970s, there was huge national concern about the difficulty of treating cancer. In 1969, Mary Lasker declared an all-out ‘war on cancer’ and set about effecting further increases in funding for cancer research by placing an advertisement in the New York Times and the Washington Post stating ‘Mr Nixon: You Can Cure Cancer’. As part of plan to make cancer research a priority in the United States, Mary Lasker assembled a national panel of consultants into a Citizens Committee for the Conquest of Cancer. The committee, which comprised 13 cancer physicians and scientists along with 13 prominent lay people, produced a report claiming that recent major advances in the fundamental knowledge of cancer meant that the field was ripe for further investment to precipitate a breakthrough in the war against cancer. The recommendations in this report were submitted to Congress and, in 1971, led to the passing of a National Cancer Act (NLM report on the Mary Lasker papers). The NCA required that a comprehensive national plan for the national cancer program be developed. It also gave the National Cancer Institute increased autonomy from the NIH in budget, planning and policy, and it increased the funds for cancer research. Critics of the NCA claimed that there was no justification for the expanded cancer effort in 1971. They argued that the nation was not on the verge of major new strides in
cancer research and that this had been overlooked by the panel’s discussions, which had instead been centred on organizational structures (Rettig 1978).

From generic cancer awareness to breast cancer campaigns

Of particular relevance to the dementia case study is that the above-mentioned discussions did not include reference to different types of cancer. It is also of interest that, while it was reported in 1977 that the NCA had not had much impact on the type of research being conducted or on the rate of discovery, it was in the 1970’s that major inroads were made on the realisation of the potential for tamoxifen to treat breast cancer.

Public awareness and understanding of breast cancer has increased dramatically since the 1970s. This is partially due to two new genres of breast cancer–related literature, namely, personal narratives of the illness, written by breast cancer survivors, and self-help manuals, for the most part written by medical professionals. The initial focus was on the immediate needs of the recently diagnosed and consequently on research to develop a cure for the disease (Leopold 1999). In 1985, Breast Cancer Awareness Month was first observed in the United States as a partnership between the American Cancer Society and the pharmaceutical division of ICI. Incidentally, 1985 was the year that ICI finally had its request for a US patent on tamoxifen approved. In the 1990s, there was a surge in breast cancer activism aimed at raising awareness and raising funding for research. Many of the cancer organizations began to adopt the use of a pink ribbon as a means to raise awareness, and in 1997 the website pinkribbon.com was launched to act as a central resource for all people in the world engaged with breast cancer, including more than 130 organizations from across the world (Pink Ribbon website 2014). More recently there has been increased lobbying for more funds to be allocated to breast cancer research that is aimed at preventing the disease from occurring in the first place.

Table 12. Key economic and regulatory enablers in innovation in breast cancer

<table>
<thead>
<tr>
<th>Economic and regulatory advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ICI invests a small amount of funds for the development of tamoxifen as a treatment for breast cancer in response to the threat by Arthur Walpole to take early retirement</td>
</tr>
<tr>
<td>• The persistence of Arthur Walpole, with his collaborator V. Craig Jordan, leads to the discovery of tamoxifen as a successful treatment for breast cancer</td>
</tr>
<tr>
<td>• ICI patent for tamoxifen approved in UK, 1965</td>
</tr>
<tr>
<td>• ICI repeatedly denied patent protection in the United States due to what is considered the primacy of Merrell’s patents on anti-oestrogens</td>
</tr>
<tr>
<td>• ICI continues clinical development with no assurance of exclusivity in the US market</td>
</tr>
<tr>
<td>• Tamoxifen approved in United States for treatment of advanced breast cancer in post-menopausal women (first medicine approved by FDA for risk reduction of any cancer), 1977</td>
</tr>
<tr>
<td>• ICI releases the drug to the US market without patent</td>
</tr>
<tr>
<td>• US patent for tamoxifen finally approved to ICI through court of appeals, 1985</td>
</tr>
</tbody>
</table>
Economic and regulatory enablers in the development of tamoxifen therapy

In 1957, the first non-steroidal anti-oestrogen was discovered by Merrell and investigated as a contraceptive, along with other applications, including breast cancer. However, this research was stopped due to extensive side effects and toxicity concerns. In the 1960s, investment by ICI in the UK lead to the discovery of another type of non-steroidal anti-oestrogen, called tamoxifen, that had fewer side effects. Initially, tamoxifen was investigated as a contraceptive. When it was found to not be effective as a contraceptive, ICI shifted its focus to try to find an alternative purpose for it. This research included investigating its potential as a drug for treating breast cancer. However, with the advent of chemotherapy, the market for breast cancer drugs was not very lucrative, and senior management decided to abandon further development of the drug. The primary reason for this decision was that the estimated financial return for co-marketing a breast cancer drug that was to be used by a limited number of patients and only for about a year, was low.

The low economic expectations on the part of ICI can also be seen in developments surrounding tamoxifen’s patent protection. ICI received a patent for tamoxifen in 1965 in the UK, but was denied the patent on tamoxifen in the United States based on a patent that Merrell had obtained for non-steroidal anti-oestrogens. After multiple further attempts were made to obtain the patent in the United States, it was eventually approved in 1985. This delay in patenting highlights an interesting development: ICI continued to invest in tamoxifen-related research without knowing whether it would have exclusive rights to sell its product to the US market. At the same time, it was clear that all the other pharmaceutical companies had no interest in the clinical development of tamoxifen, because it was thought that the drug either was not going to work very well or would not generate enough revenue (Poirot 2011).

Ultimately, however, ICI managed to recover the losses that had resulted from developing tamoxifen as a contraceptive that ultimately proved to be ineffective, by repurposing the drug as a treatment for breast cancer (Allarakhia 2013; Jordan 2003). The revenue from developing tamoxifen was increased when a further application for tamoxifen as a treatment for osteoporosis was discovered (Jordan 2014).

In conclusion, tamoxifen as a treatment for breast cancer was not initially driven by economic considerations but, instead, was driven by the persistence of the scientific researchers Walpole and Jordan. The continued development of tamoxifen was not impeded by the limited patent protection because it was considered unlikely to work or to lead to significant revenue. Ultimately tamoxifen is yielding substantial revenue because it is now used as a treatment for breast cancer, both on its own and as an adjuvant therapy; as a preventative treatment for breast cancer; and as a treatment for osteoporosis.
Appendix C: Coronary heart disease case study

The story of treatment of coronary heart disease: Statins

Background and context

Coronary heart disease/coronary artery disease (CHD/CAD) is the leading cause of death worldwide (Finegold et al. 2012; Rosamond et al. 2007; Scarborough et al. 2011), placing a major economic and resource burden on the public health system. As of 2010, CAD resulted in more than 7 million deaths globally every year (Lozano et al. 2012), and in the United States alone it accounts for approximately 600,000 deaths annually (Kochanek et al. 2009). The disease is most prevalent in middle and older age, with the risks approximately tripling with each decade of life (Finegold et al. 2012). According to established trends in the United States, one in two healthy 40-year-old men and one in three healthy 40-year-old women will develop CHD/CAD in the future (Rosamond et al. 2007).

Developing treatments for coronary heart disease

Because the main risk factors have been identified as high cholesterol levels, smoking and obesity, efforts have been made to develop treatments that would tackle these risk factors and decrease the prevalence of CHD/CAD. Today it is known that smoking is associated with about 54% of cases of CHD mortality (Kivimäki et al. 2012) and obesity with about 20% of cases of CHD mortality (Kivimäki et al. 2012). Despite that, obesity levels continue to rise worldwide, having nearly doubled since 1980 (WHO 2014b). More than 1.4 billion adults aged 20 and over were overweight in 2008 (making up 35% of the adult population), and nearly 500 million of these were obese (11% of adult population) (WHO 2014b). With increasing levels of obesity, the number of people at risk of developing CHD is also on the rise. Even more tragically, more than 40 million children under the age of 5 were overweight or obese in 2012 (WHO 2014b), increasing these children’s risk factors for diseases, including CHD, from an extremely early age. Despite the fact that the prevalence of daily smokers worldwide decreased from 41.2% to 31.1% in men and from 10.6% to 6.2% in women (Ng et al. 2014), due to population growth, the actual number of daily smokers has in fact increased, from 721 million worldwide in 1980 to 967 million worldwide in 2012, again indicating that more people in the future can be expected to suffer from smoking-related CHD.

Once the key discoveries related to cholesterol had been made, indicating that people who died of heart attacks were found to have plaques (filled with cholesterol) in their coronary arteries and indicating that rabbits fed a high-cholesterol diet would develop coronary disease similar to human atherosclerosis, a lot
of scientific time and effort have been devoted to develop treatments that tackle this cholesterol-based risk factor of CHD. Between 1949 and 1956, a series of epidemiological observations were made, including the discovery of cholesterol being contained in low density lipoprotein and the fact that heart attacks were correlated with elevated levels of blood cholesterol but that they were less frequent when the blood contained elevated levels of high density lipoprotein (Gofman et al. 1949, 1950, 1956). As further evidence emerged indicating that high blood cholesterol levels are linked to heart disease – especially after the 1955 Framingham Heart Study demonstrated clearly that blood cholesterol level is a risk factor for coronary artery disease (Dawber & Kannel 1958; Dawber et al. 1957, 1959) – scientists in both academia and industry began searching for drugs to lower blood cholesterol. In the 1950s and 1960s, many companies were searching for molecules that would block one of the 30 steps in the synthesis of cholesterol from acetyl-coenzyme A (CoA). In 1970, the earliest statin, compactin, was discovered by Endo at Sankyo, which started a series of statin discoveries and a long debate on their effectiveness. In 1994, the Scandinavian Simvastatin Survival Study (4S) demonstrated a significant reduction in mortality due to statins in people at extremely high risk for recurrent CAD, effectively ending the cholesterol debate (Scandinavian Simvastatin Survival Study Group 1994). Between 1996 and 1998, other secondary prevention trials showed the benefits of statins even in populations with lower risks of CAD (Cholesterol and Recurrent Events study; Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] study), confirming the discovery of statins as a significant breakthrough in the fight against CHD/CAD (LIPID 1998).

Despite the proven decrease of cholesterol blood levels in people treated with statins, it is important to note that there are adverse side effects which can be associated with their use, such as increased concentrations of liver enzymes, muscle problems, and an increased risk of diabetes (Bellosta & Corsini 2012; Naci et al. 2013). Moreover, as mentioned above, statins tackle only one of the risk factors, cholesterol, and thus cannot reverse the damage associated with smoking or help with the obesity reduction. It is evident that more could still be done in the fight against CHD/CAD.

The timelines below provide an overview of the history of various advances linked to the ‘fight against CHD/CAD’.

In this case study, contextual factors leading to innovations in coronary heart disease management are examined. A specific focus is on the development of statins, because to date they have offered the most substantial breakthrough in the management of heart disease. We examine the confluence of scientific, technological, social, political, economic and legal drivers of innovation and identify the key associated actors and major events, alongside the potential implications for other innovation efforts and disease areas are identified.

**Key Learning and Messages**

**Table 13. Key insights on breakthrough dynamics in coronary heart disease**

<table>
<thead>
<tr>
<th>Understanding the science and the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Most significant developments in heart disease prevention came from efforts to understand the root causes of heart disease. Two key discoveries were made: people who died of heart attacks were found to have</td>
</tr>
</tbody>
</table>
A multi-stakeholder, interdisciplinary approach

3. As evidence grew that high blood cholesterol levels were linked to heart disease, scientists in both academia and industry began searching for drugs to lower blood cholesterol. It is believed that initially it was a combination of population science and basic science, typically funded by government and led by academic institutions, that were the driving factors behind the advancements in CHD/CAD. Later on, following the discovery of statins, industry became a lot more involved. Sankyo and Merck were the two main companies involved, with Sankyo producing the first statin (compactin), proven to reduce cholesterol in animals, and Merck following suit with lovastatin (Endo 2010).

4. An importance of collaborative work can also be illustrated by the Framingham Heart Study, a long-term, ongoing cardiovascular study on residents of the town of Framingham, in the United States. The study, which began in 1948 with 5,209 adult subjects and is now on its third generation of participants (Mahmood et al. 2013), contributed extensively to the existing knowledge of the epidemiology of CHD/CAD (Dawber et al. 1951). Much of the now-common knowledge concerning heart disease – such as the effects of diet, exercise, and common medications such as aspirin – is based on this longitudinal study, which was a successful collaboration between the National Heart, Lung, and Blood Institute and Boston University (since 1971) (Mahmood et al. 2013), with health professionals from both the hospitals and the universities of Greater Boston working together towards a common goal of better understanding CHD/CAD. Another large and influential epidemiological study, the Seven Countries Study, was also a collaboration, between the University of Minnesota and seven researchers in the other countries. Both of these studies were critical in understanding how heart disease risk is linked to cholesterol, blood pressure, smoking, diabetes and other factors.

