



Neutral Citation Number: [2013] EWHC 1737 (Pat)

Case No: HC11C03400

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice, Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 25 June 2013

Before :

THE HON MR JUSTICE ARNOLD

Between :

ELI LILLY AND COMPANY **Claimant**
- and -
JANSSEN ALZHEIMER IMMUNOTHERAPY **Defendant**

Andrew Waugh QC and Thomas Mitcheson (instructed by **Simmons & Simmons**) for the **Claimant**

Simon Thorley QC and Charlotte May (instructed by **Linklaters LLP**) for the **Defendant**

Hearing dates: 24-26, 29-30 April, 1, 3 May 2013

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE HON MR JUSTICE ARNOLD

MR JUSTICE ARNOLD :

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Introduction

1. The Defendant (“JAI”) is the proprietor of European Patent (UK) No. 1 994 937 (“the Patent”) entitled “Prevention and treatment of amyloidogenic disease”. The Patent discloses and claims pharmaceutical compositions comprising an antibody to β -amyloid peptide, also referred to as amyloid- β or A β . The Patent is one of four patents granted pursuant to divisional applications from a parent application which matured into EP 1 033 996. The Claimant (“Lilly”) seeks an order for revocation of the Patent and a declaration that dealings in pharmaceutical compositions comprising an antibody called solanezumab, which Lilly currently has in Phase 3 development for the treatment of Alzheimer’s Disease (“AD”), will not infringe the Patent. Lilly attacks the validity of the Patent on the grounds of added matter, lack of novelty, obviousness, and insufficiency. There is no challenge to the claimed priority date of 2 December 1997. JAI has applied to amend the Patent by deleting claims 13, 14 and 15 and by omitting two words from claim 11. That application is unopposed.

The witnesses

Lilly’s witnesses

2. Lilly called a single expert witness, Professor Thomas Wisniewski. Prof Wisniewski has been Professor of Neurology, Pathology and Psychiatry at New York University (“NYU”) School of Medicine since 2005. He obtained an MBBS from King’s College London (“KCL”) in 1983. He moved to New York in 1984 to pursue his interest in neurodegenerative research. Having completed residences in Anatomical Pathology, Neurology and Neuropathology at NYU Medical Center and Columbia University, in 1990 he took up an academic position as Clinical Instructor in Neurology at NYU. From 1990 to 1994 he worked with the immunologist Professor Blas Frangione. He became an Assistant Professor of Neurology and Pathology in 1992 and a tenured Assistant Professor of Neurology, Pathology and Psychiatry in 1999. He has been Director of the Conformational Disorders Laboratory at NYU since 1997 and Director of the Neuropathology Core of the NYU AD Center since 2002. He has held a number of other academic and hospital appointments. These positions allow him to divide his time equally between treating patients and research. His research focuses on neurodegenerative disorders, in particular the pathogenesis and treatment of AD and prion-related diseases. He has been on the editorial boards of several academic journals. He has published 217 full length peer-reviewed publications. He has won a number of awards. He is a named inventor on a number of patents. He was an investigator in the Phase 3 trials of both JAI’s product bapineuzumab and Lilly’s product solanezumab.
3. Prof Wisniewski had expertise in neuroscience, immunology and clinical treatment. Counsel for JAI rightly accepted that Prof Wisniewski was both highly expert and gave his evidence clearly and fairly, but submitted that on some points Prof Wisniewski had had difficulty in putting himself in the position of the addressee of the Patent rather than viewing matters from his own perspective. I think there is some force in this, and I have taken this into account when assessing his evidence.
4. In addition, Lilly adduced unchallenged factual evidence from Dr Ronald DeMattos. He obtained a PhD in Molecular and Cellular Biochemistry from the State University of New York at Stony Brook in 1998. From October 1998 to June 1999 he held a

post-doctoral position at Stony Brook. From June 1999 to 2002 he held a post-doctoral position in David Holtzman's laboratory at Washington University School of Medicine. In September 1999 he received funding for a project to analyse physiologically relevant apolipoprotein/A β interactions in mouse models of AD. This work led first to the filing of US Patent Application 60/184601 in February 2000 (and later to further patent applications) and secondly to the publication of DeMattos *et al*, "Peripheral anti-A β antibody alters CNS and plasma A β clearance and decreases A β burden in a mouse model of Alzheimer's disease", *PNAS*, 98(19), 8850-8855 (2001) ("DeMattos 2001") on 17 July 2001. This was the starting point for the development of solanezumab. In late 2002 Dr DeMattos joined Lilly, where he is now a Research Fellow in Neuroscience Discovery Research. In his witness statements Dr DeMattos described aspects of the development of solanezumab.

JAI's witnesses

5. JAI called two expert witnesses, a neuroscientist, Professor Paul Francis, and an immunologist, Dr Michael Owen. Prof Francis is Professor of Neurochemistry at KCL. He obtained a BSc in Physiology and Biochemistry from the University of Reading in 1979 and a PhD in Neuroscience from the same institution in 1984. From 1982 to 1990 he was a Post-Doctoral Research Fellow and from 1990 to 1995 an Honorary Lecturer at the Institute of Neurology, Queen Square. In 1995 he became Senior Lecturer in Biochemistry and Molecular Biology at the United Medical and Dental Schools of Guy's and St Thomas' Hospitals, which merged with KCL in 2000. He was appointed Reader in 2004 and Professor in 2008. In 2008 he also became Director of Brains for Dementia Research. He is the author of over 122 publications in refereed journals. His research includes work on the mechanisms of AD and other types of dementia, such as frontotemporal dementia, Lewy body dementias and vascular dementia. He has been involved in some clinical trials relating to AD, in particular a trial of memantine in people with Down's syndrome.
6. As counsel for Lilly pointed out, Prof Francis was less experienced in the areas of neuroscience relevant to this case than Prof Wisniewski. Thus he had limited experience in amyloid research prior to 1997 and no personal experience of working with A β . Nor did he have any clinical experience. Counsel for Lilly submitted that Prof Francis was adversarial in his evidence. I do not accept that. In my judgment he did his best to assist the court. I did think that Prof Francis exhibited some discomfort in some of his evidence, but I attribute that to his relative lack of expertise with regard to A β in 1997.
7. Dr Michael Owen is an independent biotechnology consultant. He received a degree in Biochemistry from the University of Oxford in 1973 and a PhD from the University of Cambridge in 1976. From 1976 to 1979 he carried out post-doctoral research in the field of immunology at the National Institute for Medical Research in Mill Hill, London. From 1979 to 2001 he was employed by the Imperial Cancer Research Fund where he conducted research on the biological pathways and systems involved in the immune response. From 2001 to 2009 he was a senior vice president at GlaxoSmithKline ("GSK"). In 2004 he set up and headed GSK's Biopharm Centre of Excellence for Drug Discovery. While he was head of that Centre, he had responsibility for a monoclonal antibody to A β that entered Phase 1 trials, but which GSK decided not to progress further. From 2009 to 2011 he was Chief Scientific Officer of Kymab Ltd, a biotech company. He has published 157 publications.

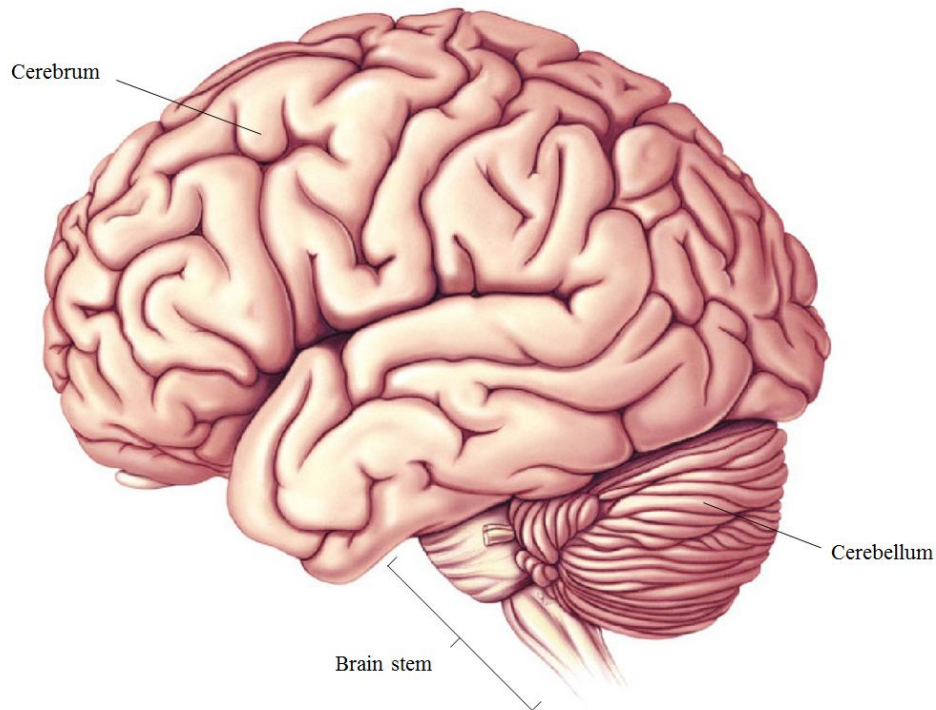
8. Counsel for Lilly rightly accepted that Dr Owen gave his evidence clearly and fairly. As counsel pointed out, however, he had no experience in AD, let alone of working with A β . Like Prof Francis, he had no clinical experience.
9. I am sure that JAI's solicitors were conscious of the need to avoid overlap in the expert reports produced by Prof Francis and Dr Owen, but they did not succeed in achieving this. In particular, Prof Francis was able to, and did, say quite a lot about immunological aspects of the case. That being so, I consider that steps should have been taken to reduce the ambit of Dr Owen's reports. The inevitable result was an overlap between the cross-examination of Prof Francis and that of Dr Owen, although I am sure that counsel for Lilly tried to keep this to a minimum.

Technical background

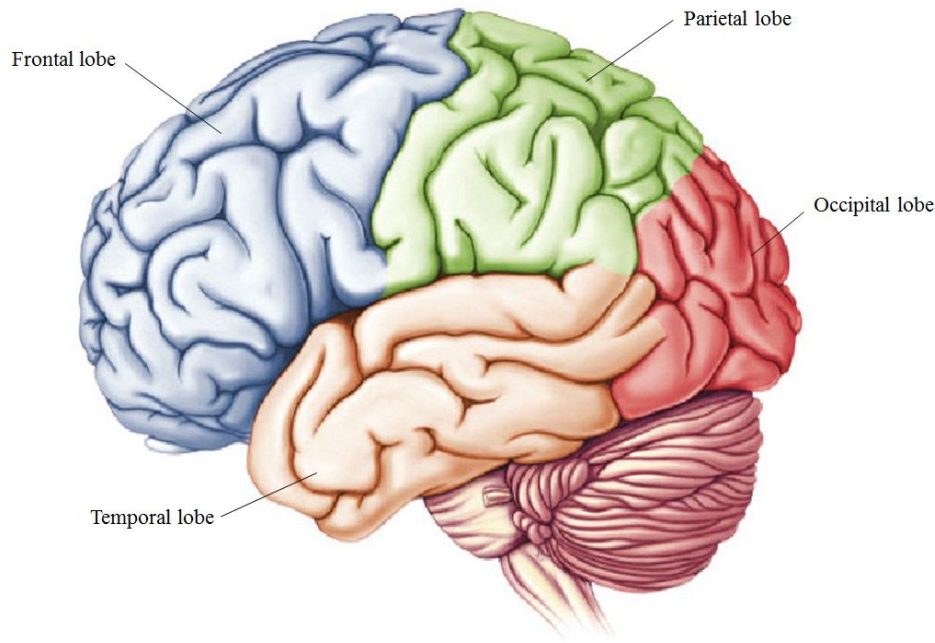
10. The technical background to this case involves two complex areas of science, namely neuroscience and immunology. Although there were certain disputes as to the common general knowledge of the skilled team which I shall consider below, much of the technical background was undisputed. Despite this, the parties did not prepare a technical primer for the court. In my view a technical primer of the kind which was prepared by the parties in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1669 (Ch) would have been of assistance. I appreciate that agreeing a technical primer is not always easy, and that the process can end up in costing more money than it saves on preparation of experts' reports and in court. Nevertheless, I consider that, in technically challenging cases such as this, parties ought if possible to agree a primer before finalising the remainder of their experts' reports.
11. My account is largely based on those given by Prof Francis and Dr Owen in their respective first reports, although I have also drawn upon Prof Wisniewski's first report.