The role of a social movement

5. A number of high-profile cases of CHD/CAD were featured in the media in the late 1980s through to the 2000s, including well-known politicians who had a heart attack and/or underwent heart surgery. This raised awareness of the disease in the public and resulted in some of them engaging in humanitarian and charitable work related to heart disease. Around that time the ‘Look after your heart’ campaign was launched. It was designed to reduce deaths from heart disease; therefore, cutting smoking prevalence and introducing smoking policies at work were vital parts of the campaign.

6. In the United States, key advocates have included patient groups and associations; foundations, such as the American Heart Foundation; but also celebrities and politicians. The media and the scientific community have also played an important role.

Regulatory and legislative scope and efficiency

7. A substantial amount of time elapsed between the development of the different statins and their subsequent approval by the FDA. The delay was partly due to controversies regarding the possibility of increased risk of cancer associated with compactin.

8. After trials of lovastatin stopped due to the cancer rumours associated with compactin, clinicians pressured the FDA for permission to restart clinical studies with lovastatin. The FDA agreed to these trials with high-risk
patients only (those who already had heart disease/high cholesterol). This pre-approval led to the discovery that lovastatin reduced LDL cholesterol, and that it did so safely. Lovastatin was launched in 1987, obtaining official approval from the FDA for high-risk patients only.

Table 14. Key scientific and technological trigger points of the statins breakthrough

<table>
<thead>
<tr>
<th>Scientific and technological advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• American cardiologist James B. Herrick concludes that the slow, gradual narrowing of the coronary arteries could be a cause of angina. He is credited with first coining the term heart attack, 1912</td>
</tr>
<tr>
<td>• A group of physicians and social workers forms the Association for the Prevention and Relief of Heart Disease in New York City, 1915</td>
</tr>
<tr>
<td>• Association for the Prevention and Relief of Heart Disease becomes the American Heart Association, 1924</td>
</tr>
<tr>
<td>• National Heart Institute established, 1948</td>
</tr>
<tr>
<td>• Arteriosclerosis (known as atherosclerosis today) is added to the International Classification of Diseases, which causes a sharp increase in reported deaths from heart disease, 1949</td>
</tr>
<tr>
<td>• Gofman makes a series of epidemiological observations, 1949–1956:</td>
</tr>
<tr>
<td>o Cholesterol is contained in low density lipoprotein (LDL)</td>
</tr>
<tr>
<td>o Heart attacks are correlated with elevated levels of blood cholesterol</td>
</tr>
<tr>
<td>o Heart attacks are less frequent when the blood contains elevated levels of high density lipoprotein (HDL)</td>
</tr>
<tr>
<td>• Framingham Heart Study demonstrates that blood cholesterol level is a risk factor for CAD, 1955</td>
</tr>
<tr>
<td>• Much interest in cholesterol biosynthetic pathway; key studies published by Konrad E. Bloch, Feodor Lynen, John Cornforth, and George Popják, 1955–1965</td>
</tr>
<tr>
<td>• Cigarette smoking found to increase the risk of heart disease, 1960</td>
</tr>
<tr>
<td>• AHA endorses prudent diet, reflecting focus on relationship between diet and blood cholesterol, 1961</td>
</tr>
<tr>
<td>• Bloch and Lynen awarded Nobel Prize for the outlines of the reduction of HMGCoA to mevalonate, 1964</td>
</tr>
<tr>
<td>• Seven Countries Study shows that the incidence of heart attacks (in 15,000 middle-aged men followed for 10 years) is linearly proportional to the blood level of cholesterol, 1965–1970</td>
</tr>
<tr>
<td>• Earliest statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor), compactin, discovered by Endo at Sankyo, 1970s</td>
</tr>
<tr>
<td>• Merck isolates a statin very similar to compactin in chemical structure, named mevinolin (later changed to lovastatin), 1979</td>
</tr>
<tr>
<td>• Endo isolates monacolin K, a compound identical to lovastatin, from a different organism, 1979</td>
</tr>
<tr>
<td>• Clinical trials for lovastatin begin at Merck, 1980</td>
</tr>
<tr>
<td>• Clinical trials of lovastatin at Merck discontinued because of rumours (to this day never substantiated) that Sankyo’s compactin (which is closely related to lovastatin) caused certain cancers in dogs, 1980</td>
</tr>
<tr>
<td>• Animal studies with lovastatin resume at Merck, 1982</td>
</tr>
<tr>
<td>• Merck makes lovastatin available to several prominent US clinicians, who had asked for it to treat patients with severe hypercholesterolemia unresponsive to available agents. The drug shows dramatic activity in lowering LDL cholesterol and total cholesterol in the blood, with very few side effects, 1982</td>
</tr>
<tr>
<td>• Coronary Primary Prevention Trial results reported (first large-scale, double-blind, placebo-controlled trial to address the lipid hypothesis, Lipid Research Clinics Program), 1984</td>
</tr>
<tr>
<td>• The Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease obtains an unanimous conclusion that there is a causal relationship between blood cholesterol levels and CAD risk, 1984</td>
</tr>
<tr>
<td>• Brown and Goldstein receive Nobel Prize for their work on LDL pathway, 1985</td>
</tr>
<tr>
<td>• National Cholesterol Education Program (NCEP) established, 1985</td>
</tr>
</tbody>
</table>
• Lovastatin given FDA approval for patients with high cholesterol levels that cannot be reduced by diet. The drug is later approved for marketing in 42 additional countries, 1987
• NCEP Adult Treatment Panel (ATP) first publishes guidelines for the detection, evaluation and treatment of hyperlipidemia, 1988
• Pravastatin launched by Sankyo, 1989
• Pravastatin approved for marketing, 1991
• Simvastatin approved for marketing, 1991
• Fluvastatin approved for marketing, 1994
• Scandinavian Simvastatin Survival Study (4S) shows significant reduction in mortality, effectively ending the cholesterol debate (though this study covered only people at extremely high risk for recurrent CAD), 1994
• Other secondary prevention trials show benefits of statins even in population with lower risks of CAD [Cholesterol and Recurrent Events study and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study], 1996–1998
• Atorvastatin approved for marketing, 1997
• Cerivastatin approved for marketing, 1998
• Cerivastatin withdrawn because of a large number of reports of rhabdomyolysis, of which more than 50 cases were fatal, 2001
• Heart Protection Study confirms and expands previous evidence, including firmly establishing the benefit of simvastatin in women and its effectiveness for reduction of the risk not only of CHD events, such as myocardial infarction, but also of strokes, 2002
• Rosuvastatin approved for marketing, 2003

The science and the evidence – early characterisation of coronary hearth disease/coronary artery disease

Although atherosclerosis was first recognized during the 19th century, its etiological and pathological significance had not yet been established. The first hint of the relationship between atherosclerosis and cholesterol took place in 1910, when Windaus discovered more than 20-fold higher concentrations of cholesterol in the atherosclerotic plaques from aortas than in normal human aortas (Goldstein & Brown 2003). Three years later the first experimental production of atherosclerosis took place, as pathologist Nikolai Anitschkow fed pure cholesterol to rabbits, producing marked hypercholesterolemia and severe atherosclerosis of the aorta in this animal model (Anitschkow 1913). In the early 1950s, John Gofman at Berkeley unfolded the epidemiologic study of the cholesterol–coronary connection and found not only that heart attacks correlated with elevated levels of blood cholesterol, but also that the cholesterol was contained in low density lipoprotein. He also observed that heart attacks were less frequent when the blood contained elevated levels of high density lipoprotein (Gofman et al. 1949, 1950, 1956). We now know that HDL helps remove LDL cholesterol from the arteries, carrying LDL cholesterol away from the arteries and back to the liver, where it is broken down and passed from the body, making the HDL the ‘good cholesterol’. From this initial discovery, the connection between blood cholesterol and coronary atherosclerosis was confirmed by a physiologist at the University of Minnesota, Ancel Keys, whose Seven Countries Study (beginning in the mid-1960s) reported that the incidence of heart attacks in middle-aged men followed for 10 years was linearly proportional to their blood level of cholesterol (Keys ed. 1970; Keys et al. 1955, 1966). Another extremely influential study – the Framingham Heart Study, carried out by the National Heart Institute in Framingham – provided the first solid and unarguable evidence that
individuals with higher blood cholesterol levels at the time of the baseline examination were more likely to experience a myocardial infarction in the subsequent years of follow-up and that the risk was increased by a number of other factors, such as high blood pressure and smoking (Wilson et al. 1980).

**Early development of drugs for coronary heart disease/coronary artery disease**

In the 1950s and 1960s, as evidence grew that high blood cholesterol levels were indeed linked to heart disease, scientists in both academia and industry began searching for drugs to lower blood cholesterol by searching for molecules that would block one of the 30 steps in the synthesis of cholesterol from acetyl-coenzyme A (CoA) (Endo 2010). Many molecules were synthesized, with some being effective in animals; however, none seemed effective at the clinical level (Steinberg 2006). Finally, in 1959, the first cholesterol-lowering agent that inhibited cholesterol synthesis, Triparanol (MER/29), was introduced into clinical use in the United States (Endo 2010). It was, however, withdrawn from the market soon after due to reported serious side effects, including cataracts (Avigan et al. 1960; Blohm & MacKenzie 1959). The search was more successful in the UK, and the product clofibrate, synthesized at Imperial Chemical Industries (ICI), was successfully marketed in 1958 (Thorpe & Warig 1962). In the 1960s, many derivatives of clofibrate, which proved even more potent and safe than clofibrate, were also developed. However, these fibrates’ cholesterol-lowering effects were minimal in most patients (Thompson 1989), and so the search continued.

**The discovery of compactin**

In late 1960s, CHD was already the main cause of death in the United States (Endo 2010; Fuster & Kelly eds 2010) and the need for a cure was becoming more urgent. Not long after, in 1973, at the laboratories of Sankyo, Endo discovered the first statin – compactin. In 1974, biologists at Sankyo evaluated the efficacy of compactin by feeding rats a diet supplemented with compactin for 7 days. Unfortunately, there was no reduction in serum cholesterol (Endo 1992), making evaluations of compactin in other animal species, such as dogs and monkeys, seem unattractive. Despite these early results, the project was not discontinued; experiments continued, and it was confirmed that compactin had a profound cholesterol-lowering effect in dogs (Tsujita et al. 1979) as well as monkeys (Kuroda et al. 1979), making compactin a valid candidate for a new type of drug. This resulted in a launch of the Compactin Development Project in August 1976 – a collaboration between Endo and various pharmacologists, pathologists, toxicologists, organic chemists and microbiologists that led to the clinical development of compactin at Sankyo. Interestingly, at around the same period, researchers at GlaxoSmithKline had also discovered compactin (Brown et al. 1976), but they were unable to develop it as a cholesterol-lowering agent due to the lack of success in lowering cholesterol in rodents (which was consistent with Endo’s rat study results) (Fears et al. 1980). Thus Sankyo remained the only player with a proven cholesterol-lowering statin. The phase 1 clinical trial for compactin began in November 1978. A year later, in phase 2 of the trial, compactin was administered to patients with serious cases of hypercholesterolemia at 12 hospitals, and positive reports of efficacy and safety came from all of the participating hospitals (VII International Symposium on Drugs Affecting Lipid Metabolism 1980). In August 1980, however, Sankyo discontinued the clinical development of compactin, which had been progressing smoothly until that time, due to reports that at extremely high doses (of 100 or 200 mg/kg/day for 2 years) the drug caused lymphoma in dogs. Despite
the fact that no abnormalities were reported in dogs receiving 20 mg/kg/day, and the dogs affected by cancer were receiving dosages 200 times larger than what would be used in human patients, compactin was discontinued, never to be resurrected again. In the development of the second statin, called pravastatin, Sankyo avoided the same trouble by limiting its maximum dose to 25 mg/kg/day (Interview Format in mevastatin [in Japanese] 1981).

Developing alternative statin-based treatments

At the end of the 1970s, when the findings showing the dramatic effects of compactin in dogs and monkeys first emerged, many pharmaceutical companies were inspired to join the search for another statin. In February 1979, under the direction of Alfred Albert at Merck, a statin very similar to compactin, named called mevinolin (later lovastatin), was first isolated. In April 1980, Merck began preliminary clinical studies of lovastatin, but the trials were discontinued after only 5 months due to emerging reports of lymphoma cases in dogs taking the chemically similar compactin. Because the chemical similarities between compactin and lovastatin are vast, these reports could not be ignored, and they resulted in the suspension of the lovastatin project (Vagelos 1991; Vagelos & Galambos 2004).