The structure of the brain

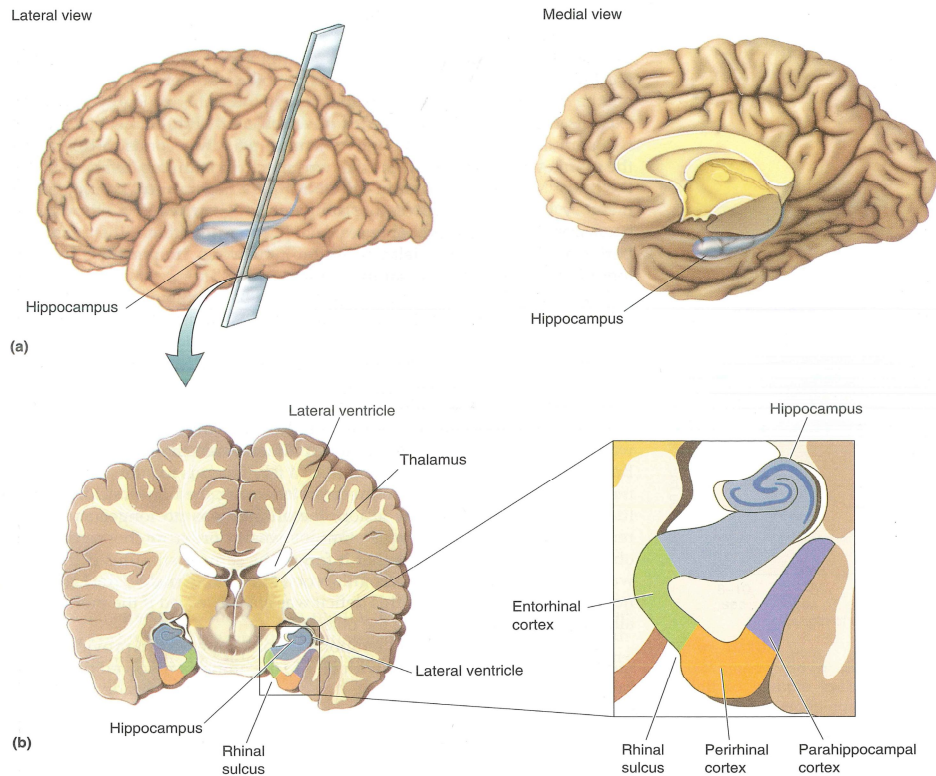
12. The mammalian nervous system is divided into the central nervous system ("CNS"), made up of the brain and spinal cord, and the peripheral nervous system. The brain and spinal cord are surrounded by a thin layer of cerebrospinal fluid ("CSF"), which (amongst other things) acts as a protective cushion. In all mammals, the brain can be divided broadly into three parts: the cerebrum, the cerebellum and the brain stem. These parts of the human brain are shown below (image adapted from Bear, Connors & Paradiso, *Neuroscience: Exploring the Brain* (2nd ed), 2000):



13. The cerebrum is the largest part of the brain in mammals. The thin sheet of neurones lying just underneath the surface of the cerebrum is called the cerebral cortex (often referred to simply as the cortex). In contrast to the cortex in mouse and rat brains, the human cortex is folded and wrinkled in order to accommodate greater development. In the human brain, the cerebral cortex contains the brain systems responsible for speech, sensations, perceptions, voluntary movement, cognition and learning. The cerebellum, lying on top of the brain stem and behind the cerebrum, is primarily a movement control centre. It contains as many neurones (nerve cells) as the cerebrum, despite being much smaller. The brain stem acts to relay information between the cerebrum and the spinal cord/cerebellum. It also controls vital functions such as breathing, consciousness and body temperature.
14. The human cerebrum is divided into four lobes, the frontal, parietal, occipital and temporal lobes, as shown below (image adapted from Bear, Connors & Paradiso, 2000):



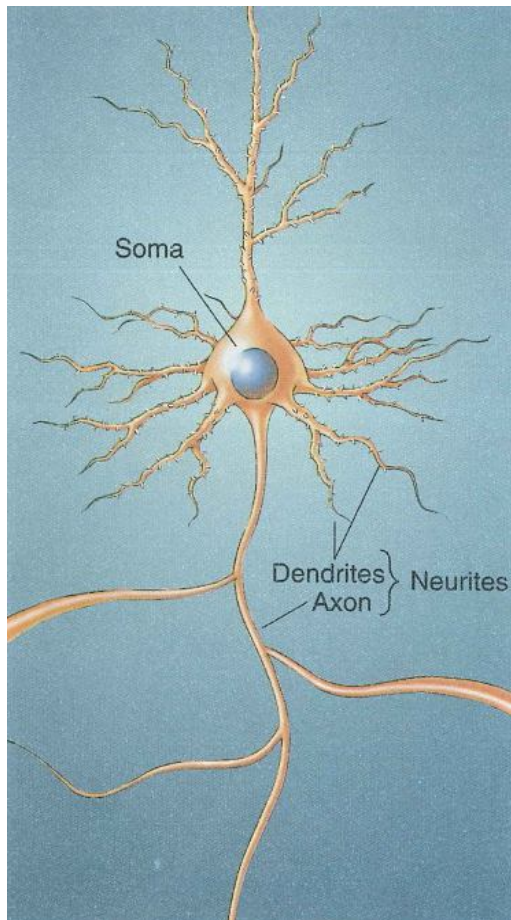
15. The frontal lobe is responsible for executive function (such as future planning, judgement, decision-making, attention span and inhibition) and the formation of longer term memories (often memories associated with emotions). The parietal lobe integrates sensory information and is involved in cognition, information processing, pain and touch sensation, spatial orientation, speech/language, reading, writing and mathematics. The occipital lobe is particularly involved with primary visual processing. The temporal lobe is responsible for registering olfactory senses and is involved in the processing of auditory input. It also partially controls speech, memory and emotion.
16. Within the temporal lobe in humans is a piece of cortex folded onto itself into a seahorse-shaped structure, called the hippocampus. Next to the hippocampus is the entorhinal cortex (image from Bear, Connors & Paradiso, *Neuroscience: Exploring the Brain*, 1996):



17. The hippocampus has a role in memory and learning. The entorhinal cortex interacts with the hippocampus to play an important role in autobiographical memories, spatial memories, memory formation and memory consolidation.
18. It is possible to recognise many of the same gross structures described above, in relation to the human cerebrum, in the cerebrum of a mouse. There are similar, analogous regions, although the mouse cerebral cortex is less well developed and arranged differently, so that the functions of the mouse cortex are not all associated with the same structures as in humans.

The cells of the brain

19. Brain tissue is made of neurones (sometimes called nerve cells) and glial cells (also referred to as glia). Neurones are the elementary functional unit of brain cells, whereas glial cells are effectively support systems for neurones. The neurone consists of three main parts: the soma, the dendrites and the axon (together, the dendrites and the axon are called neurites). These are shown below (image from Bear, Connors & Paradiso, 1996):



20. The soma contains the cell nucleus and various other organelles within the cytoplasm. The axon projects out from the soma to contact and communicate with other neurones, and in humans may be anything from less than a millimetre to over a metre in length. Axons often branch, as shown in the diagram above, enabling a neurone to communicate with multiple other cells. The point at which an axon from one neurone comes into contact with the neurites or soma of another neurone and passes on information is called a synapse. Information is relayed in the form of electrical impulses, which travel down the axon. When the electrical signal reaches the pre-synaptic terminal of the axon, at most synapses it triggers the release of a chemical signal, called a neurotransmitter, into the synapse. Examples of neurotransmitters are acetylcholine, glutamate and serotonin. These neurotransmitters diffuse across the synaptic cleft and are detected by post-synaptic receptors on dendrites of other neurones. A synapse may be excitatory or inhibitory. An excitatory synapse is one in which the neurotransmitter excites the post-synaptic membrane, making it more likely that the receptor neurone will propagate an electrical impulse. An inhibitory synapse is one in which the neurotransmitter decreases the excitation of the next neurone.

21. There are three main types of glia in the brain: astrocytes, oligodendrocytes and microglia. Astrocytes are the most numerous glia in the brain. These fill the space between neurones, regulate the chemical content of the extracellular space, and support neurones by removing waste and providing nutrients. Oligodendrocytes support and insulate axons by surrounding them with myelin. Finally, microglia internalise, and subsequently degrade, debris from dead or dying neurones or glial

cells, in a process known as phagocytosis (as to which, see below). Microglia also eliminate pathogens by producing cytotoxic chemicals.

Amyloidosis

22. The term “amyloidosis” refers to the deposition of fibrillar proteins (amyloid) in the extracellular spaces of different tissues (both cerebral and systemic) that can lead to cell damage, organ dysfunction and death. Over 20 different proteins are capable of forming amyloid deposits. Cerebral amyloid deposits can lead to cognitive deficits and/or strokes.
23. It was known by 1997 that all types of amyloid, irrespective of the protein in the amyloid, share certain physico-chemical properties:
 - i) A fibrillar, un-branched appearance on electron microscopy of varied length, diameter typically 10nm;
 - ii) a predominantly β -pleated sheet secondary structure;
 - iii) characteristic staining properties, including apple-green birefringence under polarized light after Congo Red staining and yellow-green fluorescence after thioflavin S staining;
 - iv) a high degree of insolubility under physiological conditions, which may preclude their complete proteolytic degradation *in vivo*; and
 - v) an association with presumed chaperone proteins such as amyloid P-component, proteoglycans, apolipoprotein E, apolipoprotein J and other serum proteins.

AD

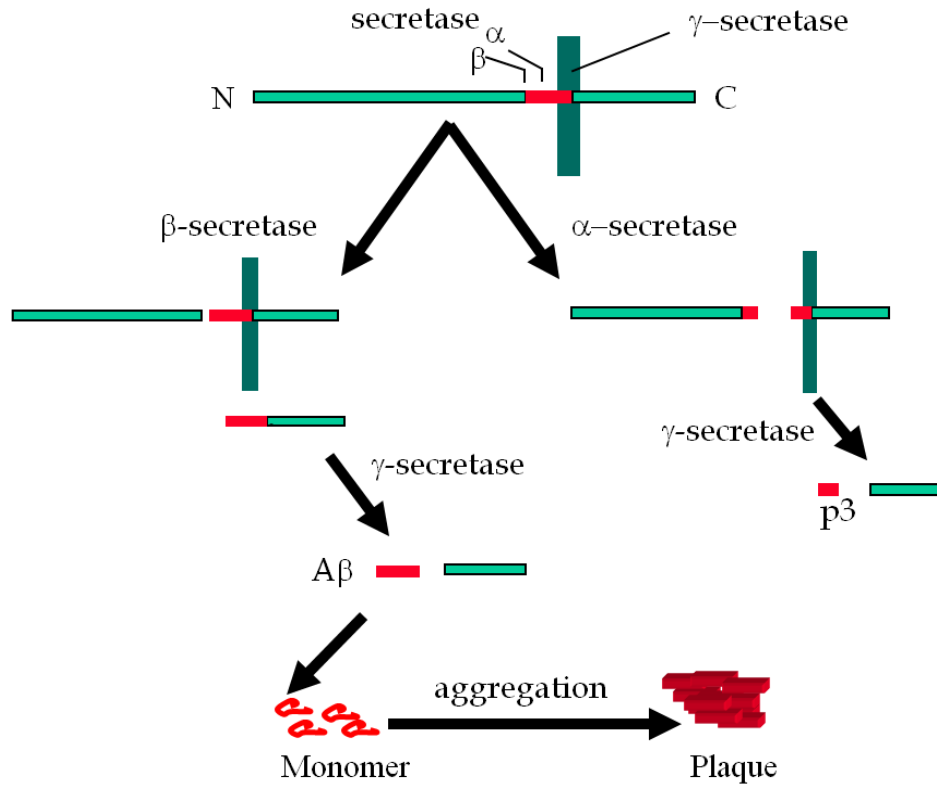
24. AD is the most common form of amyloidosis. AD was first described by the German psychiatrist and neuropathologist, Alois Alzheimer, in 1907. It is the most prevalent form of dementia worldwide. It is a chronic, neurodegenerative disorder characterized by a loss of cognitive ability and severe behavioural abnormalities, leading ultimately to death. By 1997 AD was recognised as a major problem in the aging population, but the available treatments were almost all palliative and had little or no influence on the neurodegenerative processes associated with the disease.
25. Common symptoms of AD include amnesia, aphasia, apraxia, agnosia and other associated non-cognitive features:
 - i) amnesia is characterised by short-term memory loss and reduced ability or inability to form new memories or recall information;
 - ii) aphasia is the impairment of language ability, characterised in the early stages as difficulty in remembering words and naming things and, as AD progresses, resulting in a complete loss of communication (speech, reading and writing);
 - iii) apraxia is the inability to perform volitional acts (such as eating and dressing) despite having intact sensory and motor systems;

- iv) agnosia is the inability to understand the significance of sensory stimuli, the misidentification of objects by feel, the misidentification of faces, right-left disorientation and inability to recognise one's own body parts; and
 - v) associated features can include mood disorders, delusions, hallucinations, misidentifications and behaviour disturbance, such as aggression, agitation, wandering, vocalisation, disinhibition and abnormal eating.
26. There are four major neuropathological characteristics associated with AD:
- i) Parenchymal deposits of amyloid called neuritic plaques, which are dense extracellular deposits found in the brain's grey matter. The principal component of such plaques is A β . The A β deposits are surrounded by degenerating neurites which are in turn covered in astrocytes and microglia.
 - ii) Cerebral amyloid angiopathy, also known as congophilic amyloid angiopathy ("CAA"). This is another type of amyloidosis, but it is found in almost all AD cases, and it is severe in about one third of patients with AD. It is a disease of the blood vessels, and results from amyloid deposits in the cerebral vasculature.
 - iii) Intraneuronal cytoplasmic deposits of neurofibrillary tangles ("NFT"). These are inclusion bodies which consist of an accumulation of paired helical filaments which form inside neurons. They are comprised of aggregates of a hyper-phosphorylated protein called tau.
 - iv) Synaptic loss, which refers to the loss of neurons and neuronal connectivity in the brain. This results from factors such as toxicity and inflammation and leads to loss of brain function and dementia.
27. AD can be divided into the early-onset form (<60 years) and the more common late-onset form (>60 years). AD pathology accumulates over many years. The understanding in 1997 was that there is a pre-symptomatic period, in which amyloid pathology and subsequently tau-related pathology develop in the brain. NFT formation occurs after the amyloid build-up and is thought to be a result of amyloid-related deposition. This is followed by brain structure abnormalities, signs of loss of memory and then cognitive decline.
28. The majority of AD cases are sporadic (not genetically inherited). A very low percentage of cases is genetically inherited. There are also a number of genetic risk factors linked with AD, the best known being the inheritance of the ϵ 4 allele of apolipoprotein E ("apoE4").
29. Although people with plaques, tangles and associated brain atrophy will have a diagnosis of AD, in many cases a positive diagnosis based on these criteria can only be confirmed *post mortem*. During their lifetime, patients are typically diagnosed on the basis of their cognitive and neuropsychological symptoms. The tests used for diagnosis in 1997 included:
- i) the mini-mental state examination (MMSE), a brief 30-point questionnaire which is used to screen for cognitive function;

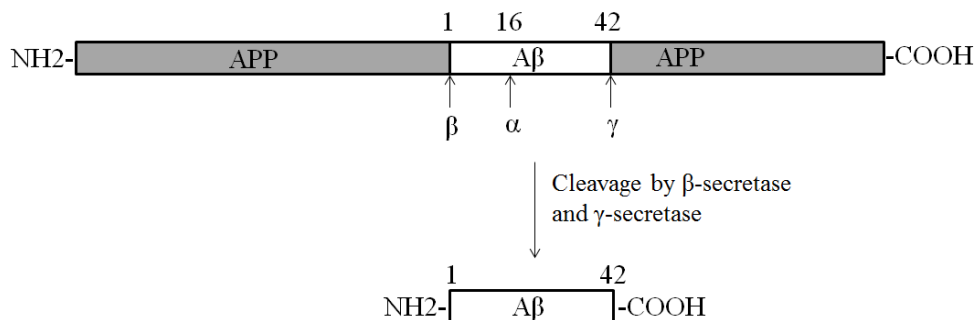
- ii) the ADAS-cog (Alzheimer's Disease Assessment Scale), which uses a cognitive test based on a 70 point scale (and so is more sensitive than MMSE);
 - iii) the McKhann criteria (otherwise referred to as the NINCDS-ADRDA criteria), which comprise a mixture of clinical and neuropathological approaches leading to a diagnosis of possible, probable or definite AD (although definite AD can only be diagnosed *post mortem*);
 - iv) Braak and Braak's classification, based on morphological evaluation of the brain, which evaluated the density and distribution of neurofibrillary tangles and classified them into different stages corresponding to normal cognition, cognitive impairment and dementia; and
 - v) the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria, which evaluate the density of neocortical neuritic plaques.
30. The first two tests are purely cognitive, whereas the remainder also assess neuropathological signs of AD to some degree. Those signs can generally only be assessed after the person has died, except in rare cases where a brain biopsy is undertaken. For most patients, MMSE would be the only test used to diagnose AD. In a clinical trial, further tests would be carried out. For example, patients might also have MRI (magnetic resonance imaging) or CT (computerised tomography) scans or blood flow measurements using PET (positron emission tomography) or SPECT (single-photon emission computed tomography). In 1997, these techniques would not have picked up plaques or tangles, but were used to rule out other problems (such as vascular lesions in the brain or tumours).