However, in 1982, small-scale clinical investigations asked Merck for lovastatin to test its effect in selected small groups of patients with severe heterozygous familial hypercholesterolaemia who weren’t responding to the existing therapy (Hajar 2011). The FDA was very cooperative and facilitated this request. The investigators found dramatic reductions in LDL cholesterol with very few adverse effects (Bilheimer et al. 1983; Illingworth & Sexton 1984), although in early 1981 Brown and Goldstein reported that lovastatin could lead to an extreme fall in plasma LDL levels in dogs (Kovanen et al. 1981). A further breakthrough in the history of statins came with a report by Mabuchi, from Kanazawa University, sharing impressive results of highly successful compactin treatment of severe heterozygous patients with familial hypercholesterolemia (Mabuchi et al. 1981). The patients displayed a decline in LDL cholesterol of 30%, with no fall in HDL cholesterol. Even greater reduction in levels of LDL cholesterol, by 50% to 60%, was achieved by a combination of compactin and cholestyramine in these patients (Mabuchi et al. 1983).

Bringing statins to the market

These successes led Merck to re-start the lovastatin project and to conduct large-scale clinical trials of lovastatin in patients at high risk. At the same time, in 1984, long-term toxicity studies in dogs began. When the drug was confirmed to dramatically reduce cholesterol levels, to be well tolerated and to not cause tumours, lovastatin was given FDA approval to become the first commercial statin, in September 1987. Lovastatin was soon followed by a new statin at Merck, named simvastatin, and another one at Sankyo, named pravastatin, which launched in 1989. In the interval since lovastatin was first commercialized, a further 6 statins, including 2 semi-synthetic statins (simvastatin and pravastatin) and 4 synthetic statins (fluvasatin, atorvasatin, rosuvastatin and pitavastatin), have been introduced to the market (Endo 1992, 2010).

Statins have now been tested in many large-scale clinical trials, involving 90,000 subjects who were followed for 5 years (Scandinavian Simvastatin Survival Study Group 1994; Shepherd et al. 1995; Steinberg 2006) with consistent results: Treatment with statins lowers plasma LDL levels by 25–35% and
substantially reduces both morbidity and mortality from CHD symptoms (Grundy 1998), thereby reducing the frequency of heart attacks by 25–30% (Endo 2010) without major adverse effects (Endo 2010; Grundy 1998). However, we now know that statins do result in higher odds of developing diabetes (Naci et al. 2013). Despite the proven decrease of cholesterol blood levels with statins, it is therefore important to maintain the continuous advancements in search of the best possible treatment for CHD/CAD. Moreover, as mentioned earlier, statins only tackle one of the risk factors, cholesterol, and thus cannot reverse the damage associated with smoking or help with the obesity reduction. It is evident that more could still be done in the fight against CHD/CAD.

Table 15. Key social influences on innovation in coronary heart disease

<table>
<thead>
<tr>
<th>Social advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A group of physicians and social workers forms the first Association for the Prevention and Relief of Heart Disease in New York City, 1915, which becomes the American Heart Association, 1924</td>
</tr>
<tr>
<td>• President Eisenhower suffers a first heart attack at age 64. He is put on a highly publicized low-fat, low-cholesterol diet, 1955</td>
</tr>
<tr>
<td>• American Heart Association conducts a TV fundraiser on all three networks, urging Americans to reduce their intake of total fat, saturated fat, and cholesterol. AHA recommends ‘heart-healthy’ margarine, corn oil, breakfast cereal, and skim milk</td>
</tr>
<tr>
<td>• Cigarette smoking found to increase the risk of heart disease, 1960</td>
</tr>
<tr>
<td>• American Heart Association raise US$35 million and officially adopts AHA board member Ancel Keys’s low-fat diet, 1961</td>
</tr>
<tr>
<td>• American Heart Association’s anti-fat guidelines are extended to children and pregnant women. As a direct consequence, the federal government’s WIC program – food assistance to women with infant children – only allows skim or low fat milk to children over age 2, 1970</td>
</tr>
<tr>
<td>• Final version of the Dietary Guidelines for Americans is issued. For the first time, an agency of the US federal government is telling the American people to eat less fat, 1977</td>
</tr>
<tr>
<td>• Dick Cheney has his first heart attack at the age of 37, 1978</td>
</tr>
<tr>
<td>• U.S. Department of Agriculture releases the official first ever low fat dietary guidelines for Americans, ‘Eat Less Fat, Saturated Fat, and Cholesterol’, 1980</td>
</tr>
<tr>
<td>• Dick Cheney has his second heart attack, 1984</td>
</tr>
<tr>
<td>• The NIH and the American Heart Association establish the National Cholesterol Education Program and a ‘war on cholesterol’, 1986</td>
</tr>
<tr>
<td>• CNN interviewer Larry King suffers a heart attack and undergoes bypass surgery. Following his recovery, he becomes active in awareness-raising and humanitarian work, receiving a plaque from the American College of Cardiology for his humanitarian and charitable work related to heart disease, 1987</td>
</tr>
<tr>
<td>• Launch of the ‘Look after your heart’ campaign, designed to reduce deaths from heart disease. Cutting smoking prevalence and introducing smoking policies at work will be an important part of the campaign, 1987</td>
</tr>
<tr>
<td>• Dick Cheney has his third heart attack and undergoes quadruple bypass surgery, which, though first performed in the 1960s, was not widely used for a decade or so, pending safety improvements. The use of the relatively new procedure constitutes important news, 1988</td>
</tr>
<tr>
<td>• Surgeon General’s Report on Nutrition and Health is released: ‘Highest priority is given to reducing fat intake’, 1988</td>
</tr>
<tr>
<td>• Dick Cheney has his fourth heart attack, 2000</td>
</tr>
<tr>
<td>• David Letterman undergoes quintuple bypass surgery. It becomes well known that his father died of heart disease at a very young age, 2000</td>
</tr>
<tr>
<td>• Bill Clinton undergoes quadruple bypass surgery, 2004</td>
</tr>
</tbody>
</table>
Social influences in the field of coronary heart disease

The role of social influences on the process of treatment developments, as well as in the fight against the risk factors of CHD/CAD, cannot be underestimated.

The fight against smoking

After the public announcement of the association between tobacco smoking and an increased risk of CHD/CAD in 1960, a number of campaigns have been launched to publicise the harming effects of smoking, with the first campaign taking place in 1969. Since then, a lot of effort has been made, especially in the western world, to make smoking look as unappealing as possible and to ultimately make it socially unacceptable (Bayer & Stuber 2006; Brandt 1998; Markle & Troyer 1979). Already by the end of the 1970s, evidence began to emerge that significant proportions of non-smokers increasingly viewed smoking as undesirable and that large proportions of the smokers themselves were agreeing with it (Bayer & Stuber 2006). In 1979, Markle and Troyer wrote: ‘In addition to being seen as harmful to health, smoking came to be seen as undesirable, deviant behaviour and smokers as social misfits. In fact data shows that people increasingly view smoking as reprehensible’ (Markle & Troyer 1979, p.617). Between 1980 and 2012, the proportion of daily smokers has decreased from 41.2% to 31.1% in men and from 10.6% to 6.2% in women worldwide (Ng et al. 2014), suggesting that the efforts to stigmatize smoking have been paying off. However, due to population growth from 1980 to 2012, the combined number of daily smokers worldwide has actually increased, from 721 million to 967 million, indicating that the number of people at risk of developing CHD/CAD is in fact rising.

Leveraging high-profile cases for awareness raising

With the first statin having been discovered after CHD/CAD had already become the main killer worldwide, the highly publicised disclosures of high-profile cases of heart problems – such as Dick Cheney’s first heart attack in 1978 and his second one in 1984 – helped to put the problem that there

---

28 In 1978, Cheney was elected to the US House of Representatives representing Wyoming’s at-large Congressional district from 1979 to 1989; he was re-elected five times. Between 2001 and 2009 he was the Vice President of the United States.
was no real cure for CHD in the spotlight (Altman 2001). The long-coming approval of lovastatin by the FDA in 1987 was an important step towards treatment advancements. In the same year another high-profile celebrity – the CNN interviewer Larry King – also suffered a heart attack and underwent a bypass surgery. He abruptly ceased smoking and devoted his life to humanitarian and charitable work related to heart disease, for which he since received a plaque from the American College of Cardiology (to the Larry King Cardiac Foundation). Only a year later, in 1988, Dick Cheney had his third heart attack and opted to undergo a quadruple bypass surgery, which made news due to the fact that, though it was first performed in the 1960s, the procedure was still considered relatively new and was not widely used for almost a decade, pending safety improvements.

From the year 2000 onwards, when Dick Cheney had his fourth heart attack, the mass of CHD/CAD-related public disclosures snowballed, further raising the public and social visibility of the issue. The high-profile cases included David Letterman, who underwent a quintuple bypass surgery in 2000; Bill Clinton, who underwent his quadruple bypass surgery in 2004; Elizabeth Taylor, who was diagnosed with heart disease in 2004 and passed away from heart failure in 2011; and the actor Robin Williams, who underwent heart surgery in 2009. In 2010, Dick Cheney had his fifth (and last) heart attack and received a heart implant transplant. He decided to raise public awareness even further by publishing a memoir in large part dedicated to his struggles with heart disease, in 2011.

Table 16. Key political and economic enablers in innovation in coronary heart disease

<table>
<thead>
<tr>
<th>Political and economic advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A group of physicians and social workers forms the first Association for the Prevention and Relief of Heart Disease in New York City, 1915, becoming the American Heart Association, 1924</td>
</tr>
<tr>
<td>• National Heart Institute established, 1948</td>
</tr>
<tr>
<td>• First World Conference on Smoking and Health held in New York, 1967</td>
</tr>
<tr>
<td>• Sankyo discontinues the clinical development of compactin due to cancer rumours, 1980</td>
</tr>
<tr>
<td>• A patent is granted for lovastatin in the United States and subsequently in a number of other countries. In other countries, patents go to Sankyo for monacolin K, 1980</td>
</tr>
<tr>
<td>• Clinical trials of lovastatin suspended due to similarities to compactin, 1980</td>
</tr>
<tr>
<td>• Small-scale, unapproved lovastatin trials unopposed by the FDA – they treat patients with severe hypercholesterolemia that is unresponsive to available agents and find dramatic positive results, 1982</td>
</tr>
<tr>
<td>• Launch of the ‘Look after your heart’ campaign, designed to reduce deaths from heart disease, 1987</td>
</tr>
<tr>
<td>• FDA approval for lovastatin granted, 1987</td>
</tr>
<tr>
<td>• National Cholesterol Education Program Adult Treatment Panel first publishes guidelines for the detection, evaluation and treatment of hyperlipidemia, 1988</td>
</tr>
<tr>
<td>• Pravastatin approved for marketing, 1991</td>
</tr>
<tr>
<td>• Simvastatin approved for marketing, 1991</td>
</tr>
<tr>
<td>• Fluvastatin approved for marketing, 1994</td>
</tr>
<tr>
<td>• Atorvastatin approved for marketing, 1997</td>
</tr>
<tr>
<td>• Cerivastatin approved for marketing, 1998</td>
</tr>
<tr>
<td>• Cerivastatin withdrawn because of a large number of reports of rhabdomyolysis, of which more than 50 cases were fatal, 2001</td>
</tr>
<tr>
<td>• An EU directive requiring bigger, bolder health warnings on tobacco packaging becomes law, 2001</td>
</tr>
</tbody>
</table>
Economic and political factors in the fight against CHD/CAD

The economic case for developing treatment in CHD is strong because ever since the 1960s CHD/CAD has been the leading cause of death worldwide (Endo 2010; Finegold et al. 2012; Rosamond et al. 2008; Scarborough et al. 2011; WHO), placing a major economic and resource burden on the public health system. As of 2010, CAD had resulted in over 7 million deaths globally (Lozano et al. 2010). In the United States alone, it accounts for approximately 600,000 deaths every year (Kochanek et al. 2009). The disease is most prevalent in middle and older age, with the risks approximately tripling with each decade of life (Finegold 2012). Estimates based on established trends in the United States foresee that one in two healthy 40-year-old men and one in three healthy 40-year-old women will develop CHD/CAD in the future (Rosamond et al. 2007).