A β

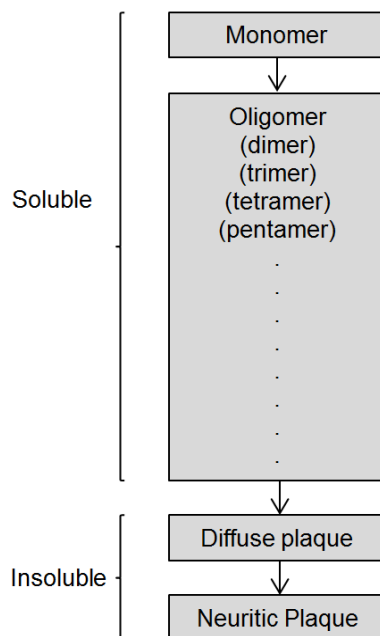
31. A β is an approximately 4kDa peptide (a peptide is a short chain of amino acids, the building blocks of proteins). It is a degradative fragment from a larger precursor protein called amyloid precursor protein ("APP"). In 1997 the role of APP was not understood, but it was thought to have a neuroprotective function. The process by which APP was cleaved to produce A β and A β aggregated to form plaques was known to be broadly as shown below (image adapted from a diagram by Lovestone, 2000):



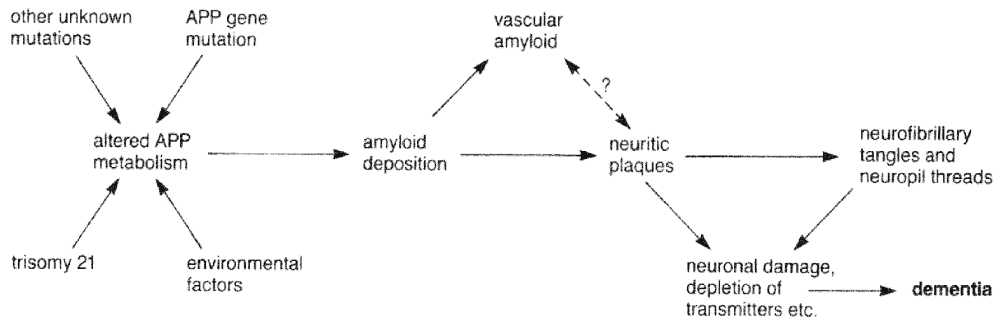
32. APP is shown as the horizontal light green line at the top of this diagram. APP is a transmembrane protein, the position of the membrane being indicated by the vertical dark green line. The Aβ region within APP is shown in red. APP is cleaved by three enzymes, known as α-, β- and γ-secretase. α-secretase cuts APP in the centre of the Aβ region, and so does not generate a fragment which contains the entire Aβ sequence. The ultimate product of α-secretase cleavage, after further cleavage by γ-secretase, is a peptide called p3, which is non-toxic. β-secretase cleaves APP at a different point, to produce C-terminal fragments which contain the entire Aβ peptide sequence (the C-terminal is the end which contains a COOH or carboxylic acid group). The products of β-secretase cleavage are further cut by γ-secretase to yield Aβ. γ-secretase cuts at more than one amino acid position, so different lengths of Aβ can be produced. Thus Aβ is not a single species.
33. Aβ peptides typically end at positions 39-43 (position 1 being the β-secretase cleavage site at the N-terminal end of Aβ and the N-terminal end being the end which contains an NH or amino group). The most common (and most studied) forms of Aβ are Aβ1-40 and Aβ1-42. Cleavage of APP to produce Aβ1-42 is shown below:



34. The conformation and aggregation state of A β influences its toxicity. The monomer exists in random coil or α -helical conformation and is soluble. It is found as a normal constituent of biological fluids, and therefore was not generally thought to be toxic. In 1997 it was not known what its normal function was, but it was thought to be involved in neurotransmission in some way.
35. It was known in 1997 that monomeric A β could aggregate to form oligomers and larger multimers. The result of aggregation was known to be the accumulation of A β in plaques, although the process of plaque formation was not well understood. It was thought that A β monomers first aggregated to form soluble A β oligomers. The larger the oligomer, the less likely it was to be soluble and the more toxic it was considered to be. Further aggregation led first to the formation of insoluble diffuse plaques and then dense neuritic plaques, as shown diagrammatically below. The A β in these plaques was known to exist predominantly in a β -sheet conformation.



36. The “amyloid cascade” hypothesis was first proposed by Hardy & Allsop to explain role of A β in the pathogenesis of AD in 1991, and was refined throughout the 1990s. According to this hypothesis, overproduction of or failure to clear A β led to a build up of insoluble aggregated A β plaques in the brain, which caused a cascade of downstream effects, including the build up of tau tangles in neurones, cell and synapse loss and neurotransmitter deficits (illustration from Hardy & Allsop, “Amyloid deposition as the central event in the aetiology of Alzheimer’s disease”, *TiPS*, 12, 383-388, 1991):



37. It was known in 1997 that the A β 1-42 form of A β is more fibrillogenic *in vitro* and is more commonly associated with the initiation of aggregation and formation of amyloid plaques in both AD and CAA than shorter forms of A β such as A β 1-40.
38. The terms “amyloid burden” and “amyloid load” refer to the amount of deposited A β in the brain or a particular region of the brain. In 1997 this could be measured by immunohistochemical staining and image analysis to quantify the percentage of a particular area that was covered by plaque. In addition to this, other possible measurements would be the amount of soluble A β in the brain or, following extensive solubilisation, the total amount of A β in the brain (the latter measurement would include A β that was originally present in both soluble and insoluble forms). Both soluble A β and total A β measurements would generally be performed by an enzyme-linked immunosorbant assay or ELISA.

Transgenic mouse models

39. A transgenic mouse is a genetically-engineered mouse that contains artificially-introduced genetic material. Transgenic mice were widely used in 1997 to investigate the effects of particular genes and to make mouse models of human diseases. The mouse models were used to study the disease itself, as well as to investigate potential treatments. By 1997, mutations had been identified in the gene for APP that led to an increased incidence of AD. These mutations were exploited to produce transgenic mouse models which displayed amyloid deposits containing human A β . Two models in particular were in use.
40. The PDAPP mouse expresses high levels of a mutated form of APP which predisposes PDAPP mice to develop AD-type neuropathology between 6 and 9 months of age, including extracellular A β plaques and synapse loss, although not tau tangles.
41. The Tg2576 mouse overexpresses a different APP mutation to PDAPP mice. The Tg2576 mouse develops A β plaques (with a particular increase in the concentration of A β 1-42) and exhibits impaired learning and memory in spatial reference and alternation tasks by 9 to 10 months of age, but does not exhibit synapse loss or develop tau tangles.

Approaches to the treatment of AD

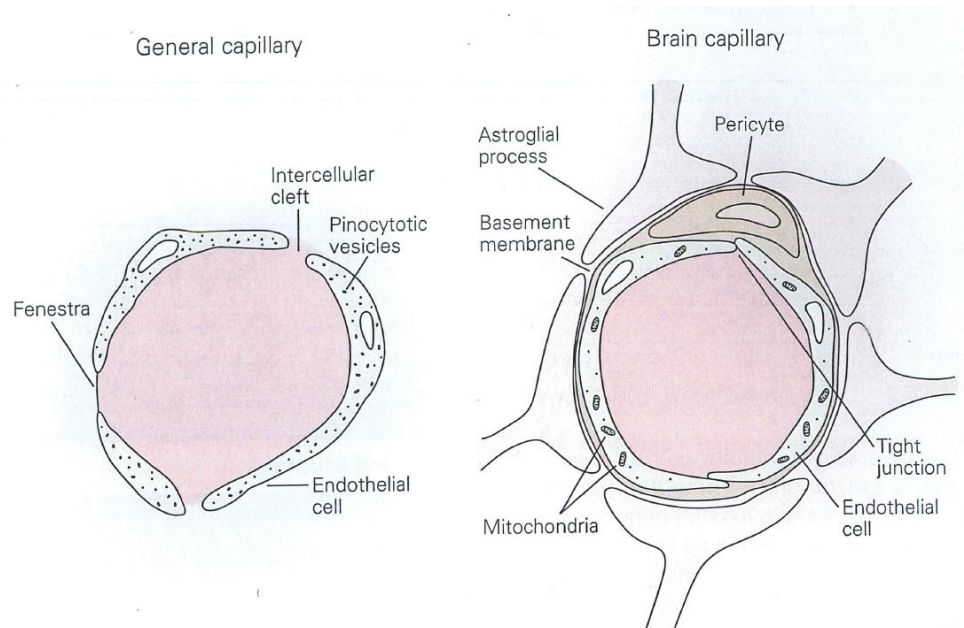
42. In 1997 a number of different approaches to the treatment and prevention of AD were being considered. These included investigating the following kinds of agents:

- i) Acetylcholinesterase inhibitors such as tacrine, donepezil, rivastigmine and galantamine act by inhibiting acetylcholinesterase (an enzyme present in the synaptic cleft which breaks down acetylcholine) and thus prolonging the availability of acetylcholine in the synaptic cleft. It was thought that this would increase cholinergic neurotransmission in the CNS.
- ii) Acetylcholine receptor agonists such as muscarinic and nicotinic agonists mimic the effect of acetylcholine by stimulating post-synaptic acetylcholine receptors.
- iii) 5-HT_{1A} antagonists block the interaction of 5-HT (5-hydroxytryptamine or serotonin) with the 5-HT_{1A} receptor, which it was thought would increase neuronal activity.
- iv) NMDA (*N*-methyl *D*-aspartic acid) receptor agonists stimulate the glutamatergic system which plays a role in a process known as long-term potentiation (an increase in transmission between two neurones, which is thought to be a neuronal correlate and prerequisite of memory).
- v) Anti-depressants, such as selective serotonin reuptake inhibitors (SSRIs), were intended to treat some of the behavioural symptoms of AD.
- vi) Anti-inflammatory treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), were thought to be of potential use in addressing inflammation in AD.
- vii) Antioxidants were intended to prevent the generation of free radicals which it was thought might cause, or at least contribute to, the pathogenesis observed in AD.
- viii) Trophic factors, such as nerve growth factor, were known to be involved in regulating neuronal survival, so it was thought that administering trophic factors to AD patients might help to reduce the neuronal loss associated with AD.
- ix) As β - and γ -secretases were known by 1997 to be involved in the synthesis of A β from APP, β - and γ -secretase inhibitors were considered to be promising targets for AD treatment.
- x) Anti-aggregation agents such as metal ion chelators were intended to reduce the levels of metal ions (particularly iron, aluminium and zinc) which were thought to have a role in aggregation of A β .