Politics also played a role with regards to the pharmaceutical developments. Because both Sankyo and Merck were working on their respective statins around the same time, there was significant pressure to become the first one with a patent and subsequently a drug on the market. As discussed above, due to compactin and lovastatin’s close structural similarity, Merck suspended clinical trials with lovastatin when the reports of compactin’s link to lymphoma in dogs emerged. However, in 1982, small-scale clinical investigations asked Merck for lovastatin to test its effect in selected small groups of patients with severe heterozygous familial hypercholesterolaemia who weren’t responding to the existing therapy (Hajar 2011). The FDA was very cooperative and facilitated this request. The investigators found dramatic reductions in LDL cholesterol, with very few adverse effects (Bilheimer et al. 1983; Illingworth & Sexton 1984), and soon afterwards clinical trials of lovastatin re-started. In 1980, the first statin patent was granted for lovastatin in the United States (and it was subsequently granted in a number of other countries). In the end, Merck was the first company to patent a statin, despite Sankyo being the first to develop one, due to the fact that Merck addressed the safety concerns associated with the use of statins more quickly than Sankyo did. In the same year, a patent was also granted to Sankyo in other countries, for a different statin, named monacolin K (with a clearly stated maximum safety dose of 25 mg/kg/day) (Endo 2010). Following the FDA approval for lovastatin in 1987, sales for statins reached US$25 billion in 2005 (Endo 2010) and US$35.3 billion worldwide in 2009 (Hajar 2011). Finding an effective treatment for a very common disease is an extremely lucrative business, which no doubt will provide an incentive for further treatment advancements in the future.
Appendix D: Parkinson’s disease case study

The story of treatment of Parkinson’s disease: From levodopa to deep brain stimulation to cell therapy

Background and Context

After Alzheimer’s disease, Parkinson’s disease (PD) is the second most common neurodegenerative disorder, affecting approximately 7 million people globally and 1 million people in the United States alone (de Lau & Breteler 2006; Yao et al. 2013). The prevalence rates are about 0.3% of the whole population in industrialized countries. PD becomes more common with age, and prevalence rises from 1% in those over 60 years of age to 4% in those over 80 (de Lau & Breteler 2006).

Since the first time Parkinson’s disease was documented in the literature, in 1817 (Parkinson 1817, reprinted in 2002), medical advances and innovation in treatment have considerably improved the quality of life of the sufferers. Efforts to manage the disease have been targeted at mitigating symptoms, because no disease-modifying therapy has yet been found. One of the biggest breakthroughs in the treatment of PD was the development of the drug levodopa. Once it transpired that the positive effects of levodopa diminish after a few years of treatment, as the human body becomes resistant to the drug, a second breakthrough followed, in the form of deep brain stimulation as a potential treatment of PD. This was followed by ongoing advancements and developments regarding cell therapies, with some promising results so far.

Key learning and messages

Table 17. Key insights on breakthrough dynamics in Parkinson’s disease

<table>
<thead>
<tr>
<th>Understanding the science and the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Scientific curiosity and technological developments were crucial driving factors behind the discovery and development of new treatments for Parkinson’s disease (PD). The discovery of mechanisms of dopamine deficiency, alongside the technological advances in science, led to the development of new treatments. This was a lengthy process, starting from the synthesis of levodopa in a chemistry laboratory in 1911, through the first reported trial of intravenous levodopa in PD in 1961, and finally to the demonstration of its beneficial effects (from oral use) in PD in 1967. Overall, it took 60 years from the synthesis of levodopa to its approval by the FDA. Similarly, deep brain stimulation therapy has been first developed in 1950s but only approved as treatment for PD in 2002, and cell therapy developments in medicine span an 80 year period, from the first attempt to cure cancer using calf embryos (Wolf 2002) to the long-term goal of making dopamine-producing neurons from patients’ own skin or hair cells (Robson 2012).</td>
</tr>
</tbody>
</table>

A multi-stakeholder, interdisciplinary approach
2. Advancements in research took place in both academia and industry. Not directly related to any potential treatments, levodopa was first isolated from fava bean seedlings at Roche laboratories in 1913. Later work by Hornykiewicz, which showed dopamine deficiency in PD and suggested using L-dopa to treat the disease for the first time, took place at Oxford University and the University of Vienna. Similarly, the development of deep brain stimulation (DBS) was characterised by an extensive degree of collaboration between academia and industry. The initial modern form of DBS was heralded by the neurosurgeon/neurologist team of Benabid and Pollak (Benabid et al. 1987) and enabled by the later involvement of Medtronic, the largest medical device company in the world. The National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH), supported research on DBS to determine its safety, reliability and effectiveness as a treatment for PD. This NINDS-supported research on brain circuitry was critical to the development of DBS. Cell therapies, according to Mason et al. (2011), were based initially on clinical trial and error and later on laboratory science, and are now a distinct industry in its own right, constituting the fourth and final therapeutic pillar of global healthcare, alongside pharmaceuticals, biopharmaceuticals and medical devices.

3. Clinical trials indicated that:
   - Levodopa is effective in treatment of PD, but side effects may be present.
   - Symptoms often return after a few years; thus new treatments should be developed and evaluated.
   - DBS reduces symptoms, but pharmacological treatment may still be needed alongside it.

4. Stem cell transplants are a recent research target in cell therapy. Recently Studer’s group (Kriks et al. 2011) succeeded in making highly efficient dopamine-producing neurons from human embryonic stem cells and transplanted them into the brains of rodents with Parkinson’s disease.

The need for continued innovation

5. The aging of the population in the western world entails that the number of people living with PD is expected to continuously rise in the future. This trend, together with the fact that the improvements in symptoms due to levodopa treatment often only last for a few years before symptoms worsen again, has led to the realisation that new and supplementary treatments need to be developed and evaluated.

The role of a social movement

6. A number of high-profile cases of PD patients, including Muhammad Ali and Michael J. Fox, started to reach the public in the 1980s and 1990s, and this raised awareness of the disease. This increased public awareness was accompanied by activism, both in raising awareness and in supporting research, by these individuals. Activism contributed to the establishment of a number of foundations and charities, and it inspired an increase of depictions of PD in the media. Further support for PD research came from celebrities, such as Diana, Princess of Wales (patron of Parkinson’s UK). The active and vocal support of stem cell research in treatment of PD by Michael J. Fox placed this controversial topic further in the public domain.

7. In the United States, key advocates have included patient groups and associations, celebrities and influential community leaders. The media and the scientific community also played an important role.

Regulatory and legislative scope and efficiency

8. The development of treatments for PD is characterised by exceptionally long timespans. Despite the discovery that L-dopa was biologically active in 1927, it took 40 years to demonstrate its efficacy in patients with Parkinson’s disease and another 3 for it to be approved by FDA as a treatment for PD.

9. The controversy surrounding cell therapy and the subsequent number of court cases regarding patents are factors that further slow down the progress of treatment advancements in PD.

Other

10. At present, no cure for PD exists; all the treatments discussed above are designed to slow the onset of the debilitating motor symptoms or to slow the progression of the disease. Furthermore, no tool is available to uniformly and reliably diagnose PD.

Table 18. Key scientific and technological trigger points of the levodopa breakthrough

<table>
<thead>
<tr>
<th>Scientific and technological advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis of D,L-dopa in the laboratory, 1911</td>
</tr>
</tbody>
</table>
• Isolation of levodopa from fava bean seeds, 1913
• Discovery of biological activity of levodopa, 1927
• Development of a new chemical fluorescent assay technique to measure dopamine in tissue and thus discovery that dopamine is present in the brain, and that it can be depleted with reserpine and restored with L-dopa. Speculation that dopamine is involved in PD, international pharmacology meeting, 1959
• Landmark paper published showing for the first time a marked depletion of dopamine in the caudate and putamen of patients only in the PD and postencephalitic parkinsonian brains, 1960
• First reported trial of intravenous levodopa in PD, 1961
• Effectiveness of oral levodopa demonstrated in patients with parkinsonism, 1967
• High-dosage levodopa introduced, 1967
• First double-blind, placebo-controlled study showing efficacy of levodopa (but with development of choreiform movements), 1969
• Discovery that combined levodopa-decarboxylase inhibitor RO4-4602 (benserazide) proves more effective than levodopa alone, 1969
• Levodopa approved by the FDA as PD treatment, 1970
• Clinical use of carbidopa-levodopa reported, 1974
• L-dopa–induced dyskinesias first described, 1974
• Continuous levodopa administration tried for preventing complications, 1975
• Sustained-release carbidopa-levodopa is found to reduce ‘off’ time and improve clinical disability better than standard carbidopa-levodopa, but with variable effects, 1989
• First clinical trial of enteral carbidopa-levodopa infusion, with 7 out of 10 patients experiencing increased functional ‘on’ hours and decreased number of ‘off’ episodes (Kurth et al. 1993), 1993
• ELLDOPA trial does not conclusively resolve the question of when to start L-dopa treatment, 2004

Table 19. Key scientific and technological trigger points of the deep brain stimulation breakthrough

Scientific and technological advances – key milestones
• Electrical stimulation of the brain used as a means of exploring the brain target prior to lesioning in surgery, 1947
• First ever pallidotomy performed, 1951
• Pallidotomy performed for the first time to exploratively treat PD tremor, 1952
• Modern deep brain stimulation (DBS) pioneered in France by Benabid and colleagues, Medtronic DBS Therapy implanted for the first time in Grenoble, France, 1987
• Introduction of subthalamic nucleus (STN) DBS and documentation of the safety and efficacy of DBS when applied bilaterally (essentially making pallidotomy redundant), 1993
• Medtronic DBS Therapy receives approval (CE Mark) in Europe for essential tremor, 1993
• Medtronic DBS Therapy receives CE Mark approval in Europe for treating tremors associated with Parkinson’s disease, 1995
• DBS approved for essential tremor by the FDA, 1997
• Medtronic DBS Therapy approved in Europe for advanced Parkinson’s disease, 1998
• DBS approved for PD by the FDA, 2002

Table 20. Key scientific and technological trigger points of the cell therapy breakthrough

Scientific and technological advances – key milestones
•
• Attempt to cure cancer in a human patient by injecting material from calf embryos, 1931
• Discovery that organ transplants in laboratory animals can be less prone to rejection by pre-inoculating the animals with cells from donor animals, 1953
• First successful human bone marrow transplantation, 1968
• Foetal, porcine, carotid or retinal tissues used in cell transplants for treatment of PD, 1980s
• Dopamine-producing tissue transplanted into the human brain for the first time, 1980s
• Rodents treated with neurons made from human skin cells using induced pluripotent stem (iPS) cell techniques show an improvement in PD symptoms, 2010

The science and the evidence: Ongoing search for causes and a cure for Parkinson’s disease

While the understanding of the underlying cause of Parkinson’s disease remains limited, scientists have made large advances in identifying the cells and areas of the brain that are affected by the condition, as well as in understanding the mechanisms of the disease. Since first realising the key role of dopamine in the brain in the development of the debilitating motor symptoms of PD, researchers have made a number of advancements in treatment within a relatively short period of time.

Early research on L-dopa

Despite the fact that the racemate D,L-dopa was already synthesised in 1911, not much was known about its properties. From the original synthesis by Funk, conducted in order to test the idea that it may be the parent substance of adrenaline (Funk 1911), it took 2 more years to isolate the enantiomer levodopa (L-dopa) from natural products, and it was not until fourteen years later, in 1927, that it was announced that the L-dopa enantiomer is, in fact, biologically active. The real breakthrough in terms of linking the available active compound and the mechanism of the disease came in 1958, when Carlsson et al. developed a new chemical fluorescent assay technique to measure dopamine in tissue (previously there had been no method to measure the microgram quantities that were suspected to be present). They discovered not only that dopamine present in the brain, but also that it was depleted with reserpine and restored with L-dopa (Carlsson et al. 1958). A year later, at the 1959 international pharmacology meeting, Carlsson speculated that dopamine might be responsible for PD (Carlsson 1959). In 1960, his speculation was proven true, as Hornykiewicz published a landmark paper showing for the first time a marked depletion of dopamine in the caudate and putamen of exclusively the PD and postencephalitic parkinsonian brains (Ehringer & Hornykiewicz 1960). This discovery was a key event in the efforts to make a drug targeting the causes of motor symptoms of PD available, to commercialise it, and to improve the quality of life of those suffering with PD.

29 Induced pluripotent stem cells are stem cells that can be generated directly from adult cells (as opposed to from embryonic cells). This technique was pioneered by Yamanaka’s lab (Takahashi & Yamanaka 2006).
30 In organic chemistry a ‘racemate’ mixture is one that has equal amounts of left- and right-handed enantiomers of a chiral molecule. A chiral molecule indicates that there are two molecules of identical composition, but arranged in a non-superposable mirror image to each other; here, D-dopa and L-dopa.
Developing levodopa for clinical use

The first reported trial of intravenous levodopa in PD took place in 1961. The remainder of the 1960s saw a number of randomised controlled trials and levodopa activity being continuously manipulated to try to enhance it. Levodopa was successfully enhanced with peripheral dopa decarboxylase inhibitor in 1967. In that same year, the effectiveness of oral levodopa was also demonstrated in patients with parkinsonism and a high-dosage levodopa was introduced. The first double-blind, placebo-controlled study was conducted in 1969, showing the efficacy of levodopa but with development of choreiform movements (Birkmayer & Hornykiewicz 1998, cited in Hauser 2009). In that same year another improvement to the treatment took place, with the discovery that a combination of levodopa-decarboxylase inhibitor RO4-4602 (benserazide) is more effective than levodopa alone. A year later levodopa was formally approved by the FDA in 1970.

Clinical use of carbidopa-levodopa began to be reported starting in 1974 (Stocchi et al. 2010), and continuous levodopa administration was tried for preventing complications in 1975. This was the same year in which levodopa-benserazide (Madopar) and carbidopa-levodopa (Sinemet) were commercialized. In 1989, sustained-release carbidopa-levodopa (Sinemet CR) was demonstrated to reduce ‘off’ time and to improve clinical disability better than standard carbidopa-levodopa (Sinemet), but the effects were variable (Jankovic 2002). After its effects were demonstrated on a large enough sample of patients, however, the sustained-release carbidopa-levodopa became commercially available in 1991. The first clinical trial of enteral carbidopa-levodopa infusion took place in 1993 with 7 out of the 10 tested patients experiencing increased functional ‘on’ hours and a decreased number of ‘off’ episodes (Kurth et al. 1993). However, 2 out of the 10 patients experienced deterioration in their condition and 1 person experienced no change in the motor symptoms at all (Kurth et al. 1993). While a 70% success rate provided some optimism regarding the effectiveness of the carbidopa-levodopa infusion, the extremely small sample size made it very difficult to generalise results to the wider PD population. Furthermore, the deterioration in the condition of 20% of those in the trial showed that the treatment may not be suitable for all PD patients.

Refining combined treatments

The next improvement to the levodopa PD treatment came in 1999, when entacapone (a COMT inhibitor), one of several enzymes that degrade catecholamines such as dopamine, became commercially available. Pharmacologically, entacapone is somewhat similar to carbidopa, in that it is an inhibitor of an enzyme that converts L-dopa into a compound that cannot cross the blood–brain barrier. It has been found that up to 50% of patients develop motor complications and end-of-dose ‘wearing-off’ after 5 years of treatment with levodopa (Standaert & Young 2001). The COMT inhibitors, such as entacapone, are added to levodopa treatment to overcome these complications and to prolong the bioavailability of}

31 COMT is one of several enzymes that degrade catecholamines such as dopamine.

32 All of the second-generation COMT inhibitors, including entacapone, were already developed simultaneously by three laboratories during the late 1980s (Bäckström et al. 1989; Borglylua et al. 1989; Waldmeier et al. 1990).
levodopa (Rivest et al. 1999). In 2003, the combination carbidopa-levodopa-entacapone tablets (Stalevo by Novartis) became commercially available, making it the most 'improved' form of levodopa treatment to date. Four randomized, double-blind, 6-month, phase 3 clinical trials had evaluated the efficacy and safety of levodopa-carbidopa and entacapone therapy compared with levodopa-carbidopa and placebo in PD patients with motor fluctuations (Brooks & Sagar 2003; Larsen et al. 2003; Parkinson Study Group 1997; Poewe et al. 2002; Rinne et al. 1998). Data from these trials demonstrated the greater efficacy of the combined treatment, in that it provides significant benefits in terms of symptom control compared with conventional levodopa. For example, Rinne et al. (1998), found that the levodopa-carbidopa-entacapone therapy increased ‘on’ time by 16% and reduced ‘off’ time by 24% over a 6-month period (Novartis 2007).

Confronting side effects and limited effectiveness

Recently, concerns have been reported regarding a potential increased risk for cardiovascular events (heart attack, stroke, and cardiovascular death) of patients taking the carbidopa-levodopa-entacapone treatment (Stalevo) compared with those taking carbidopa-levodopa alone (Brooks 2004; Stocchi et al. 2010)). Previous clinical trials with Stalevo did not show an imbalance in myocardial infarction, stroke, and cardiovascular death (Stocchi et al. 2010; U.S. FDA 2010a). On August 20, 2010, the FDA conducted a meta-analysis that included 15 clinical trials based on the findings from the STRIDE-PD trial and confirmed a small increased risk of cardiovascular adverse events in the Stalevo group (U.S. FDA 2010b). Moreover, the results of a study by Alshammari and AlMutairi (2014) found an association between the use of the entacapone-containing drug combination and death, which was not seen in patients using the levodopa-carbidopa combination (87 directly attributable deaths out of 2,532 reports where the levodopa-carbidopa-entacapone drug was the primary suspect of the death, compared with 27 directly attributable deaths out of 1,670 suspected deaths due to levodopa-carbidopa alone), suggesting that perhaps more research needs to be done and more advancements still need to be made in the levodopa treatment of PD.

After recognizing that levodopa often leads to the motor complications of wearing-off and dyskinesias, there have been debates among clinicians about when levodopa therapy should be started. It has been suggested that the development of motor complications could potentially be delayed by delaying the therapy itself. This view grew in popularity as the dopamine agonists became available because, despite being less potent than levodopa in ameliorating the symptoms, these drugs were also significantly less likely to produce the unwanted motor complications (Fahn 2008).

A new concern arose with the recognition that dopamine itself might be a factor leading to the death of dopaminergic neurons, due to its contribution to the formation of oxyradicals. This notion led to the concern that levodopa, through its conversion to brain dopamine, might add to the existing oxidative stress and possibly enhance neurodegeneration of dopaminergic neurons (Fahn 2008). Although there was no evidence, the possibility alone was sufficient to make some clinicians further delay the start of levodopa therapy in PD. In 2004, the ELLDOPA trials took place to test this hypothesis. The clinical component of the study indicated that the symptoms had progressed much less in the levodopa condition than in the placebo, and that they had done so in a dose-response manner. This suggests that levodopa may actually have neuroprotective, rather than long-term neurodegenerative, properties. All dosages of levodopa
exerted clinical benefit compared with the placebo throughout the study, including 2 weeks after discontinuation of levodopa. The clinical outcomes not only indicated that levodopa is effective in a dose-dependent manner in overcoming the signs and symptoms of PD; they also supported the concept that the drug does not hasten disease progression. Rather, the drug may slow down the rate of the disease. The clinical study failed to demonstrate any evidence of levodopa worsening early PD. However, a neuroimaging substudy indicated the opposite effect, namely, that levodopa causes a more rapid decline in the integrity of the dopamine transporter located in the nigrostriatal nerve terminals in the striatum. These contradictory findings warrant further investigation into the effect of levodopa on PD (Fahn & Parkinson Study Group 2005).

**Levodopa-based treatments do not result in lower mortality**

Despite the undeniable success of levodopa, it has transpired that in many patients who have prolonged treatment, the symptoms return and in some cases become more severe than before. Moreover, it has been established that mortality of those diagnosed with PD is not reduced comparing with the healthy, unaffected population despite the use of levodopa (Clarke 2000). Prior to the introduction of levodopa, mortality in PD was approximated to be 2.9 times higher than that of the general population adjusted for age, gender and race (Hoehn & Yahr 1967). Although it initially appeared that mortality rates in PD post-introduction of levodopa were normalized (Joseph et al. 1978; Shaw et al. 1980; Sweet & McDowell 1975; Yahr ed. 1976), it has now become clear that the majority of studies over the past 30 years have demonstrated no normalization of mortality rates in PD patients due to levodopa after all (Clarke 2000). The standardized mortality ratio in PD patients continues to range from 1.52 (Herlofson et al. 2004) to 3.38 (Chen et al. 2001). As a result, new or supplementary treatments have been explored.

**Potential and risks of Deep Brain Simulation**

From 1947 onwards electrical stimulation of the brain was used initially as a mean of exploring the brain target prior to lesioning in surgery (e.g. Gildenberg 2005). In the modern form, it was first developed in France in 1987. DBS is a surgical procedure that involves placing an electrode deep in the brain (in the thalamus, subthalamic nucleus, or globus pallidus) and connecting it via an insulated wire to a stimulator inserted under the skin on the chest or abdomen. The patients has to stay awake throughout the electrode implantation. At present, the procedure is used only for individuals whose symptoms cannot be adequately controlled with medication. However, only individuals who improve to some degree after taking medication for Parkinson’s have been found to benefit from DBS (National Institute of Neurological Disorders and Stroke [NINDS] 2015). DBS was officially approved by the FDA in 2002 for use in the treatment of PD. New advancements are still being made, and lately a novel technique has been established that allows the patient to be under general anaesthesia during the procedure. This in turn allows for more comfort during the surgery than the previous approach, whereby the patient remained awake (developed in 2011 by Dr. Kim Burchiel [Oregon Health & Science University Brain Institute 2014]).

Deep brain stimulation has proven helpful in treating the motor symptoms of PD as a supplement to levodopa, and the improvements can be remarkable. However, as with any surgery, DBS poses risks of
infection, complications and even death. Moreover, it is not a treatment that works for everyone, and it cannot be administered without the continuation of levodopa treatment (albeit usually with reduced dosages) (NIH 2014; Office of Communications and Public Liaison et al. 2014). Several alternative forms of therapy may address the challenge posed by the use of levodopa and deep brain stimulation, of which perhaps the most noteworthy is cell-based therapy.33

**Cell therapy: Promising but controversial**

The origins of cell therapy can be traced to the 19th century, when Charles-Édouard Brown-Séquard injected animal testicle extracts into humans in an attempt to stop the effects of aging (Lefrère & Berche 2010). In 1931, Paul Niehans (sometimes called the inventor of cell therapy) attempted to cure cancer in a human patient by injecting material from calf embryos (American Cancer Society 1991). A couple of decades later, in 1953, researchers found that organ transplants in laboratory animals could be less prone to rejection if the animals were pre-inoculated with cells from donor animals. This finding, which was an enormous breakthrough in cell therapy, led to the first successful human bone marrow transplantation, in 1968 (Starzl 2000). Recently, cell therapy using human material has been recognized as an important field in the treatment of human disease (Gage 1998). It is supported by a distinct healthcare industry, which sees strong prospects for future growth (Brindley et al. 2011; Mason et al. 2011). Based initially on clinical trial and error and subsequently on laboratory science, cell-based therapies have progressed from the first recorded human–human blood transfusion by James Blundell (Guy’s Hospital, London, UK) through to the advanced cellular therapies of today (Ellis 2007). According to Mason et al. (2011), cell therapies today constitute one of the four pillars of global healthcare (alongside pharmaceuticals, biopharmaceuticals and medical devices).

Cell therapy remains a controversial area of research, mainly due to the usage of human embryonic cells, which entails that human embryos are destroyed in the process of harvesting cells. A recent research target in cell therapy is stem cell transplantation. Recently, Studer’s group (Kriks et al. 2011) succeeded in making highly efficient dopamine-producing neurons from human embryonic stem cells, and they have transplanted them into the brains of rodents with Parkinson’s disease. The cells did not multiply abnormally, and the procedure improved some symptoms. The neurons were also transplanted into monkeys to show that they would survive and function in larger animals. More work is still needed before tests can begin on human patients: the neurons need to be made in sufficient numbers to be effective, and they need to be produced in a way that ensures the cells are safe. The scientists hope early clinical trials may be able to start in 2015.

---

33 There is also research on treatments to promote the survival of original dopamine cells rather than introduction of new cells; for example, gene therapy, whereby genes that will help dopamine cells to survive and keep producing dopamine are injected. This treatment has so far produced mixed results, but, according to an interviewed expert in the field of PD, there is anecdotal evidence that it could work.
Collaboration among academia, industry and government

All PD treatments that have been developed to-date have originated in academia, with industry following the proof of principle through to the clinical trials phase. For instance, the original levodopa experiments attracted the attention of industry early on: carbidopa-levodopa (under the name Sinemet) was commercialised by Merck in 1975, while Roche manufactured and commercialised benserazide-levodopa under the name Madopar in the same year. Similarly, DBS was first developed in an academic setting, although with extensive involvement from Medtronic from the beginning. The company played an important role in driving the research forward and moving the treatment to the clinical phase. Ultimately it enabled DBS to become a major treatment worldwide, potentially because all the technology involved had already been manufactured by Medtronic.

Cell research so far remains largely the domain of academia and public research institutions. One obstacle to greater industry involvement may lie in uncertainty over patenting rules. The EU holds that human cells cannot be patented. The lack of possibility to attain market exclusivity renders industry investments less likely. Therefore, as one interviewee observed, it is possible that Europe will not attract funding to take treatments to the clinical level, which will put European PD research at a disadvantage relative to the rest of the world, as other countries may see industry involvement rise as cell therapy progresses towards the clinical trial phase. At the same time, one of the landmark rulings regarding the use of stem cells has recently been found to be unsupported by science by a European court. This ruling offers new potential for cell research advances and industrial involvement in Europe in the near future.