Blood-brain barrier

43. The brain is separated from the vascular system by a specialised arrangement of cells in and around capillary walls, referred to as the blood-brain barrier (“BBB”). Movement of molecules between the blood and the extracellular space of the brain is regulated by this barrier. The walls of capillaries in the brain are made of endothelial cells, which are packed together more tightly than in capillaries in other tissues of the body. These “tight” junctions mean that it is harder for molecules to pass between the

cells of the capillary wall, as shown below (image from Kandel, Schwart & Jessell, *Principles of Neural Science* (4th ed), 2000):

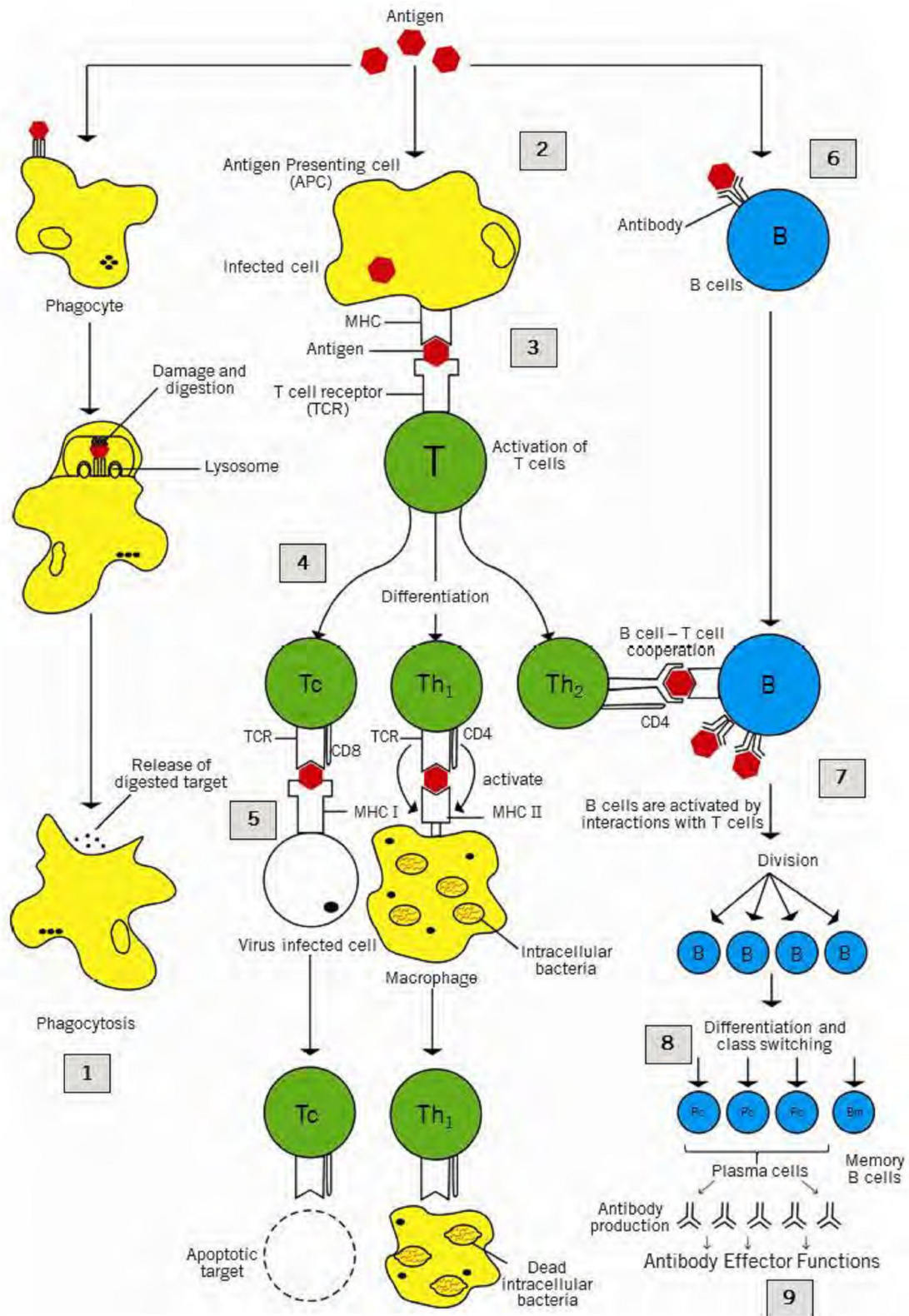


44. It was well known by 1997 that small, non-polar molecules could cross the BBB, but that large, charged or polar molecules could not in general get across, unless there were specific transport mechanisms for those molecules. This is because the tight junctions prevent the diffusion of molecules around the endothelial cells of the blood-brain barrier, so that most molecules have to pass through the endothelial cells of the blood-brain barrier instead. While small, non-polar molecules can pass through the lipid bilayer of the endothelial cell membrane, large, charged or polar molecules cannot.
45. It was also known in 1997 that the membranes of the endothelial cells of the BBB contain transport proteins which specifically and actively transport certain large, charged or polar molecules (for example charged amino acids and transferrin). In the absence of a specific transport mechanism, it was generally thought that large, polar or charged molecules could not get across the BBB unless it was damaged in some way, for example following a stroke.
46. The cut-off in terms of size, for molecules that could diffuse through the BBB in the absence of a specific transport mechanism, was thought to be a relatively low molecular weight. Antibodies were considered to be above this limit, and thus were not thought to cross the BBB (at least in therapeutically relevant quantities).

Innate and adaptive immunity

47. The body's immune system has two types of defence against pathogens (micro-organisms that can cause disease when they infect the host): (i) innate, non-adaptive mechanisms that continuously provide barriers against pathogens and (ii) adaptive responses against specific pathogens which develop during the life of an individual and become activated when needed.

48. The innate mechanisms include epithelial cell surfaces that act as physical barriers to infection, phagocytic cells and the complement system. As explained in more detail below, phagocytes internalise micro-organisms and other foreign agents in a process known as phagocytosis, thereby removing them from the body. As described below, some cells of the innate immune system also have a role in activating certain cells of the adaptive system.
49. The adaptive arm of the immune system involves the generation of effector cells that target specific pathogens and memory cells that can prevent re-infection with the same pathogens. The effector cells are known as lymphocytes. Lymphocytes are divided into B lymphocytes (“B cells”) and T lymphocytes (“T cells”). The latter are further sub-divided into helper T (T_H) and cytotoxic T (T_C) cells. The primary role of B cells is to produce antibodies. T_H cells interact with B cells, an interaction which is essential for the activation of B cells to produce highly potent antibodies (which is why these T cells are referred to as “helper” cells). T_C cells destroy host cells which have become infected with viruses or other intracellular pathogens (which is why they are referred to as “cytotoxic”, i.e. toxic to cells). “Humoral” immunity refers to the adaptive immune response mediated by B cells while “cell-mediated” immunity refers to the adaptive immune response mediated by T cells.
50. The operation of these different aspects of the immune system is shown in the following diagram from Dr Owen’s first report:



51. This diagram shows phagocytosis on the left (section 1), the operation of the T cells in the middle (sections 3-4) and the operation of the B cells on the right (sections 6-8).

Phagocytosis

52. Phagocytes include macrophages, neutrophils, monocytes and dendritic cells. Macrophages in the brain include microglia and monocytes. In phagocytosis the pathogen is surrounded by the phagocyte membrane and is then internalised in a membrane-bound vesicle called a phagosome, which becomes acidified. The phagosome then fuses with a lysosome containing proteolytic enzymes, creating a phagolysosome into which the lysosomal contents are released to destroy the pathogen.
53. T_H1 cells (as to which, see below) can activate macrophages. Activated macrophages fuse their lysosomes more efficiently to form phagosomes and also make a variety of other toxic products that assist with the destruction of pathogens, including oxygen radicals and nitric oxide (both of which have antimicrobial activity), as well as synthesising antimicrobial peptides and proteases that can be released to attack extracellular parasites.
54. Pathogens which have been coated by antibodies are referred to as being “opsonised”. As explained below, opsonised pathogens interact with macrophages through the binding of the Fc domain of antibodies to Fc receptors on the macrophage cell surface. Opsonisation also refers to a pathogen coated with complement proteins, which similarly can lead to phagocytosis.

Antigen-Presenting Cells

55. A major role of the innate immune system is to present antigens to the cells of the adaptive arm of the immune system. An antigen is any substance that can be recognised by the adaptive arm of the immune system (the word “antigen” is short for antibody generator). This substance may derive from a micro-organism, an allergen (such as grass pollen or house dust mite) or can be a component of a vaccine. (In addition, in the case of auto-immunity, the antigen can be a self protein i.e. a protein deriving from the host.)
56. Certain cells of the innate immune system, such as monocytes, macrophages and dendritic cells, are known as antigen-presenting cells or APCs. These cells can take up antigen, for example, by engulfing a micro-organism, an allergen or a vaccine component by phagocytosis, using a variety of non-specific recognition systems. Alternatively, cells that are infected by a virus can act as antigen-presenting cells. This is shown in section 2 of the diagram above.
57. Once inside the APC, the antigen is degraded, generally resulting in the formation of peptides. The peptides are then externalised and “presented” at the surface of the antigen-presenting cell. Antigen is presented on the surface of APCs within the context of a molecule known as major histocompatibility complex (MHC) class I or class II. This is shown in section 3 of the diagram.

T cells

58. The antigens on the surface of the APCs are recognised by T cells. At this point, cells of the innate immune system (the APCs) are interacting directly with cells of the adaptive immune system (the T cells).

59. The T cells bind to the APCs via specific receptors on the surface of the T cells, known as T cell receptors (“TCRs”). This is also shown in section 3 of the diagram. Each T cell expresses a particular TCR with a single specificity for antigen, but the whole population of T cells will include millions of cells with different TCRs and different antigen specificities. At the surface of the APC, MHC class I or II molecules with specific antigen peptide bound are specifically recognised by the antigen binding site on the TCR on the surface of the T cell. As a result of this interaction, the T cells are activated.
60. Once activated, the T cells undergo a process of differentiation to become activated T_H cells or activated T_C cells. This is shown in section 4 of the diagram. Typically, T_H cells recognise antigen bound to MHC class II molecules whereas T_C cells recognise antigen bound to MHC class I molecules. This is known as MHC restriction.
61. T_H and T_C cells express a variety of other molecules on their cell surface that augment the initial MHC-peptide/TCR interaction. These are called co-receptors. An important co-receptor for T_H cells is CD4 and, for T_C cells, CD8. T_H and T_C cells are thus often referred to as CD4-positive (CD4+ve) and CD8-positive (CD8+ve) T cells, respectively.
62. T_C cells bind to virally infected cells via their TCRs as shown in section 5 of the diagram, leading to death of the infected cell. T_H cells are subdivided into T_{H1} and T_{H2} cells. Upon activation, T_{H1} cells activate macrophages allowing them to phagocytose intracellular micro-organisms more efficiently (leading to cell-mediated immunity). T_{H2} cells are the most effective activators of B cells (leading to humoral immunity), although T_{H1} cells can also activate B cells.

B cells

63. Prior to the interaction between T_H cells and B cells, B cells initially express proteins, known as antibodies, on their surface membrane. Each B cell expresses a particular antibody, with a population of B cells expressing millions of different antibodies. The antibodies specifically bind to antigens, as shown in section 6 of the diagram, leading to internalisation of the antigen. Once inside the B cell, the antigen is processed and presented at the B cell surface (similar to the processing and presentation of antigen by APCs). The B cell then interacts with the activated T_H cells. This is shown in section 7 of the diagram.
64. The part of an antigen that is recognised by the immune system (specifically, by T cells, B cells and antibodies) is referred to as an epitope. Although, as part of an immune response as described above, T and B cells recognise the same antigen, they will in general recognise different parts of that antigen, referred to as T cell epitopes and B cell epitopes respectively.
65. The interaction between B cells and T_H cells is mediated by the antigen on the B cell surface and T cell receptors on the surface of activated T_H cells, such that the B cell is activated only by a T_H cell that has been activated by the same antigen that binds to the B cell. This latter process is referred to as B cell – T cell co-operation and is essential for the development of a strong immune response for the majority of antigens.

66. The interaction between the B cells and the activated T_H cells results in activation of those B cells, leading to proliferation of the B cells, as shown in section 7 of the diagram, and differentiation of the B cells into specialised cells. This leads to the production by B cells of antibodies, which bind to the original antigen.
67. As the response to antigen matures, further interactions occur between cells of the innate immune system and lymphocytes. These take place within specialist parts of lymphoid organs called germinal centres and result in the further differentiation of the B cells. The differentiation process generates antibodies with increasing affinity for the antigen, and also results in a switch of the antibody from a membrane-bound form to a secreted form which is released into the serum and tissue fluids. At the same time, the “class” of the antibody may change, in a process known as class switching (antibody classes are explained below).
68. The B cells ultimately differentiate to generate either plasma cells or memory B cells, as shown in section 8 of the diagram. Plasma cells produce large quantities of antibodies which bind with very high affinity to the original antigen. Memory B cells do not secrete antibody (although express membrane-bound antibody on their surface) but are long lived, which enables a rapid antibody response in the event of subsequent contact with the same antigen.
69. The binding of antibodies to their antigens triggers a number of downstream “effector functions” (see section 9 of the diagram). These effector functions include: (i) Fc-receptor mediated phagocytosis of the antigen; (ii) the activation of a cascade of enzymes, known as the complement pathways, which degrade the antigen or kill cells to which the antibody binds; and (iii) antibody dependent cellular cytotoxicity. These effector functions are described below.
70. The processes outlined above may also trigger the release of chemical signals, known as cytokines, by cells of the innate and adaptive immune systems. Cytokines are soluble molecules which induce cells of the immune system to proliferate or differentiate, and some of which help to generate an inflammatory response. Inflammation is the response of vascularised tissue to injury or infection. It is a process that increases the local concentration of immunomodulatory molecules and cells at the site of damage or infection, resulting from an increase in vascular permeability and increased migration of cells of the adaptive and innate immune systems from blood to inflamed tissue. The inflammatory response helps amplify the immune response and resolve the tissue damage.

The structure of antibodies

71. An antibody (or immunoglobulin (“Ig”)) is a protein secreted by B cells which binds specifically to a particular antigen. The basic structural features of antibodies are shown below using an IgG antibody by way of example (image from Lydyard, Whelan & Fanger, *Immunology*, 2001):

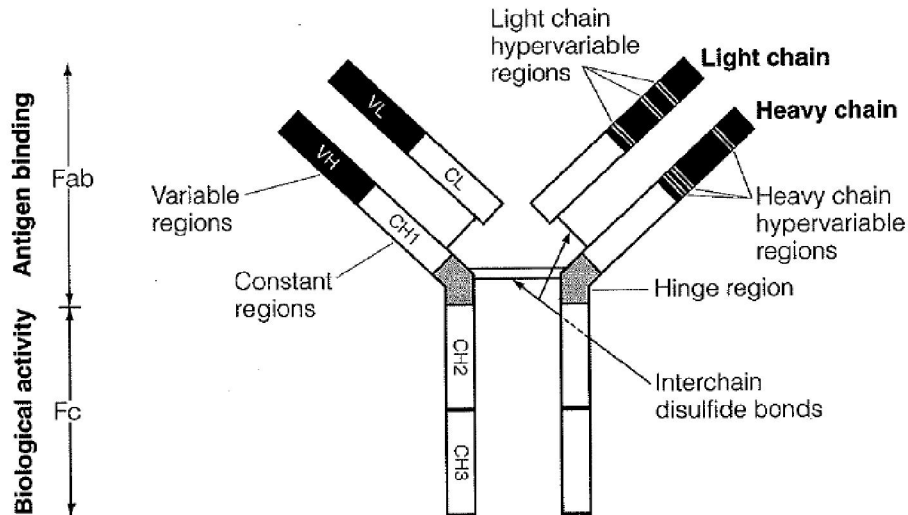


Fig. 1. IgG immunoglobulin: basic 4 chain structure representative of all immunoglobulins.

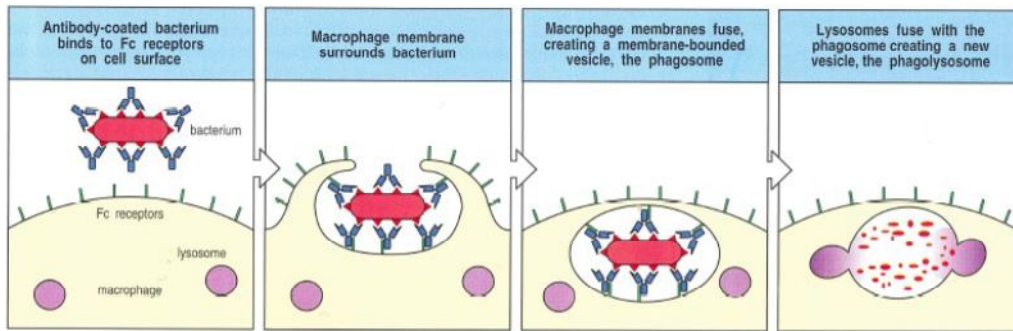
72. As shown above, antibodies have a Y-shaped structure which consists of two “heavy” and two “light” polypeptide chains linked together by disulphide bonds. Each light chain consists of one variable (“V_L”) region and one constant (“C_L”) region. Each heavy chain consists of one variable (“V_H”) region and three or four constant regions (“C_{H1} – C_{H4}”).
73. Antibodies are bifunctional molecules. The arms (N-terminal regions) of the Y are responsible for binding to antigen, whereas the stem (C-terminal region) mediates the effector functions of the antibody.
74. Each variable region has three segments of particular variability, designated the “hypervariable” regions, which form loop structures. The three hypervariable loops on each of the heavy and light chains, commonly referred to as the complementarity-determining regions (“CDRs”), determine antigen specificity by forming a binding site complementary to the epitope on the antigen. Each antigen binding site therefore has six CDRs, within each of which amino acid sequence variability may change the antibody binding site, resulting in an extremely high level of diversity in the structure and binding properties of different antibodies, even when comparing antibodies that are able to bind to the same antigen.
75. Antibody molecules can be cleaved *in vitro* into various fragments by enzymes, known as proteases, which cleave proteins at specific sites. The protease papain cleaves an antibody of the IgG class into two Fab fragments (short for “Fragment antigen-binding”) and an Fc fragment (short for “Fragment crystallisable”). A Fab fragment comprises the variable regions and the first constant region domain of a heavy and a light chain held together by a disulphide bond. The Fc fragment comprises the remaining two constant domains of the Ig heavy chain, also held together by a disulphide bond. In an intact antibody, the part of the antibody that corresponds with the Fc fragment is known as the Fc region. A different protease, pepsin, cleaves an antibody of the IgG class into an F(ab')₂ fragment and degrades the constant region into several smaller fragments. An F(ab')₂ fragment comprises both heavy and light chain variable regions together with the first constant region of the heavy and light chains, held together by multiple disulphide bonds.

Antibody classes or isotypes

76. Antibodies are divided into different classes and subclasses depending on the heavy chain. There are five distinct classes (also referred to as isotypes) of antibody called IgA, IgD, IgE, IgG and IgM, the heavy chains of which are known as α , δ , ϵ , γ and μ chains respectively. The classes or isotypes differ in a number of aspects, most importantly in size and amino acid sequence. In the blood of humans and mice, the most commonly found class of antibody is IgG, which accounts for about 75-80% of the total antibody pool. The next most prevalent is IgA, which accounts for about 10-15%.
77. The process of B cell differentiation in the germinal centres results in a change of the class of the antibody, a process referred to as class switching. The somatically hypermutated heavy chain V region switches its constant region from IgM to IgG, IgA or IgE.
78. IgG and IgA are further divided into subclasses. Human IgG is divided into four subclasses which differ only slightly in their amino acid sequences: IgG1, IgG2, IgG3 and IgG4. Human IgA is divided into IgA1 and IgA2. Mouse IgG is also divided into subclasses, namely, IgG1, IgG2a, IgG2b and IgG3. Although IgG subclasses are very similar in sequence, they have different properties.
79. The Fc region of an antibody mediates the effector functions of the antibody via binding to Fc receptors on the cells of the immune system. Different Fc receptors exist which show specificity for different classes and subclasses of antibody. The receptors that recognise IgG are known as Fc γ receptors (Fc γ Rs). In 1997, it was known that there are multiple Fc γ receptors which differ in their cell type distribution and in their affinity for IgG. One of the main differentiators between IgG subclasses in both human and mouse is the ability of the Fc regions of the different subclasses of the antibodies to bind to Fc receptors (FcRs). This in turn affects the ability of each IgG subclass to activate the various effector functions, as described below.
80. Despite the similarity in nomenclature of human and mouse IgG subclasses, the human and mouse IgG subclasses are not equivalent. Thus human IgG1 is not an equivalent of mouse IgG1, either in terms of sequence or function.

Fc receptor-mediated phagocytosis

81. In Fc receptor-mediated phagocytosis, larger complexes of antigen and antibody, for example antibody that is bound to the surface of a bacterial cell, can be removed by direct binding of antigen-bound antibodies to FcRs on phagocytic cells. The large antigen/antibody complexes are internalised into the phagocytic cells and then transported to lysosomes, where they are degraded. Degraded antigens may then become presented on the surface of the phagocytic cells (i.e. the phagocytic cells are also APCs, as described above). The presented antigen may bind to T cell receptors on the surface of T cells, thereby further stimulating an immune response, as previously described. Fc receptor-mediated phagocytosis is shown below (image from Janeway & Travers, *The Immune System in Health and Disease* (3rd ed), 1997):



82. There are four types of Fc γ receptors: Fc γ RI, Fc γ RII, Fc γ RIII-B and Fc γ RIII-A. Each receptor has a different ability to bind monomeric and aggregated IgG. Fc γ RII, Fc γ RIII-B and Fc γ RIII-A bind to aggregated IgG but not to monomeric IgG, whereas Fc γ RI binds to both monomeric and aggregated IgG. Aggregated IgG is formed where multiple antibodies bind to the same antigen, for example where the antigen forms a dimer.
83. It was known in 1997 that a single antibody bound to one or two antigens is not enough to trigger Fc receptor-mediated phagocytosis of the antigen(s) because cross-linking of Fc receptors, which requires the binding of more than one antibody to an antigen, is necessary in order to trigger the signalling cascades within the effector cell which ultimately lead to phagocytosis. Therefore, binding of monomeric IgG by Fc γ RI is not sufficient to trigger phagocytosis by the effector cell.
84. In addition to the cross-linking of Fc γ receptors being required to initiate signalling events that lead to phagocytosis, binding of multiple IgG molecules also has another important effect, referred to as the “bonus effect of multivalency”. This means that the binding of more than one IgG to an antigen is stronger than the sum of the strengths of each individual IgG to that antigen. This is illustrated below (image from Roitt, *Essential Immunology* (9th ed), 1997:

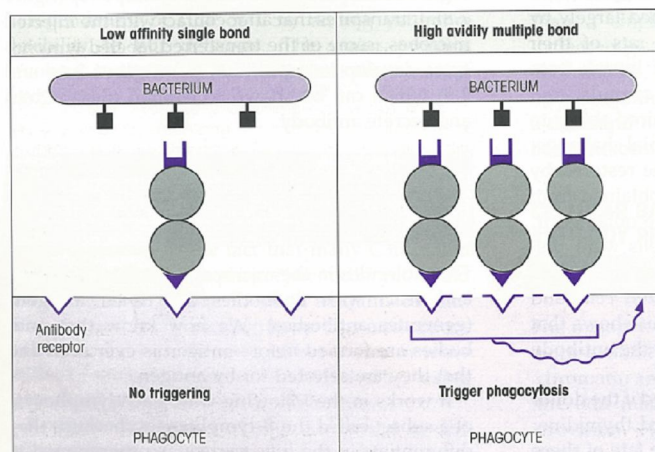


Figure 2.5. Binding of bacterium to phagocyte by multiple antibodies gives strong association forces and triggers phagocytosis by cross-linking the surface receptors for antibody.

The complement pathways

85. Phagocytosis can also be triggered by activation of the complement pathways. Complement proteins are an important part of the innate immune system (the “lectin” and “alternative” pathways) and can also be recruited by antibodies which are bound

to pathogens (the “classical” pathway). These three pathways are shown below (image from Janeway & Travers, 1997):

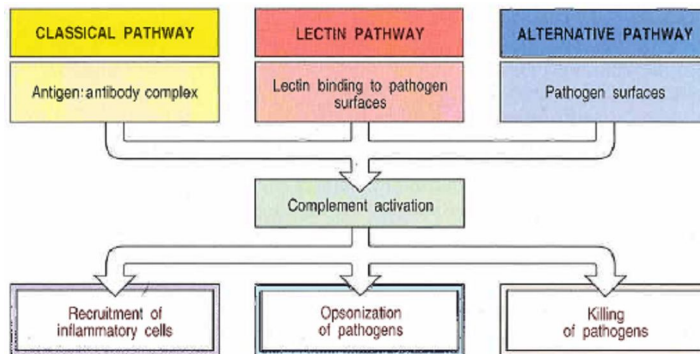


Fig. 8.31 Schematic overview of the complement cascade. There are three pathways of complement activation: the classical pathway, which is triggered by antibody; the lectin-mediated pathway, which is triggered by normal serum proteins that bind some encapsulated bacteria; and the alternative pathway, which is triggered directly on pathogen surfaces. They all generate a crucial enzymatic activity that, in turn, generates the effector activities of complement. The three main consequences of complement activation are opsonization of pathogens, the recruitment of inflammatory cells, and direct killing of pathogens.

86. The classical pathway is triggered by the Fc region of IgG antibodies binding to the C1q, a complement protein in the C1 complement protein complex, the first step in the cascade. Activation of the complement pathway via C1q results in the pathogen being coated with covalently-attached fragments of complement proteins (principally C3b) that act as opsonins to promote the uptake and removal of the pathogen by phagocytes. The complement cascade is only triggered if a C1 molecule binds (via its C1q globular heads) to at least two antibody Fc portions. The IgG molecule is monomeric and contains one C1q binding site. Accordingly, a monoclonal IgG bound to a single epitope on a monomeric antigen in solution would be extremely unlikely to be able to activate complement, because to do so would require two or more IgG:antigen complexes to be in sufficient proximity to each other so as to be bound by a single C1 molecule.

Antibody-dependent cellular cytotoxicity (ADCC)

87. ADCC is a process of cell killing via triggering apoptosis (programmed cell death) of pathogens or virus-infected host cells. It is mediated by an immune cell binding, via the Fc receptors on its surface, to the Fc region of IgG molecules bound to surface antigen. ADCC is most commonly carried out by so-called “natural killer” (NK) cells, through the FcγRIII-A receptors on their surface. These are the only class of Fcγ receptors which are expressed by NK cells and this class cannot bind to monomeric IgG.
88. Monocytes and IFNγ-activated neutrophils can also mediate ADCC, via their FcγRI and FcγRII receptors. FcγRII receptors cannot bind monomeric IgG, and although FcγRI can bind monomeric IgG, occupancy of the FcγRI receptor by one IgG is not sufficient to stimulate ADCC as cross-linking of receptors by more than one IgG molecule is required to activate immune cells.

Plasma half-life of antibodies

89. In addition to mediating antibody effector functions, the Fc region has an effect on the plasma half-life of antibodies. The plasma half-life is the time taken for half of the antibody present in the plasma to be cleared from the plasma. It is therefore a measure of the stability of the antibody in plasma. All plasma proteins are subject to various processes by which they are cleared from the plasma and degraded, for example by liver cells. Antibodies are protected to a certain extent from these degradative

pathways by a process involving the binding of the Fc region of antibodies (including IgG antibodies of all sub-classes) to an Fc receptor known as the neonatal Fc receptor (FcRn), which is expressed on the surface of many cells. Antibodies in the plasma are internalised into acidic compartments within cells which express FcRn. In the acidic environment, the antibody binds to FcRn, and the antibody/FcRn complex is recycled back to the cell surface. In the less acidic pH of the plasma, the antibody dissociates from the FcRn receptor and is released back into the plasma. In this way, antibodies are sheltered in the cell from generic protein degradation pathways in the plasma, thereby contributing to the relatively long plasma half-life of antibodies.

Monoclonal antibodies

90. In the *in vivo* antibody response to most antigens, numerous different antibodies are produced which bind to different epitopes on the antigen. Such antibodies are referred to as polyclonal antibodies.
91. Monoclonal antibodies are antibodies of a single specificity that bind to one epitope, and derive from a single B cell. Monoclonal antibodies do not in general arise directly from *in vivo* responses to antigen, but are synthesised *in vitro* (at least in part). They were first generated by injecting mice with antigen to produce a polyclonal response. B cells were then harvested from the spleens of the mice and fused with cells from a myeloma cell line. These cells are derived from a B cell cancer that is selected for its ability to grow in tissue culture, but which does not secrete its own antibody. The resulting fused cell, known as a hybridoma, is immortalised and produces only one type of antibody (i.e. the antibody produced by the B cell that was fused with the myeloma cell). The hybridoma cells can be grown in large amounts, and from these a large quantity of a single antibody can be purified. The monoclonal antibodies produced by the hybridoma method are of the species which was immunised with antigen and from which the splenic B cells were harvested, usually mouse or rat. However, other techniques can be used to produce partly human or fully human monoclonal antibodies.
92. Chimaeric antibodies are monoclonal antibodies in which the V_H and V_L regions from the original antibody (e.g. mouse or rat) are joined using recombinant DNA technology to a constant region of an antibody from another species (usually human). Since the constant region has no effect on antigen binding, the specificity of the original monoclonal antibody will be retained.
93. Humanised antibodies are antibodies in which a greater proportion of the amino acid sequence of the antibody is derived from human genes. The process of humanisation starts with a monoclonal antibody from a mouse or other non-human species (isolated using the hybridoma technology described above). DNA encoding the CDRs from the V_H and V_L regions of the monoclonal antibody is transplanted using recombinant DNA technology into the DNA encoding the corresponding positions in the remainder of a human V region framework. As the binding specificity of an antibody to antigen is largely derived from its CDRs, this process transplants the antigen-binding specificity of the mouse monoclonal antibody to the human V region, although the majority of the V region is of human origin. Amino acid changes are often introduced into the human V region framework in order to reconstitute the original binding affinity of the mouse monoclonal antibody. The humanised V region can then be cloned upstream of a fully human constant region in order to express an antibody

heavy or light chain that contains at least 95% human sequences. The humanised heavy and light chains can be co-expressed to produce large amounts of humanised monoclonal antibody.