Table 21. Key social influences on innovation in Parkinson’s disease

<table>
<thead>
<tr>
<th>Social advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Parkinson’s Disease Foundation established in United States, 1957</td>
</tr>
<tr>
<td>Parkinson’s UK established (then called Parkinson’s Disease Society), 1961</td>
</tr>
<tr>
<td>Muhammad Ali retires from boxing and begins to show signs of PD, 1981</td>
</tr>
<tr>
<td>A series of high-profile disclosures from the 1980s–2000s, including Muhammad Ali, Michael J. Fox, Johnny Cash and Pope John Paul II</td>
</tr>
<tr>
<td>Parkinson’s UK Brain Bank opens, enabling crucial research into Parkinson’s (now it is the UK’s largest human brain bank dedicated to Parkinson’s, and it provides brain tissue to researchers around the world), 1984</td>
</tr>
<tr>
<td>First ever Parkinson’s Disease Day celebrated on 11 April, 1997</td>
</tr>
<tr>
<td>Muhammad Ali Parkinson Centre launched, 1997</td>
</tr>
<tr>
<td>First fundraising event by Parkinson’s UK, raising money for PD research, 1988</td>
</tr>
</tbody>
</table>

34 In a recent court ruling (July 2014), it transpired that the ruling in the Brüstle vs Greenpeace case forbidding patenting of embryonic stem cells was incorrect as a matter of scientific fact. According to the court, a fertilized human ovum possesses the inherent capacity to develop into a human being; however, chemically activated oocytes or ‘parthenotes’ (cells created via parthenogenesis) are incapable of ultimately developing into human beings. Since the ruling in Brüstle vs Greenpeace was only intended to ban patents on the use of organisms that could ultimately develop into human beings, parthenotes, which lacked such capacity, should not be regarded as human embryos for purposes of the Biotechnology Directive and should be patentable under the EU law (International Stem Cell Corporation 2014).
Social Influences in putting Parkinson’s disease in the spotlight

Advocacy around Parkinson’s disease has gained momentum particularly over the past few decades. This observation is in line with views expressed by a key informant, who pointed out that social activism did not play a large role in the beginnings of PD treatment. Although it was more limited than in the case of other diseases such as HIV/AIDS, the impact of social influences on the process of treatment developments in PD cannot be underestimated. Despite the fact that PD patients have not traditionally been very active in campaigning for new therapies, they are now being encouraged by physicians and others to take control and to drive campaigns for new treatments. High-profile celebrity cases, made publically known in the 1980s and 1990s, most notably Muhammad Ali and Michael J. Fox, contributed to public awareness and to advancement of research on treatment options. Michael J. Fox made his condition known to the public in 1998, and 2 years later he launched a foundation, which raised more than US$450 million between 2000 and 2014 (Michael J. Fox Foundation 2014). There is much controversy regarding stem cell research. Fox’s defined stance as an active supporter of such research, along with his books advocating for facilitating of stem cell research, send a very clear message to the public, his fans and fellow PD sufferers. Moreover, to date the Michael J. Fox Foundation has been involved in funding a number of influential case studies, from ‘backing the Parkinson’s “vaccine”’ through ‘looking beyond dopamine’ to ‘translating genetic findings into real treatments’ (Michael J. Fox Foundation 2014). Similarly, Muhammad Ali launched the Muhammad Ali Parkinson Center, which encompasses the Muhammad Ali Movement Disorders Center, the Muhammad Ali Parkinson Community Outreach and Wellness Center, and an Outpatient Rehabilitation Center. The Muhammad Ali Parkinson Center is a National Parkinson Foundation Centre of Excellence and is considered an outstanding resource for people with Parkinson’s disease and other movement disorders. A component of the Muhammad Ali Movement Disorders Center provides the latest information in diagnosis and

35 Called World Parkinson Congress at the time; the name was changed in 2006.
treatment, including clinical trials and the most recently developed DBS surgery, which uses general anaesthesia. The publicity surrounding both celebrities and their active and open support of novel therapies may be one of the contributing factors to the growing popularity of the mentioned treatments, especially in the case of DBS.

High-profile PD sufferers and their subsequent work in raising awareness and funds were not the only factors that helped elevate the global importance of PD. Publicity awarded to researchers and experts had an impact as well, especially in the case of Dr Langston, the Scientific Director, Chief Executive Officer and Founder of the Parkinson’s Institute (Herpich 2012; Michael J. Fox Foundation 2014; Parkinson’s Disease Foundation 2007). Dr. Langston was recently awarded the 2012 Robert A. Pritzker Prize for Leadership in Parkinson’s Research. His contributions started almost 30 years ago, with the famous case of the ‘frozen addicts’, which enabled a breakthrough in PD research.36

Organisations such as the Parkinson’s Disease Foundation (PDF) also played – and still do play – a role in advocacy of PD. The Parkinson’s Disease Foundation for more than a decade has assumed the role of advocate on behalf of and in collaboration with people with Parkinson’s, their families and caregivers (Parkinson’s Disease Foundation). This takes a variety of forms, such as ‘representing the interests of the Parkinson’s community with government leaders; supporting advocates in their individual efforts to influence change; facilitating conversations with researchers on clinical trial outcomes; working with news media on healthcare issues that affect those living with Parkinson’s disease; and creating a formal place at the decision-making table for people with Parkinson’s’ (Parkinson’s Disease Foundation 2007). In the spring of 2006, PDF launched the People with Parkinson’s Advisory Council (PPAC) to provide the perspective of the patient to the PDF’s processes of program development and priority setting. Of the 14 founding members of PPAC, 11 are Parkinson’s disease sufferers and 3 are caregivers. Representatives originate from around the United States. One last thing to note is that Parkinson’s is included in one of the topics of the regular Breakthrough Prize in Life Sciences, established in 2013 by a group of prominent entrepreneurs.

36 In 1983, six young people presented with symptoms of PD, which in a matter of only days became as advanced and debilitating as symptoms that would normally take a patient decades to develop. It transpired that they were all heroin users. After a few days of usage of a new heroin batch, they became completely unable to move or speak but remained conscious. This fascinating medical mystery was solved by Dr. Langston, who first decided to treat the patients with levodopa, temporarily elevating their symptoms and enabling them to move and speak; soon after he pioneered foetal-tissue transplants, which led to a complete recovery of two of the ‘frozen addicts’; and lastly he discovered that it was the neurotoxin MPTP in the heroin that was responsible for the Parkinson’s-like symptoms. This discovery ‘would prove to yield results that would forever alter the landscape of Parkinson’s research’ (Michael J. Fox Foundation). Langston discovered that the MPTP neurotoxin ‘lasers like a Nike missile on the same nerve cells in the brain that die in Parkinson’s, [in the] substantia nigra’ (Langston, in an interview), which revolutionized research, ’as it for the first time provided an experimental model enabling the study of neurological cell death in Parkinson’s’ (Langston, in an interview). The creation of this first pre-clinical model of PD allowed for the replication virtually all of the motor features of Parkinson’s, enabling the re-creation of the disease in the lab, and thus greatly enhancing the ability to study disease process and subsequently allowing to test potential treatments (Michael J. Fox Foundation 2014; Scott 2012).
Table 22. Key political and economic enablers in innovation in Parkinson’s disease

<table>
<thead>
<tr>
<th>Political and economic advances – key milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First patent for a human product granted (for a purified form of adrenaline), 1906</td>
</tr>
<tr>
<td>• Adrenaline patent challenged but upheld, 1911</td>
</tr>
<tr>
<td>• Parkinson’s Disease Foundation established in the United States, 1957</td>
</tr>
<tr>
<td>• American Parkinson Disease Association, Inc. founded, including the National Young Onset Center, 1961</td>
</tr>
<tr>
<td>• Parkinson’s UK established, 1969</td>
</tr>
<tr>
<td>• Scientists patent methods on their biotechnological inventions with recombinant DNA for the first time, 1970</td>
</tr>
<tr>
<td>• First fundraising event by Parkinson’s UK, raising money for PD research, 1988</td>
</tr>
<tr>
<td>• European Parkinson’s Disease Association is founded (this is the only European Parkinson’s disease umbrella organisation, representing national Parkinson’s organisations in 36 countries, advocating for the rights and needs of more than 1.2 million people with Parkinson’s and their families across Europe), 1992</td>
</tr>
<tr>
<td>• Dickey-Wicker Amendment introduced in the United States, prohibiting the Department of Health and Human Services from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed, 1995</td>
</tr>
<tr>
<td>• U.S. Patent and Trademark Office issues a broad patent claiming primate (including human) embryonic stem cells, entitled ‘Primate Embryonic Stem Cells’ (Patent 5,843,780), 1998</td>
</tr>
<tr>
<td>• Michael J. Fox launches his foundation (which to date has raised more than US$90 million), 2000</td>
</tr>
<tr>
<td>• Second patent (6,200,806) is issued, with the same title but focused on human embryonic stem cells, 2001</td>
</tr>
<tr>
<td>• George W. Bush bans federal funding of embryonic stem cell research – causing outrage because it means a halt in possible advances in curing PD. Michael J. Fox becomes an activist for the cause, 2001</td>
</tr>
<tr>
<td>• The National MS and Parkinson’s disease Registries Act (S. 1273) passes, 2009</td>
</tr>
<tr>
<td>• President Obama reverses the federal funding ban. He signs the Omnibus Appropriations Act of 2009, which still contains the long-standing Dickey-Wicker provision. The Congressional provision effectively prevents federal funding being used to create new stem cell lines by many of the known methods. As a result, scientists are not free to create new lines with federal funding, but the policy does allow researchers to apply for such funding into research involving the hundreds of existing stem cell lines, as well as any further lines created using private or state-level funding, 2009</td>
</tr>
<tr>
<td>• Another freeze on stem cell research ruled by a court – a case won by Christian medical groups, 2010; the Obama administration Justice Department asks the U.S. Court of Appeals for the District of Columbia Circuit to lift the injunction, 2011</td>
</tr>
<tr>
<td>• Brüstle vs Greenpeace case: patent on a method for generating neurons from human embryonic stem cells rejected by the European Court of Justice on the grounds of the Biotechnology Directive, which forbids patent protection for inventions using human embryos for industrial and commercial purposes, 2011</td>
</tr>
<tr>
<td>• Parkinson’s UK produces the first ever public awareness campaign, with Parkinson’s UK adverts to raise awareness appearing on billboards, on trains and in newspapers across the UK, 2012</td>
</tr>
<tr>
<td>• The Pledge for Parkinson’s is launched in the European Parliament on 11 April 2012, World Parkinson’s Disease Day. It was signed by nearly 50 members of the European Parliament (MEP) and has since been signed by 70 MEPs, plus more than 1,600 public supporters globally, 2012</td>
</tr>
<tr>
<td>• The Supreme Court of the United States rules that mere isolation by itself is not sufficient for something to be deemed inventive subject matter, 2013</td>
</tr>
<tr>
<td>• Realisation that the ruling in Brüstle vs Greenpeace was incorrect as a matter of scientific fact: chemically activated oocytes are incapable of ultimately developing into human beings, and since the ruling in Brüstle vs Greenpeace was only intended to ban patents on the use of organisms that could ultimately develop into human beings, chemically activated oocytes thus should be patentable under EU law, 2014</td>
</tr>
</tbody>
</table>
Economics and Politics of PD treatments

The economic case for developing PD treatment has been, and remains, strong. PD is the second most common neurodegenerative disorder after Alzheimer’s disease, affecting approximately 7 million people globally, of whom one million live in the United States alone (de Lau et al. 2006; Yao et al. 2013). In Europe there are more than 1.2 million people living with PD today, and this number is forecast to double by 2030 (European Parkinson’s Disease Association). The prevalence rates are about 0.3% of the whole population in industrialized countries, with PD becoming more common with age. Prevalence rises from 1% in those over 60 years of age to 4% in those over 80 (de Lau & Breteler 2006).

The annual cost of PD to the society in the UK is estimated at 449 million, and the total burden is £3.3 billion. The cost per patient per year in the United States is thought to be approximately US$10,000, with the total burden being approximated at US$23 billion (Findley 2007). The annual European cost of the disease is estimated at €13.9 billion. As our population continues to live longer, this cost will continue to rise dramatically – especially in the later stages of the disease, where the impact is greatest, on people with Parkinson’s, their families and carers, and society as a whole (European Parkinson’s Disease Association). Direct costs derive in a larger proportion from inpatient care and nursing homes, with medication costs being substantially lower (Findley 2007). Indirect costs, however, are also high, due to reduced productivity of the patients, combined with a burden on caregivers (Findley 2007). These trends emphasize the importance of developing treatments that can restore the mortality rates as well as the quality of life to those affected by PD. The same trends and the size of the market are also potential reasons why PD can be attractive for the pharmaceutical industry.