94. It is possible also to produce fully human monoclonal antibodies. One technique for doing this which was known in 1997 was phage display. In this technology, a DNA “library” of human V_H and V_L regions is expressed on the surface of a bacteriophage (a virus which infects bacteria) and the resulting V_H - V_L regions screened for their ability to bind to the antigen of interest and V_H - V_L regions which recognise antigen are selected. The affinities of human V_H - V_L for the antigen can be increased by making small sequence changes (in a process known as mutagenesis). After several rounds of mutagenesis, high affinity fully human variable regions can be identified. These can then be attached to human constant regions to generate a fully human antibody.
95. Another technology for producing fully human monoclonal antibodies that was known in 1997 uses transgenic mice in which genes that encode human immunoglobulin heavy and light chains have been inserted. When antigen is injected into these mice, they produce a polyclonal population of fully human antibodies, rather than mouse antibodies. B cells can be harvested from the spleen of these mice and fused with myeloma cells, in order to produce a cell line which expresses human monoclonal antibodies.

Active and passive immunisation

96. The immune system can be used in the prevention and treatment of disease in one of two ways, referred to as active and passive immunisation.
97. Active immunisation, which is also referred to as vaccination, is a process in which antigen is injected into the body in a form which is likely to stimulate the immune system. Vaccination requires administration of a specific antigen of interest (which will be recognised by the adaptive immune system) usually accompanied by an adjuvant (which is a substance designed to stimulate the innate arm of the immune system to enhance antibody production). In experimental animals, a variety of adjuvants can be used, including Complete Freund’s Adjuvant or CFA. CFA, despite its name, contains an antigen, namely inactivated tuberculosis bacteria. CFA cannot be used in humans because it is toxic. Incomplete Freund’s Adjuvant or IFA, which can be used in humans, does not contain the bacterial component and is just a water-in-oil emulsion.
98. In practice, to achieve a good immune response, it is necessary to have an initial prime of the immune system followed by boosts with antigen and adjuvant in order to generate a high titer of serum antibodies. An antibody titer is a measurement of the amount of antibody that recognises a particular epitope, expressed as the greatest dilution that still gives a positive result in the assay used. The time course can be monitored by the removal of serum samples.
99. Passive immunisation refers to the direct administration of antibodies into either experimental animals or humans (rather than the administration of antigen).

100. A major advantage of active immunisation over passive immunisation is the duration of immunity generated by the procedure. There are many vaccines for which boosting as infrequently as every ten years is sufficient (e.g. tetanus). This is important for patient compliance and cost. In contrast, the effects of passive immunisation typically only last for the length of time that the drug is maintained in the body. For antibodies of the human IgG1 isotype, the plasma half-life is about 21 days, although this can vary depending on antibody clearance mechanisms. Therefore it is likely that monthly, or even weekly, injections of antibodies would be required in a chronic disease. Antibodies are also very expensive compared with the materials used for active vaccinations.
101. On the other hand, a potential advantage of passive immunisation over active immunisation is that, if toxicity issues in the patient are observed, the duration of toxicity is likely to be short since the antibody is cleared from the body relatively quickly. Another advantage of passive immunisation is that it can be used in populations that have reduced active immune responses, for example the elderly or infants under two years old.
102. Whereas active immunisation results in a polyclonal antibody response, passive immunisation can utilise polyclonal or monoclonal antibodies. Polyclonal antisera have been used successfully to treat infectious disease particularly where toxins or viruses are already circulating in the body, for example, in tetanus, diphtheria, rabies or hepatitis B. In this last example, serum is taken from patients who have had a hepatitis B infection and a fraction enriched for serum IgG (referred to as a gamma globulin fraction) is prepared. This fraction is then injected into humans who have not had a previous hepatitis B infection, but are travelling to countries where hepatitis B is endemic. This passive vaccination will be efficacious for about a month, during which time the injected antibody will be cleared from the system.
103. Passive immunisation using a monoclonal antibody is no different in principle except that a monoclonal preparation is used. The advantage of passive immunisation using a monoclonal antibody over a polyclonal serum from pre-immunised individuals is that the precise composition of the drug is reproducible (serum from different individuals will always be different) and in principle safer (there is no potential issue, for example, of infection with viruses also carried in the serum).
104. Although a non-human antibody such as a mouse monoclonal antibody could be used for a single administration, non-human antibodies are unsuitable for chronic human therapeutic use, because after injection the protein will be recognised as foreign in humans. This causes the patient to produce their own antibodies to the therapeutic antibody, which may lead to elimination of the therapeutic antibody, as well as various side effects.
105. A key advance in the application of monoclonal antibody technology to therapeutic use in humans was the advent of technology to prepare chimaeric, humanised and fully human antibodies, as described above. These types of antibodies, in particular humanised and fully human antibodies, have enabled the use of passive administration with much less immune response to the administered antibody. By December 1997, there were a number of monoclonal antibodies on the market for use in immunotherapy, including abicximab (for the prevention of blood clots) and rituximab (for the treatment of B cell lymphomas).

The Patent

106. The Patent is of some length and complexity, the specification running to 26,355 words, 177 paragraphs and 54 pages. I shall summarise the disclosure as briefly as I can, using the headings in the specification.

Background

107. The specification begins with a brief description of AD which it says in [0002] is:

“... characterized by two types of lesions in the brain, senile plaques and neurofibrillary tangles. Senile plaques are areas of disorganized neuropil up to 150 μ m across with extracellular amyloid deposits at the center visible by microscopic analysis of sections of brain tissue. Neurofibrillary tangles are intracellular deposits of tau protein consisting of two filaments twisted about each other in pairs.”

108. The specification then points out at [0003] that:

“The principal constituent of the plaques is a peptide termed A β or β -amyloid peptide. A β peptide is an internal fragment of 39-43 amino acids of a precursor protein termed amyloid precursor protein (APP). Several mutations within the APP protein have been correlated with the presence of Alzheimer’s disease. ... Such mutations are thought to cause Alzheimer’s disease by increased or altered processing of APP to A β , particularly processing of APP to increased amounts of the long form of A β (i.e. A β 1-42 and A β 1-43). Mutations in other genes ... are thought indirectly to affect processing of APP to generate increased amounts of long form A β ... These observations indicate that A β , and particularly its long form, is a causative element in Alzheimer’s disease.”

109. After acknowledgement of some prior art, it is said at [0006] that:

“By contrast, the present disclosure is directed to treatment of Alzheimer’s and other amyloidogenic diseases by administration of an antibody to A β to a patient under conditions that generate a beneficial immune response in the patient. The invention thus fulfils a longstanding need for therapeutic regimes for preventing or ameliorating the neuropathology of Alzheimer’s disease.”

Summary of the claimed invention

110. This section of the specification states:

“[0007] In one aspect, the invention provides a pharmaceutical composition comprising an antibody to A β and a pharmaceutically acceptable non-toxic carrier or diluent, for

use in methods of preventing or treating a disease characterized by amyloid deposition in a patient, wherein the isotype of the antibody is human IgG2 [*sic* – it is common ground that this is a typographical error and should read ‘IgG1’]. Such methods entail inducing an immune response against a peptide component of an amyloid deposit in the patient by administration of an antibody that has the human IgG1 isotype. In some patients, the amyloid deposit is aggregated A β peptide and the disease Alzheimer’s disease. In some methods, the patient is asymptomatic. In some methods, the patient is under 50 years of age. In some methods, the patient has inherited risk factors indicating susceptibility to Alzheimer’s disease. Such risk factors include variant alleles in presenilin gene PS1 or PS2 and variant forms of APP. In other methods, the patient has no known risk factors for Alzheimer’s disease.

[0008] In some methods, the immune response is directed to aggregated A β peptide without being directed to dissociated A β peptide. For example, the antibodies bind to aggregated A β peptide without binding to dissociated A β peptide. The immune response is induced by administering an antibody to A β to the patient.

[0009] The antibody is typically administered orally, intranasally, intradermally, subcutaneously, intramuscularly, topically or intravenously. In some methods, the patient is monitored followed administration to assess the immune response. In some methods, the patient is monitored following administration to assess the immune response. If the monitoring indicates a reduction of the immune response over time, the patient can be given one or more further doses of the antibody.”

Definitions

111. The specification sets out a series of definitions at [0013]-[0028]. For present purposes, the important definitions are as follows:

“[0019] The term ‘antibody’ is used to include intact antibodies. Optionally antibodies can be chemically conjugated to, or expressed as, fusion proteins with other proteins.

...

[0022] The term ‘immunological’ or ‘immune’ response is the development of a beneficial humoral (antibody mediated) and/or a cellular (mediated by antigen-specific T cells or their secretion products) response directed against an amyloid peptide in a recipient patient. Such a response can be an active response induced by administration of immunogen or a passive response induced by administration of antibody or primed T-

cells. A cellular immune response is elicited by the presentation of polypeptide epitopes in association with Class I or Class II MHC molecules to activate antigen-specific CD4+ T helper cells and/or CD8+ cytotoxic T cells. The response may also involve activation of monocytes, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils or other components of innate immunity. The presence of a cell-mediated immunological response can be determined by proliferation assays (CD4+ T cells) or CTL (cytotoxic T lymphocyte) assays The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating IgG and T-cells from an immunized syngeneic animal and measuring protective or thereapeutic effect in a second subject.

[0026] The term ‘patient’ includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

[0027] Disaggregated or monomeric A β means soluble, monomeric peptide units of A β . One method to prepare monomeric A β is to dissolve lyophilized peptide in neat DMSO with sonication. The resulting solution is centrifuged to remove any nonsoluble particulates. Aggregated A β is a mixture of oligomers in which the monomeric units are held together by noncovalent bonds.”

Detailed description

112. This part of the specification is divided into five sections.

113. *I General.* This section begins by stating in [0029]:

“The invention provides pharmaceutical compositions for use in methods for prophylactic or therapeutic treatment of diseases characterized by accumulation of amyloid deposits. Amyloid deposits comprise a peptide aggregated to an insoluble mass.”

114. *II Therapeutic Agents.* This section begins by saying at [0030] that:

“Therapeutic agents for use in the present invention induce an immune response against A β peptide. These agents are human IgG1 antibodies reactive with A β peptide. Induction of an immune response is passive, as an antibody is administered that itself binds to A β in patient.”

115. It goes on:

“[0032] A β has the unusual property that it can fix and activate both classical and alternate complement cascades. In particular, it binds to Clq and ultimately to C3bi. This association facilitates

binding to macrophages leading to activation of B cells. In addition, C3bi breaks down further and then binds to CR2 on B cells in a T cell dependent manner leading to a 10,000 increase in activation of these cells. This mechanism causes A β to generate an immune response in excess of that of other antigens.

[0033] The antibody of the invention can bind to any of the naturally occurring forms of A β peptide, and particularly the human forms (i.e. A β 39, A β 40, A β 42 or A β 43)....”

116. The specification states in [0035] that “A β peptides can be synthesised by solid phase peptide synthesis or recombinant expression, or can be obtained from natural sources”.

117. At [0036] it states:

“Therapeutic agents of the invention include human IgG1 antibodies that specifically bind to A β . Such antibodies can be monoclonal or polyclonal. Some such antibodies bind specifically to the aggregated form of A β without binding to the dissociated form. Some bind specifically to the dissociated form without binding to the aggregated form. Some bind to both aggregated and dissociated forms. The production of non-human monoclonal antibodies, e.g., murine or rat, can be accomplished by, for example, immunizing the animal with A β Such an immunogen can be obtained from a natural source, by peptides synthesis or by recombinant expression.”

118. *III Patients Amenable to Treatment.* This section of the specification describes the patients who are amenable to treatment, emphasising that “the present methods” can be administered prophylactically and are especially useful for individuals with a known genetic risk of AD.

119. *IV Treatment Regimes.* This section describes possible treatment regimes in broad terms. The specification explains at [0044] that “Effective doses of the compositions of the present invention, for the treatment of the above described conditions vary depending upon many different factors ...”.

120. The specification goes on:

“[0045] Agents for inducing an immune response can be administered by parenteral, topical, intravenous, oral, sub-cutaneous, intraperitoneal, intranasal or intramuscular means for prophylactic and/or therapeutic treatment. The most typical route of administration is subcutaneous although others can be equally effective. The next most common is intramuscular injection. This type of injection is most typically performed in the arm or leg muscles. Intravenous injections as well as intraperitoneal injections, intraarterial, intracranial, or intradermal injections are also effective in generating an

immune response. In some methods, agents are injected directly into a particular tissue where deposits have accumulated.

[0046] Agents of the invention can optionally be administered in combination with other agents that are at least partly effective in treatment of amyloidogenic disease. In the case of Alzheimer's and Down's syndrome, in which amyloid deposits occur in the brain, agents of the invention can also be administered in conjunction with other agents that increase passage of the agents of the invention across the blood-brain barrier."

121. *V Diagnosis.* This section outlines methods for detecting the level of the immune response against A β in a patient suffering from or susceptible to AD.