Political and legal controversies around cell therapy

In addition to considerations regarding the market and society, there are also political and legal considerations that may affect innovation efforts in the field of PD. This is especially apparent in the case of cell therapy and questions surrounding human product patents. The issue of patenting human products dates back over a century, with the first ever human product patent being awarded for a purified form of adrenaline in 1906. The patent was challenged (though upheld) in the Parke-Davis vs Mulford case in 1911 because the judge argued that natural substances when they are purified are more useful than the original natural substances (Dutfield 2006). In 1970, scientists patented methods on their biotechnological inventions with recombinant DNA (such as cloning) for the first time, but 10 more years passed before patents for whole-scale living organisms were permitted. In 1980, the Supreme Court of the United States, in the Diamond vs Chakrabarty case, upheld the first ever patent on a newly created living organism (a bacterium created to digest crude oil in oil spills). The patent of a living organism was initially rejected, but Chakrabarty appealed and won because, even though raw natural material is generally rejected for patent approval, as long as the organism is truly ‘man-made’ – for example, through

---

37 This is in line with an observation made by an interviewed key informant, who made an explicit comparison with Huntington’s disease, which, largely due to its smaller prevalence, is not as attractive and does not enjoy as much attention as PD.
genetic engineering – it is deemed patentable. Because the DNA of Chakrabarty’s organism was modified, it was patentable (US Patent 4,259,444).

**The controversy in the United States**

In 1998, the U.S. Patent and Trademark Office issued a broad patent claiming primate (including human) embryonic stem cells, entitled ‘Primate Embryonic Stem Cells’ (Patent 5,843,780), which presented a purified preparation of primate embryonic stem cells. In 2001, a second patent (Patent 6,200,806) was issued with the same title but focused on human embryonic stem cells exclusively, which raises the controversy even further. Due to the controversy associated with embryonic stem cell research – and emphasising the power of politics – in the same year that the patent was granted, George W. Bush banned federal funding of embryonic stem cell research. This caused outrage because it meant a halt in possible advances in curing PD (National Institutes of Health 2009). Around the same time, Michael J. Fox became an activist for the cause, supporting the stem cell research. But with a new political leader came changes in political views; after 8 years of no federal funding, President Obama lifted the ‘freeze’ and reversed the federal funding ban (The White House 2009). However, this was only a modest improvement, as he still signed the Omnibus Appropriations Act of 2009, which contained the long-standing Dickey-Wicker provision (1995), which banned federal funding of ‘research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death’ (Kearl 2013). The Congressional provision effectively prevented federal funding being used to create new stem cell lines by many of the known methods, meaning that scientists were not free to create new lines with federal funding. However, the policy allowed the potential of applying for such funding into research involving the hundreds of existing stem cell lines, as well as that involving any further lines created using private funds or state-level funding. However, soon after, another freeze on stem cell research was ruled by a court – in the Sherley vs Sebelius case, which was won by Christian medical groups (Palmer 2010). Judge Royce C. Lamberth granted the injunction against federally funded embryonic stem cell research on the grounds that the guidelines violated the Dickey-Wicker Amendment (Sherley vs Sebelius 2010). In September 2010, he refused to lift the injunction. At this point the US Justice Department asked the Court of Appeals for the District of Columbia Circuit to lift the injunction via an order (Katsnelson 2010) forcing Judge Lamberth to reverse his ruling and dismissing the case entirely in 2011 (Kaiser 2011). It is now being argued that, although federal funds cannot be used to directly destroy an embryo, the Dickey-Wicker Amendment does not, in fact, prohibit funding a research project using embryonic stem cells. This makes it an important distinction under the law, because using federal funds to directly support the destruction of embryos is supposedly a violation of the Hyde Amendment (which prohibits abortions using federal funds). An indirect use of federal funds in embryo stem cell research that avoids killing the embryo does not violate the amendment (Sherley vs Sebelius 2010).

**Cell therapy research in Europe**

Legal issues over human embryonic stem cells existed not only in the United States. In October 2011, Oliver Brüstle, director of the Institute of Reconstructive Neurobiology at the University of Bonn,
Germany, had a patent on a method for generating neurons from human embryonic stem cells rejected by the European Court of Justice. This became known as the Brüstle vs Greenpeace case (Callaway 2011). He called the ruling ‘the worst possible outcome’ and ‘a disaster for Europe’, explaining that the ruling would cause European companies and scientists to miss out on commercial applications for embryonic-stem-cell research, especially now that such stem cells were finally deemed patentable in the United States (Callaway 2011). The technology covered by the German patent in the Brüstle vs Greenpeace case regarded the use of pluripotent embryonic stem cells (these cells, which are isolated from an embryo, can produce almost all of the cells in the body) for producing isolated and purified precursor cells to treat neurological diseases. Greenpeace challenged the patent, citing the Biotechnology Directive, which forbids patent protection for inventions using human embryos for industrial and commercial purposes. Due to ambiguities in the language of the directive, the German court referred the question of what constitutes a ‘human embryo’ to the European Court of Justice. That court decided to interpret the directive broadly, and defined ‘human embryo’ as ‘an organism that is capable of commencing the process of developing into a human being, including within the meaning of the term, an ovum that has been fertilized by sperm, a non-fertilized ovum subjected to somatic-cell nuclear transfer, and, notably, a non-fertilized ovum activated through parthenogenesis’ (from International Stem Cell Corporation press release, July 2014). Parthenogenesis is a biological reproduction involving a development of a sex cell (gamete) without fertilization.

July 2014 saw a new development in terms of patentability of embryonic stem cells. It transpired that the ruling in Brüstle vs Greenpeace was incorrect as a matter of scientific fact, regarding the parthenogenetic stem cells. Although a fertilized human ovum possesses the inherent capacity to develop into a human being, chemically activated oocytes, or ‘parthenotes’ (cells created via parthenogenesis), are incapable of ultimately developing into human beings. Since the ruling in Brüstle vs Greenpeace was only intended to ban patents on the use of organisms that could ultimately develop into human beings, parthenotes, which lack such capacity, should not be regarded as human embryos for purposes of the Biotechnology Directive and should be patentable under the EU law.

The political battles regarding stem cell research posed a barrier to the advancements of the therapy as well as being an obstacle to the economic involvement in PD (years of no funding of the research; lack of incentive for industry to get involved). The US political system has a large impact on the advancements in PD treatments, as different states and different presidents take different views and push for different laws. This is especially the case for cell therapy and, to a lesser extent, for pharmacological or DBS treatments. Seeing as both levodopa and DBS treatment have some substantial limitations, cell therapy (and potentially gene therapy) are potential treatments that could overcome the limitations and provide real breakthroughs in the fight against PD. It is therefore imperative that the research be facilitated and not hindered. The fact that embryonic stem cells are now patentable in the United States (and since very recently also under EU law) and the fact that the federal funding ban has been lifted in the United States may enable both scientific and economic progress in the near future.
Appendix E: Case study timelines

Figure 2. HIV timeline
Figure 3. Breast cancer timeline
Beatson studies lactation in sheep and establishes causal link with removal of ovaries (already known by cow farmers!). Continues studies in rabbits in 1878.

Beatson reports "curing" patient by removing ovaries (Beatson, 1896). Boyd (1900) also supports role of oestrogen withdrawal on breast tumours.

Antoine Lacassagne speculates that if increased sensitivity to oestrogen was responsible for the hereditary susceptibility to breast cancer, then perhaps an antagonist of oestrogen accumulation could prevent the disease (Jordan, 2003).

The initial report of the anti-oestrogen actions of a non-steroidal compound. The compound was, unlike tamoxifen, anti-oestrogenic in all species tested (Lerner et al, 1958).

The first non-steroidal anti-oestrogen: Merrell cardiovascular program tests ethamoxytriphetol as part of an endocrinology programme evaluating synthetic oestrogens and discovers that it is in fact anti-oestrogenic. It was investigated as a contraceptive in rat models, shortly followed by clomiphene. Ethamoxytriphetol proved too toxic and clomiphene was found to have the opposite effect in humans. Numerous applications, but experimental treatments for breast cancer stopped due to extensive side effects and toxicity concerns (see below). (Patent US 2914563 A)

A pioneering study which showed the target site-specific action of radiolabelled oestradiol injected into immature rats (Jensen and Jacobsen, 1962).

ICI file patent for tamoxifen, developed as a potentially safer anti-fertility agent (than, for example, triparanol).

Failure of Merrell to market non-steroidal anti-oestrogens as contraceptives attracted the attention of Arthur Walpole and his colleagues Michael J. K. Harper—a reproductive endocrinologist — and Dora M. Richardson — a synthetic organic chemist—at ICI Pharmaceuticals Division. Tamoxifen is discovered.

ICI patent published in the UK, GB1013907.

President's Commission on Heart Disease, Cancer and Stroke established.
1967
First detailed report of the antifertility activity of tamoxifen in rats. The anti-oestrogen lowered circulating cholesterol but did not increase demosterol (Harper et al 1967)

1970
Enthusiasm for chemotherapy in the treatment of breast cancer. Tamoxifen not considered breakthrough. Focus on tamoxifen in reproductive endocrinology instead.

1971
Lars Terenius published two important papers in the European Journal of Cancer that described the action of nafoxidine for the treatment of DMBA-induced rat mammary tumours and the ability of the first non-steroidal antioestrogen MER 25 to prevent rat mammary carcinogenesis. These studies demonstrated ‘proof of principle’ for the application of antioestrogens to treat breast cancer, but neither compound showed any promise in the clinic because of serious toxic side-effects. In fact, this was the consistent story for all of the antioestrogens, except for tamoxifen. (Jordan 2008)

1971
The first clinical trial testing tamoxifen as a breast cancer treatment carried out at the Christie Hospital in Manchester (Cole et al, 1971). Showed that tamoxifen had equivalent efficacy to historical results of standard endocrine therapy, but fewer side effects.

1971
ICI consider numerous applications for tamoxifen and stop development programme as market prospects were not promising

1972
US Congress passes National Cancer Act of 1971 (beginning of ‘war on cancer’)

1972
ICI consider numerous applications for tamoxifen and stop development programme as market prospects were not promising

1972
Approved for clinical use in the UK

1972 ~ 1974
Walpole finds ICI funding for Jordan’s work at Worcester

1972 ~ 1979
Walpole convinces ICI to market in the UK for breast cancer treatment

1973
Jordan commences work at Worcester exploring tamoxifen as breast cancer treatment

1974
Approved for clinical use in the UK

1974
Betty Ford undergoes mastectomy

1974
Jordan works on tamoxifen research at the University of Leeds as a University Joint/Research Scheme

Panel of Consultants on the Conquest of Cancer report to US Senate

1970
1975
Tamoxifen marketed as inducer of ovulation

1976
Publication demonstrates that tamoxifen could not only be used to treat mammary cancer, but could also act as a preventative (Jordan, 1976)

1977
Approved in US for advanced breast cancer in post-menopausal women, but patent protection repeatedly denied due to perceived primacy of Merrell patents. Tamoxifen first medicine approved by the FDA for risk reduction of any cancer.

1978
Publication of clinical report demonstrating that extended adjuvant tamoxifen therapy saved lives (Baum et al, 1983)

1979
Publication of clinical report demonstrating the use of tamoxifen as an adjuvant treatment in early breast cancer. (NATO, 1983)

1980
The first study to demonstrate, in the lab, that long-term anti-oestrogen therapy and a strategy of oestrogen blockade was the best way to treat patients with receptor-positive disease (Jordan and Allen, 1980) long-term adjuvant therapy

1981

1982

1983
NCI state tamoxifen is the adjuvant endocrine treatment of choice for breast cancer (Jordan, 2003)

1984
Barr Labs files an ANDA for a generic version of tamoxifen (later followed by a Paragraph IV certification, immediately challenged by Zeneca) (Perry 2006)

1985
US patent approved through court of appeals, after over a decade of clinical development advancing with no assurance of exclusivity. This may also illustrate the perceived lack of importance of the drug in the pharmaceutical industry (Jordan, 2003). Patent granted with precedence to the patent dating back to 1965.

1986
Publication of clinical report demonstrating that extended adjuvant tamoxifen therapy saved lives (Baum et al, 1983)

1987
The first report that both tamoxifen and raloxifene would maintain bone density selectively, despite the fact that both prevented mammary cancer in rats (Jordan et al, 1987)

1988
First pilot trial in breast cancer prevention in 3,000 high-risk women (Powles et al., 1989) – underpowered to show significant effect

1989
First pilot trial in breast cancer prevention in 3,000 high-risk women (Powles et al., 1989) – underpowered to show significant effect

US trial of 13,388 high-risk women showed 50% reduction in invasive breast cancer (Fisher et al, 1989)
Study starts which finds that tamoxifen produces liver tumours in rats (Greaves et al, 1993) (no significant increase in liver cancer has been reported in humans, but Jordan notes that had rat effects been established in early 1970s, development would have stopped – Jordan, 1995)

The first prospective randomised study to demonstrate that tamoxifen had the potential to increase bone density in postmenopausal patients is published (Love et al, 1992)

US patent held invalid on the grounds of withholding information from PTO. Zeneca and Barr (the other plaintiff intending to market generics) reached an out-of-court agreement while case on appeal (Perry 2006)

First prospective randomised trial of high-risk pre and postmenopausal women to show that tamoxifen reduced the risk of breast cancer. (Fisher et al, 1998)

Study showing that long-term tamoxifen users have a worse prognosis of endometrial cancers, and questioning the widespread use of tamoxifen as a preventive agent against breast cancer in healthy women (Bergman et al, 2000).

1990

1991

Publication makes first suggestion that tamoxifen has potential as a chemopreventive agent for breast cancer, based on aspects of its pharmacology, and existing laboratory research and clinical experience (Nayfield et al, 1991)

1992

The first prospective randomised study to demonstrate that tamoxifen had the potential to increase bone density in postmenopausal patients is published (Love et al, 1992)

1997

Raloxifene receives FDA approval for osteoporosis prevention (Grabowski 2008)

1998

2-year Multiple Outcomes for Raloxifene Evaluation study (which primarily evaluated raloxifene effects on fractures in postmenopausal osteoporosis patients) shows a secondary end point reduction in breast cancers

1999

Clinical proof of the concept proposed in 1990 that women taking a selective oestrogen-receptor modulator to present or treat osteoporosis would have a reduced incidence of breast cancer (Cummings et al, 1999)

2000

Study showing that long-term tamoxifen users have a worse prognosis of endometrial cancers, and questioning the widespread use of tamoxifen as a preventive agent against breast cancer in healthy women (Bergman et al, 2000).
2001

Study comparing use of tamoxifen over 10 rather than 5 years (Fisher et al, 2001)

Global sales of tamoxifen reach $1,024m

2002

First evidence on prevention from the International Breast Cancer Intervention Study (IBIS) published (Cuzick et al, 2002)

2003

Review of existing trial data published showing that tamoxifen can reduce the risk of ER-positive breast cancer (Cuzick et al, 2003)

2005

Important evidence published on the use of tamoxifen for the prevention of breast cancer cited on NICE guidance. (Fisher, et al., 2005)

2007

Further importance evidence based on research conducted partially in the UK on the use of tamoxifen for the prevention of breast cancer published. The work is cited as important on NICE guidance. (Cuzick, et al., 2007)

2013

Meta-analysis of 9 prevention trials published showing that incidence of invasive oestrogen (ER)-positive breast cancer was reduced both during tamoxifen treatment and for at least 5 years after completion (Cuzick et al., 2013)

NICE recommends the use of tamoxifen as a preventive treatment in women who have a family history of breast cancer

Evista (raloxifene) received FDA approval for additional labeling for breast cancer risk reduction in postmenopausal women with osteoporosis and in postmenopausal women at a high risk of breast cancer.
Figure 4. Coronary heart disease timeline
1912
James B. Herrick concludes that the slow, gradual narrowing of the coronary arteries could be a cause of angina. He’s credited with inventing the term “heart attack.”

1915
A group of physicians and social workers forms the first “Association for the Prevention and Relief of Heart Disease” in New York City.

1924
“Association for the Prevention and Relief of Heart Disease” becomes the American Heart Association.

1947
Ancel Keys starts the first major study into looking at a relationship between diet and heart disease.

1948
Researchers under the direction of the National Heart Institute (now called the National Heart, Lung and Blood Institute) initiated the Framingham Heart Study, the first major study to help understand heart disease.

1949
The term “arteriosclerosis” (known as “atherosclerosis” today) is added to the International Classification of Diseases, which causes a sharp increase in reported deaths from heart disease.

1948
National Heart Institute established
American Heart Association established
Total US heart research $500k, similar to Long Island potato bug

1950
John Gofman identifies cholesterol types: low-density lipoprotein (LDL) and high-density lipoprotein (HDL). He discovered that men who developed atherosclerosis had elevated levels of LDL and low levels of HDL.
1956
Gofman makes a series of epidemiological observations:
- cholesterol contained in low density lipoprotein (LDL)
- heart attacks correlated with elevated levels of blood cholesterol
- heart attacks less frequent when the blood contained elevated levels of high density lipoprotein (HDL) (Gofman)

1955
Framingham study demonstrates that blood cholesterol level is a risk factor for CAD

1958
The Seven Countries Study Led by Ancel Keys begins.

1960
Cigarette smoking found to increase the risk of heart disease

1961
AHA endorses prudent diet, reflecting focus on relationship between diet and blood cholesterol

1964
Bloch and Lynen awarded Nobel Prize for the outlines of the reduction of HMGCoA to mevalonate

1955 - 1965
Much interest in cholesterol biosynthetic pathway. Key studies published by Konrad E. Bloch, Feodor Lynen, John Cornforth, and George Popják
Seven Countries Study shows that the incidence of heart attacks (in 15,000 middle-aged men followed for 10 years) linearly proportional to the blood level of cholesterol.

1979
Merck filed for a U.S. patent on lovastatin, complete with structural details.

1979
Endo isolated monacolin K, a compound identical to lovastatin, from a different organism, and filed for a Japanese patent, based on inhibitory activity alone, without providing structural data.

---
Merck isolated a statin very similar to compactin in chemical structure, called mevinolin (later changed to lovastatin).

1976
Roy Vagelos, President of Merck Research Laboratories, signs a confidentiality agreement with Sankyo and obtains samples of compactin and confidential experimental data.

1976
Earliest statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor), compactin, discovered by Endo.

1980
Clinical trials for lovastatin began at Merck.
Clinical trials of lovastatin at Merck discontinued because of rumors (to this day never substantiated) that the closely related compound, compactin, caused certain cancers in dogs.

A patent was granted for lovastatin in the United States and subsequently in a number of countries abroad. In other countries, patents went to Sankyo for monacolin K.

Merck made lovastatin available to several prominent US clinicians, who had asked for it to treat patients with severe hypercholesterolemia unresponsive to available agents. The drug showed dramatic activity in lowering LDL cholesterol and total cholesterol in the blood, with very few side effects.

Animal studies resumed at Merck.

Coronary Primary Prevention Trial results reported (first large scale double-blind placebo-controlled trial to address the lipid hypothesis), followed by: the Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease.

Brown and Goldstein receive Nobel Prize for their work on LDL Pathway.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) first Published guidelines for the detection, evaluation and treatment of hyperlipidemia.

A patent was granted for lovastatin in the United States and subsequently in a number of countries abroad. In other countries, patents went to Sankyo for monacolin K.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) first Published guidelines for the detection, evaluation and treatment of hyperlipidemia.

Dick Cheney has his third heart attack and undergoes quadruple bypass surgery, a relatively new procedure at the time.
**1992**

Cholesterol debate is alive with an overview by Davey Smith and Pekkanen ('Should there be a moratorium on cholesterol lowering drugs?')

**1994**

Scandinavian Simvastatin Survival Study (4S) shows significant reduction in mortality, effectively ending the cholesterol debate (Scandinavian Simvastatin Survival Study Group 1994) – though this covered only people at extremely high risk for recurrent CAD, not individuals with mild to moderate elevations in total cholesterol and LDL levels, who represent a majority of people ever developing CAD

Fluvastatin approved for marketing

**1996 - 1998**

Other secondary prevention trials show benefits of statins even in population with lower risks of CAD (Cholesterol and Recurrent Events study and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study)

**1997**

Atorvastatin approved for marketing

**1998**

Cerivastatin approved for marketing

**2000**

David Letterman undergoes quintuple bypass surgery

**2001**

Cerivastatin withdrawn because of a large number of reports of rhabdomyolysis, of which more than 50 cases were fatal

**2001**

An EU directive requiring bigger, bolder health warnings on tobacco packaging becomes law. Measures to be phased in from 30 September 2002 include increasing the size of health warnings to cover 30% and 40% of the main pack faces

**2002**

Heart Protection Study confirms and expands previous evidence, including firmly establishing the benefit of simvastatin in women, and its effectiveness for reduction of the risk not only of CHD events such as myocardial infarction, but also of strokes
2003
- Rosuvastatin approved for marketing

2004
- Bill Clinton undergoes quadruple bypass surgery
- Elizabeth Taylor diagnosed with heart disease

2010
- Dick Cheney has his fifth heart attack and receives a heart implant transplant

2011
- Dick Cheney publishes his memoir (in large part on his struggles with heart disease) called “In My Time”
- Elizabeth Taylor dies from congestive heart failure
- Barbara Walters’ 2011 TV special on heart disease starring David Letterman, Bill Clinton, and Robin Williams.
- Pfizer’s patent on Lipitor (best-selling drug of all times) expires

Classification of factors and events:
- Political
- Economic
- Social
- Technological
- Legal
- Environmental
Figure 5. Parkinson's disease timeline
1911
D,L-Dopa synthesized in laboratory by Casimir Funk

1913
Levodopa isolated from Vicia faba (fava bean) seedlings at Roche laboratories by Marcus Guggenheim

1927
Levodopa found to be biologically active

1938
L-Dopa decarboxylase enzyme identified by Peter Holtz

1957
Parkinson's Disease Foundation established in America

1958
Carlsson et al. develop a new chemical fluorescent assay technique to measure dopamine in tissue, for there was previously no method to measure the microgram quantities suspected. It shows that not only was it present in the brain, but that it was depleted with reserpine and restored with L-dopa

1959
Carlsson speculates, at the 1959 international pharmacology meeting, that dopamine is responsible for PD

1960
Hornykiewicz publishes a landmark paper showing for the first time a marked depletion of dopamine in the caudate and putamen of patients only in the PD and postencephalitic parkinsonian brains

1961
First reported trial of intravenous levodopa in PD
1967
Levodopa activity enhanced with peripheral dopa decarboxylase inhibitor (benserazide)
***
Effectiveness of oral levodopa demonstrated in patients with parkinsonism
***
Cotzias introduces high dosage levodopa

1969
First double-blind, placebo-controlled study showing efficacy of levodopa but with development of choreiform movements

1970
Levodopa approved by the FDA as PD treatment

1974
Clinical use of carbidopa-levodopa reported
***
L-dopa-induced dyskinesias first described

1975
Continuous levodopa administration tried for preventing complications
***
Levodopa-benserazide (Madopar) commercialized
***
Carbidopa-levodopa (Sinemet) commercialized

1964
Nagatsu et al. discover the enzyme tyrosine hydroxylase that converts L-tyrosine to L-dopa

1969
Parkinson’s UK established (then called “Parkinson's Disease Society”)

1971
First publication - 'Parkinson's disease - a booklet for patients, friends and families'
1997
Johnny Cash announces he has PD

1998
First COMT inhibitor becomes commercially available (tolcapone; Tasmar)

1998
Michael J Fox makes his condition known to the public

1999
Entecapone (COMT inhibitor) commercially available (as COMTan in the US by Novartis)

2000
Michael J Fox launches his foundation (over $90 millions raised to date)
Maurice White announces he has Parkinson’s disease.

2001
The book "Saving Milly: Love, Politics and Parkinson’s Disease" is published.

2001
George W Bush bans federal funding of embryonic stem cell research, causing outrage as it meant a halt in possible advances in curing PD. Michael J Fox began being an activist for the cause.

2002
Michael J Fox published first book on his struggles and life with PD: Lucky Man: A Memoir

2003
Pope John Paul II’s diagnosis of PD confirmed

2004
ELLDOPA trial does not conclusively resolve the question of when to start L-Dopa treatment

2005
A lot of portrayals and mentions of PD in film and TV

2003
Combination carbidopa-levodopa-entacapone tablets (Stalevo by Novartis) become commercially available
2011
The National MS and Parkinson's disease Registries Act (S. 1273) passed

2012
- Another freeze on the stem cell research ruled by a court - a case won by Christian medical groups.
- Love and Other Drugs. A Hollywood film starring Anne Hathaway

2013
- Parkinson’s UK produced the first ever public awareness campaign with Parkinson’s UK adverts.
- Parkinson’s UK won the ‘Charity of the Year with income of more than £1million’ category at the prestigious Charity Times Awards.
- Dickey-Wicker Amendment introduced. Although federal funds cannot be used to directly destroy an embryo, the amendment does not prohibit funding a research project using embryonic stem cells. This is an important distinction under the law, because for federal funds to be used directly to support the destruction of embryos.

Classification of factors and events
- Political
- Economic
- Social
- Technological
- Legal
- Environmental