Examples

122. Examples I to IV and VII to XI are directed to active immunisation. Only Examples V and VI are directed to passive immunisation. Examples V, VI and XI are "armchair" or "prophetic" examples with no data. Example XII is actually a general materials and methods section.
123. *I Prophylactic Efficacy of A β Against AD.* This example describes the administration of A β 42 (i.e. A β 1-42) to young PDAPP transgenic mice to test whether active immunisation has a prophylactic effect. The specification explains that these mice have a disposition to develop Alzheimer's-like neuropathology and begin to deposit A β at six months onwards. By 15 months, they exhibit levels of A β deposition equivalent to that seen in AD. The specification states in [0061] that aggregated A β 42 was chosen "because of its ability to induce antibodies to multiple epitopes of A β ".
124. Nine PDAPP mice were injected with 100 μ g of aggregated A β 42 (referred to in places as "AN1792") in phosphate buffered saline ("PBS") together with CFA followed by a boost of the same amount of immunogen with IFA after two weeks. Two additional doses with IFA were given at monthly intervals. Five mice were injected with PBS/adjuvant or PBS, five mice were injected with serum amyloid protein ("SAP") and ten mice were not injected with anything. The titers of the mice to aggregated A β 42 were monitored every other month from the fourth boost until the mice were one year old. The mice were sacrificed at 13 months.
125. Eight of the nine mice injected with AN1792 developed a high antibody titer, whereas the SAP- and PBS-treated mice did not (see [0067]-[0068], Table 1 and Figure 1). Seven of the nine mice injected with AN1792 had no detectable amyloid in their brains, one had a greatly reduced amyloid burden and one had an isolated plaque. By contrast, brain tissue from the SAP and PBS groups contained numerous 3D6-positive (3D6 being a monoclonal antibody specific to A β) amyloid deposits, the pattern of deposition being similar to that of the untreated controls. These results were confirmed by quantitative imaging analysis (see [0069]-[0070] and Figure 2). With one exception, the AN1792-treated brains were also devoid of neuritic plaques, whereas the brains from the remaining groups had numerous plaques (see [0071] and Figure 3). Astrocytosis was also absent in the brains of the AN1792-treated group,

unlike the other groups (see [0072]-[0073] and Figure 4). Evidence from a subset of the AN1792-treated mice indicated that plaque-associated MHC II immunoreactivity was absent. In addition, plaque-associated MAC-1 labelling was lower in the AN1792-treated mice compared to the PBS group. Both findings are said to be consistent with a lack of an A β -related inflammatory response (see [0074]-[0075]).

126. The conclusion drawn at [0076] is as follows:

“The lack of A β plaques and reactive neuronal and gliotic brains of the A β 1-42 injected mice indicate that no or extremely little amyloid was deposited in their brains, and pathological consequences, such as gliosis and neuritic pathology, were absent. PDAPP mice treated with A β 1-42 show essentially the same lack of pathology as control nontransgenic mice. Therefore, A β 1-42 injections are highly effective in the prevention of deposition or clearance of human A β from brain tissue, and elimination of subsequent neuronal and inflammatory degenerative changes. Thus, administration of A β peptide has therapeutic benefit in prevention of AD.”

127. *II Dose Response Study.* This example is a dose-response study performed in Swiss-Webster (i.e. non-transgenic) mice investigating the antibody titers of the mice following immunisation with diminishing doses of A β peptide and CFA/IFA. The antibody response is being used as a means of assessing the level of immune response induced by active immunisation.
128. *III Screen for Therapeutic Efficacy Against Established AD.* This example describes the administration of A β 42 to older PDAPP mice which have already developed amyloid plaques. 24 PDAPP mice aged 11 to 11.5 months were immunised with AN1792 and CFA/IFA and 24 with PBS. The first three doses were administered at two-week intervals followed by injections at four-weekly intervals. Approximately half were euthanised at 15 months of age and the remainder at 18 months. Eight animals died during the study. Ten 12 month-old, ten 15-month old and ten 18-month old untreated mice were included in the ELISAs and the one-year old animals were also included in the immunohistochemical analyses.
129. Quantitative image analysis showed that AN1792-treated mice had a significantly reduced cortical amyloid burden at 15 months and a greatly reduced cortical amyloid burden at 18 months compared to the PBS-treated mice (see [0088]-[0090] and Figure 7).
130. In several AN1792-treated mice, a population of A β -positive cells was found in brain regions that typically contain amyloid deposits. They were immunoreactive with antibodies recognising ligands expressed by activated monocytes and microglia (MHC class II and a protein called CD11b). Detailed examination of the AN1792-treated brains revealed that the MHC II-positive cells were restricted to the vicinity of the limited amyloid remaining in these animals. The cells did not stain for markers of T cells (proteins known as CD3 and CD3e) or B cells (CD45RA and CD45RB), but did stain for a marker of monocytes (CD43). No such cells were found in the PBS-treated mice ([0091]). MHC II-positive cells were also observed in the vicinity of extracellular amyloid in AN1792-treated animals ([0093]). Quantitative image

analysis of MAC 1-labelled sections showed increased reactivity in the hippocampus of AN1792-treated mice ([0094]). The conclusion is drawn at [0095] that these results “are indicative of active, cell-mediated removal of amyloid in plaque-bearing brain regions”.

131. Two ELISA analyses of A β levels in the cortex, hippocampus and cerebellum in AN1792-treated, PBS-treated and untreated mice were carried out. One analysis was for total A β using the monoclonal antibody 266 (a central region antibody specific for A β 13-28) and biotinylated 3D6 (an N-terminal antibody specific for A β 1-5). The other was for A β 1-42 using monoclonal antibody 21F12 (a C-terminal antibody specific to A β 33-42). Compared to PBS-treated mice, the cortices of AN1792-treated mice showed a reduction in total A β at 15 months and statistical significant reduction at 18 months. Significant reductions in A β 1-42 were also observed at both 15 and 18 months. Similar, if less impressive, results were obtained for hippocampal levels. A significant reduction in total A β in the cerebellum was also found at 18 months ([0096]-[0098] and Tables 2-4).
132. No significant reduction was found in APP levels in the AN1792-treated mice ([0099]).
133. Neuritic plaque burden was significantly reduced in the frontal cortex of AN1792-treated mice compared to the PBS group at both 15 and 18 months ([0100] and Figure 8). Astrocytosis was also significantly reduced ([0101] and Figure 9).
134. Antibodies to A β were again found in the sera of the AN1792-treated mice, but not in the controls ([0102]-[0103]). At [0104] the specification states:

“To determine if the A β -specific antibodies elicited by immunization that were detected in the sera of AN1792- treated mice were also associated with deposited brain amyloid, a subset of sections from the AN1792- and PBS-treated mice were reacted with an antibody specific for mouse IgG. In contrast to the PBS group, A β plaques in AN1792-treated brains were coated with endogenous IgG. This difference between the two groups was seen in both 15-and 18-month groups. Particularly striking was the lack of labeling in the PBS group, despite the presence of a heavy amyloid burden in these mice. These results show that immunization with a synthetic A β protein generates antibodies that recognize and bind in vivo to the A β in amyloid plaques.”
135. A splenocyte proliferation assay was carried out showing that a cellular response to A β had been induced in the AN1792-treated animals, but not in the controls ([0105]).
136. The conclusion drawn at [0106] is as follows:

“The results of this study show that AN1792 immunization of PDAPP mice possessing existing amyloid deposits slows and prevents progressive amyloid deposition and retard consequential neuropathological changes in the aged PDAPP mouse brain. Immunizations with AN1792 essentially halted

amyloid developing in structures that would normally succumb to amyloidosis. Thus, administration of A β peptide has therapeutic benefit in the treatment of AD.”

137. *IV Screen of A β Fragments.* This example tests the ability of fragments of A β to produce similar effects to those shown for the full length aggregated A β 42, which is used as a positive control ([0107]-[0128] and Figures 11-13). Prof Wisniewski exhibited to his first report a convenient tabular summary of the results which I reproduce below:

A β fragment - [0107]	1-5*	1-12*	13-28*	32-42*	APP (pBx6)	aggr 1-40 (AN1528)	aggr 22-35	aggr 1-42 (AN1792)	aggr 1-42 [†]
Reduce cortical Aβ burden (total Aβ) - [0116] and Fig 11 and [0122]	✓ (-61%)	x	x	x	x	x	x	✓ (-75%)	✓ (-79%)
Reduce brain Aβ burden (plaque only) - [0121] and Fig 12 and [0122]	✓ (-67%)	x	x	nt	nt	✓ (-95%)	nt	✓ (-97%)	nt
Binding Aβ plaque - [0123]	✓	✓	✓	nt	nt	✓	nt	✓	nt
Antibody titer achieved - [0124] and Fig 13	lower	high	lower	lower	lower	high	lower	high	high
T cell response - [0125] – [0127]	x	x	x	x	x	✓	x	✓	✓

* conjugate + sheep IgG / [†] rodent (others are human) / nt = not tested

138. In the context of discussing the histochemical analyses, the specification states:

“[0122] The results obtained by quantitation of total A β or A β 1-42 by ELISA and amyloid burden by image analysis differ to some extent. Treatment with AN1528 had a significant impact on the level of cortical amyloid burden when measured by quantitative image analysis but not on the concentration of total A β in the same region when measured by ELISA. The difference between the two results is likely to be due to the specificities of the assays. Image analysis measures only insoluble A β aggregated into plaques. In contrast, the ELISA measured all forms of A β , both soluble and insoluble, monomeric and aggregated. Since the disease pathology is thought to be associated with the insoluble plaque-associated forms of A β , the image analysis technique may have more sensitivity to reveal treatment effects. However since the ELISA is a more rapid and easier assay, it is very useful for screening purposes. Moreover it may reveal that the treatment-associated reduction of A β is greater for plaque-associated than total A β .

[0123] To determine if the A β -specific antibodies elicited by immunization in the treated animals reacted with deposited brain amyloid, a subset of the sections from the treated animals and the control mice were reacted with an antibody specific for mouse IgG. In contrast to the PBS group, A β -containing plaques were coated with endogenous IgG for animals immunized with the A β peptide conjugates A β 1-5, A β 1-12, and A β 13-28; and the full length A β aggregates AN1792 and AN1528. Brains from animals immunized with the other A β peptides or the APP peptide pBx6 were not analyzed by this assay.”

139. The specification goes on at [0127]:

“These results show that AN1792 and AN1528 stimulate strong T cell responses ... The absence of an A β specific T cell response in animals immunized with A β 1-5 is not surprising ... Since the A β 1-5 conjugate was effective at significantly reducing the level of A β in the brain, in the apparent absence of A β -specific T cells, the key effector immune response induced by immunization with this peptide appears to be antibody.”

140. *V Preparation of Polyclonal Antibodies for Passive Protection.* This example describes raising polyclonal antibodies in mice by immunising non-transgenic mice with A β peptide or another immunogen, optionally plus adjuvant, collecting their blood and extracting antibodies using affinity chromatography.

141. *VI Passive Immunization with Antibodies to A β .* This example describes a protocol for carrying out an experiment where groups of ten 7-9 month old PDAPP mice are injected intraperitoneally with either polyclonal anti-A β or a specific monoclonal anti-A β antibody in PBS over a four month period. Antibody titers are monitored according to the methods used in the Patent and mice are euthanised at the end of four months so that histochemistry, A β peptide levels and toxicology experiments can be performed post mortem.

142. Table 6 lists four monoclonal antibodies which are identified by number (2H3, 10D5, 266 and 21F12) and one polyclonal antibody preparation (mouse polyclonal anti-human A β 42) together with their respective epitopes:

Antibody	Epitope
2H3	A β 1-12
10D5	A β 1-12
266	A β 13-28
21F12	A β 33-42
Mouse polyclonal anti-human A β 42	Anti-Aggregated A β 42

143. The epitopes cover the full extent of the A β peptide, including 1-12 (N terminus), 13-28 (central domain), 33-42 (C terminus) and any epitope to which a polyclonal might be raised against A β 1-42. None of the antibodies is said to have been deposited, no sequence information is given for them and no reference or publication is given. It is common ground that none of them were commercially available in December 1997.

144. *VII Comparison of Different Adjuvants.* This example compares the capacity of four different types of adjuvant (CFA, alum, squalene and monophosphoryl lipid A or MPL) to stimulate an immune response to AN1792 in guinea pigs. The comparison between the adjuvants is not important for present purposes, but the example includes measurements of the level of A β in the brains of 14 week old guinea pigs after immunisation with CFA, MPL and alum plus AN1792 and with PBS. The specification concludes at [0144]:
- “The levels of A β protein in the hippocampus, the cortex and the cerebellum were very similar for all four groups despite the wide range of antibody responses to A β elicited by these vaccines. ... Thus, the presence of a high circulating antibody titer to A β for almost three months in some of these animals did not alter the total A β levels in their brains. The levels of A β in the CSF were also quite similar between the groups. The lack of large effect of AN1792 immunization on endogenous A β indicates that the immune response is focused on pathological formations of A β .”
145. *VIII Immune Responses to Different Adjuvants in Mice.* This example compares the capacity of four different types of adjuvant (MPL, squalene, alum and QS21), and combinations thereof, to stimulate an immune response to AN1792 in mice. QS21 is a mixture of saponins (triperpenoids) extracted from the bark of the *Quillaja saponaria* tree. Again, the comparison is not important for present purposes.
146. *IX Therapeutic Efficacy of Different Adjuvants.* This example compares the therapeutic efficacy of AN1792 and AN1528 with four different types of adjuvants (alum, MPL, QS21 and QS21) in PDAPP mice. The only combination said to give rise to a statistically significant reduction in cortical amyloid burden in 12 month old mice was AN1792 with CFA/IFA (see [0156] and Figure 15).
147. *X Toxicity Analysis.* This example describes toxicity analyses carried out to investigate further the safety of the treatments used in Examples II, III and VII.
148. *XI Prevention and Treatment of Subjects.* This example describes the design of a Phase 1 trial to determine safety and two Phase 2 trials. The first Phase 2 trial is to be performed “to determine therapeutic efficacy”. Patients are selected who have early to mid AD based on their score in the MMSE, who are likely to survive the duration of the study and who lack complications such as interfering medications. Patients are assessed using psychometric measures such as MMSE and ADAS. Disease progression may also be monitored by MRI, and blood assays can be performed e.g. of immunogen-specific antibodies. Patients are randomly assigned to groups treated with a therapeutic agent or with placebo and are monitored at least every six months. The specification states at [0160] that “Efficacy is determined by a significant reduction in progression of a treatment group relative to a placebo group”.
149. The second Phase 2 trial is to be performed “to evaluate conversion of patients from non-Alzheimer’s Disease early memory loss, sometimes referred to as age-associated memory impairment (AAMI), to probable Alzheimer’s disease as defined by ADRDA criteria”. Patients are randomly assigned and their scores on suitable metrics including ADAS and MMSE are followed at intervals of about six months. The specification

states at [0161] that “the endpoint for each patient is whether or not he or she converts to probable Alzheimer’s Disease as defined by ADRDA criteria at the end of the observation”.

The claims

150. The only claims which featured in argument are claims 1 and 4-6. These are as follows:

- “1. A pharmaceutical composition comprising an antibody to A β and a pharmaceutically acceptable non-toxic carrier or diluent, for use in preventing or treating a disease characterised by amyloid deposit in a patient, wherein the isotype of the antibody is human IgG1.
4. The pharmaceutical composition for use in preventing or treating a disease characterised by amyloid deposit in a patient of any preceding claim wherein the antibody binds specifically to the aggregated form of A β peptide without binding to the dissociated form.
5. The pharmaceutical composition for use in preventing or treating a disease characterised by amyloid deposit in a patient of any of claims 1-3 where the antibody binds specifically to the dissociated form of A β peptide without binding to the aggregated form.
6. The pharmaceutical composition for use in preventing or treating a disease characterised by amyloid deposit in a patient of any of claims 1-3 where the antibody binds specifically to both aggregated and dissociated forms of A β peptide.”

The skilled team

151. A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and he (or she) reads it knowing that its purpose is to describe and demarcate an invention. He is unimaginative and has no inventive capacity. In some cases, such as the present one, the patent may be addressed to a team of persons having different skills.

152. There is a minor dispute as to the skilled team to whom the Patent is addressed. It is common ground that the Patent is addressed to a skilled team consisting of a neuroscientist, an immunologist and a clinician with a research interest in the prevention and treatment of amyloidosis, particularly AD. These skills could be combined in one or two people, however. Thus Prof Wisniewski combined most of the necessary expertise, although a specialist immunologist would be required for tasks such as humanisation. As noted above, however, neither Prof Francis nor Dr Owen had clinical expertise.

153. Lilly contends that the research clinician would be a full member of the team, whereas JAI contends that he would be a subsidiary member whose principal contribution would be when the candidate molecule was taken into clinical development. I do not think it matters who is right about this, but I agree with Lilly. Clinical researchers were prominent in the field in 1997, and many of the neuroscientists had clinical backgrounds. Furthermore, I consider that the Patent assumes that the skilled team has clinical expertise.

Common general knowledge

154. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[115]. That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6].
155. There is little, if any, dispute that everything I have set out in the technical background section of this judgment formed part of the skilled team's common general knowledge. There were four main areas of dispute with regard to common general knowledge.

Terminology with regard to A β

156. Prof Wisniewski's evidence in chief was that the term "soluble A β ", abbreviated to "sA β ", was used to refer to monomeric A β , whereas the term "A β " was used to refer to plaque unless it was made clear that another meaning was intended. In cross-examination, however, he agreed that people in the field were not as precise as they should be with their terminology and it was necessary to get the precise meaning from the context. Similarly, he thought that the term "aggregated A β " typically referred to multimeric A β in plaques, but accepted that the meaning depended on the context.

Methods for assisting the passage of antibodies across the BBB

157. Lilly, supported by Prof Wisniewski, contends that there were at least three common general knowledge methods of assisting the passage of therapeutic agents across the BBB, namely (a) osmotic opening of the BBB by mannitol infusion, (b) chemical modification of the agent, in particular cationisation and (c) coupling the agent to a carrier molecule. JAI, supported by Prof Francis and Dr Owen, disputed this. Counsel for Lilly put it to Prof Francis and Dr Owen that these methods were more likely to be known to the clinician than the neuroscientist or the immunologist, which they accepted. In addition, Dr Owen agreed with Prof Wisniewski that the clinician would be aware that the BBB was compromised in a number of conditions. Dr Owen also accepted that the Patent appeared to presume at [0046] that its readers knew about the use of agents that could increase the passage of antibodies across the BBB. Accordingly, counsel for Lilly submitted that Prof Wisniewski's evidence was to be preferred on this point. Counsel for JAI riposted that, even if the matter rested on Prof Wisniewski's evidence, that did not establish that any of three methods was common general knowledge.
158. The strongest case relates to osmotic opening. This is very briefly described in Appendix C of Kandel, Schwartz & Jessell, *Principles of Neural Science* (3rd ed), 1991, a standard textbook. The method described appears to relate to patients with

brain tumors. In any event, as Prof Wisniewski accepted, the passage makes it clear that the procedure is not always therapeutically effective and can have adverse effects. Prof Wisniewski also relied on three papers on the subject, but these do not advance Lilly's case much further. In relation to cationisation, Prof Wisniewski relied on a single paper, but accepted that this described a theoretical possibility. In relation to coupling, he was unable to identify the paper he had relied on.

159. The conclusion I draw from the evidence is that the clinical member of the team would have been aware from his common general knowledge that there were one or two methods (particularly osmotic opening) that could be tried in order to assist the passage of antibodies across the BBB, but he would not have regarded such methods as proven in that context, let alone routine. In my judgment this is consistent with the passage in the Patent relied on by Lilly.

Effect of CFA on the BBB

160. Lilly, supported by Prof Wisniewski, contends that it was common general knowledge that CFA would compromise the BBB and thereby facilitate the passage of antibodies across the BBB. In support of this Prof Wisniewski relied on two papers, one of which he mentioned for the first time in cross-examination. Dr Owen's evidence was that neither paper was common general knowledge. Prof Francis undertook a search which showed that the first paper had been cited 28 times by December 1997 and the second just twice. On the other hand, both Prof Francis and Dr Owen accepted that the effect of CFA on the BBB was more likely to be known to the clinician. Nevertheless, I am not satisfied that this formed part of the common general knowledge even of the clinician.

A β as a target for AD research

161. It is common ground that A β was a major target for research into the prevention and treatment of AD in 1997, but there was some dispute as to the extent to which monomeric A β was a target. Prof Wisniewski identified four strategies that were being pursued: (i) suppressing APP production, (ii) preventing the production of soluble A β , (iii) preventing or reversing A β aggregation and (iv) blocking neurotoxicity caused by aggregated A β . He agreed that three of these did not exclude targeting monomeric A β . Furthermore, a review published by Prof Wisniewski in 1997 contemplated monomeric A β as target. This is not surprising given that monomeric A β was known to be the precursor to amyloid deposits. Accordingly, the skilled team would not have discounted the possibility of targeting monomeric A β in order to prevent it aggregating into plaques. Nevertheless, it seems clear that the main focus of attention was on multimeric A β , and in particular aggregated A β in plaques.

Matters that were not common general knowledge

162. It is convenient before proceeding further to identify and explain two matters that were not common general knowledge at the priority date of the Patent, and indeed were published subsequently.

The Schenk Paper

163. Schenk *et al.*, “Immunization with amyloid- β attenuates Alzheimer-disease-like pathology in the PDAPP mouse”, *Nature*, 400, 173-177 was published by a team of authors from Elan Pharmaceuticals on 8 July 1999 (“the Schenk Paper”). It showed that immunisation of young PDAPP mice with A β 1-42 prevented the build-up of A β plaques. Immunisation of older PDAPP mice was also effective in reducing the number of A β plaques. Much of the data in this paper came from Examples I and III of the Patent, Dr Dale Schenk being the sole named inventor in the Patent. Like the Patent, the paper did not include any data showing any improvement in the cognitive performance of the mice.

164. The paper concludes (emphasis added):

“To our knowledge, this is the first report of a clinically relevant treatment that reduces the progression of AD-like neuropathology in a transgenic animal model of the disease. Although it remains unproven, it is not unreasonable to expect that a similar reduction of neuropathology in AD patents would be of clinical benefit. Although our understanding of the precise aspects of the immune response that result in reduced pathology is incomplete, we have shown that A β ₄₂ immunization results in the generation of anti-A β antibodies and that A β -immunoreactive monocytic/microglial cells appear in the regions of remaining plaques. *Thus, one possible mechanism of action is that anti-A β antibodies facilitate clearance of amyloid- β either before deposition, or after plaque formation, by triggering monocytic/microglial cells to clear amyloid- β using signals mediated by F_c receptors.*

It has been suggested that a chronic inflammatory state exists in the brain of patents with Alzheimer’s disease: specifically the levels of complement, cytokines and acute-phase proteins are raised. These observations have led to the hypothesis that anti-inflammatory regimens might be of therapeutic value. The findings presented here argue that an alternative approach, one that augments a highly specific immune response, can markedly reduce pathology in an animal model of the disease. Collectively, the results suggest that amyloid- β immunization may prove beneficial for both the treatment and prevention of Alzheimer’s disease.”

165. The sentence I have highlighted postulated that the mechanism of action for the effects reported in the Schenk Paper, and hence Examples I and III of the Patent, was that active immunisation with A β generated anti-A β antibodies which crossed the BBB and induced an Fc-mediated immune response in the brain that cleared A β .

166. It is common ground that the Schenk Paper was a seminal paper that received considerable attention in the field when it was published.

DeMattos 2001 and the peripheral sink hypothesis

167. In DeMattos 2001 Dr DeMattos and his co-authors reported that (to quote the summary in the abstract):

“... In exploring factors that alter A β metabolism and clearance, we found that that a monoclonal antibody (m266) directed against the central domain of A β was able to bind and completely sequester plasma A β . Peripheral administration of m266 to PDAPP transgenic mice, in which A β is generated specifically within the central nervous system (CNS), results in a 1,000-fold increase in plasma A β due, in part, to a change in A β equilibrium between the CNS and plasma. Although peripheral administration of m266 to PDAPP mice markedly reduces A β , m266 did not bind to A β deposits in the brain. Thus, m266 appears to reduce brain A β by altering CNS and plasma clearance.”

168. Thus DeMattos 2001 proposed the “peripheral sink hypothesis”, namely that an antibody to A β could reduce the level of A β in the brain by binding to soluble A β in the periphery, thereby altering the equilibrium between the brain and the periphery. In this way, administration of the antibody could reduce deposition of A β in the brain without crossing the BBB. Dr DeMattos explained in his evidence that he devised the experiments which led him to this hypothesis before reading the Schenk Paper.

Construction

169. The general principles applicable to the construction of patent claims were summarised by Jacob LJ in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8 at [5].

170. In the present case there are a number of important issues of construction of the claims. Before addressing those issues, however, it is important to note that it is common ground that the claims are all restricted to passive immunisation even though most of the disclosure of the Patent, and all of the actual data reported in it, concerns active immunisation.

Immune response

171. Although it is not a feature of the claims, there is a dispute as to the correct interpretation of the definition of “immune response” at [0022] of the Patent which it is convenient to address first for reasons which will appear.

172. It is common ground that the term “immune response” would normally be understood to refer to the response to active immunisation, and that the reference to “a beneficial humoral ... and/or a cellular ... response” would, without more, be consistent with that. As JAI points out, however, the specification states in [0022] that the immune response “can be an active response induced by administration of immunogen *or a passive response induced by administration of antibody or primed T-cells* [emphasis added]”. JAI contends that it is clear that the Patent is providing its own dictionary in this respect. Furthermore, JAI says that this is consistent with how the term is used

elsewhere in the specification, in particular in [0007], [0008] and [0030]. Thus far, I do not understand JAI's interpretation to be disputed by Lilly.

173. The dispute is as to what counts as "a passive response induced by administration of antibody" in this context. JAI contends that this would be understood by the skilled team as embracing any response to the administration of antibody, including mere binding of the antibody to A β . Lilly contends that it would be understood as referring to the downstream effects of engaging the immune system, in particular so as to induce phagocytosis, complement binding or ADCC.
174. Prof Wisniewski's evidence was that, at first blush, the definition of "immune response" was contradictory: the reference to the "development of a beneficial humoral ... and/or a cellular ... response directed against an amyloid peptide in a recipient patient" would be understood as referring to the immune response induced upon administration of an amyloid peptide as an immunogen, i.e. by active immunisation, but the skilled team would know that passive immunisation by administration of an antibody would not trigger a humoral or cellular response. His view was that the skilled team would interpret "a passive response induced by administration of antibody" as involving engagement of the rest of the immune system in some way, such as phagocytosis, complement binding or ADCC.
175. Dr Owen's evidence in his first report was that the skilled team would interpret "a passive response induced by administration of antibody" as meaning "the binding of antibodies to antigen and any subsequent effector functions of the antibodies". In his second report, he said that he had not intended to limit the meaning of "immune response" in this context to effector functions and that he understood it to mean all consequences of the binding of the antibody to antigen, including effector functions. In cross-examination, however, he qualified this somewhat by saying that binding of antibody to antigen could be considered as an immune response if the response was beneficial in some way.
176. In my judgment JAI's interpretation of the definition involves stretching it to breaking point. It takes little or no account of the context in which the words "a passive response induced by administration of antibody" are used in [0022], let alone in the Patent more broadly, and it gives little weight to the words "response induced by". As noted above, Dr Owen did not support the full breadth of JAI's interpretation in cross-examination. Furthermore, it is unclear what the criterion for a beneficial response would be if the term were interpreted in the manner in which he suggested in cross-examination. Accordingly, I prefer Lilly's interpretation.
177. The dispute does not end there, however. Lilly goes on to contend that the skilled team would understand the immune response to be one in which an antibody crosses the BBB, binds to multimeric A β and engages Fc-mediated phagocytosis in the brain. This is because Fc-mediated phagocytosis is the only mechanism suggested in the Patent and is the only effector function that the skilled team would regard as relevant to clearing multimeric A β . JAI dispute that the skilled team would understand the immune response to be limited to this.
178. This is really an argument about the construction of claim 1, and I will deal more fully with it in that context. At this stage, I will confine myself to the interpretation of the term "immune response".

179. It was common ground between the experts that the only mechanism of action suggested in the Patent was phagocytosis: see in particular the statement at [0095] that the results in Example III “are indicative of active cell-mediated removal of amyloid in plaque-bearing regions”. As JAI points out, however, that statement is made in the context of a specific example involving active immunisation.
180. Although Prof Wisniewski supported Lilly’s interpretation in his written evidence, I do not think it was supported by his oral evidence which I have summarised above. Thus he expressly accepted that both complement binding and ADCC would also count as an immune response within the definition in the Patent. Accordingly, I do not accept that the definition is limited to Fc-mediated phagocytosis.
181. Finally, there is also a specific issue with regard to FcRn-mediated clearance. Prof Wisniewski’s opinion was that the skilled person would not consider FcRn-mediated clearance of antibody or antibody:A β complex as falling within the definition of an immune response since it was not a mechanism by which a therapeutic antibody effected clearance of its target antigen. Dr Owen’s opinion was that it would be, since it was a consequence of binding of anti-A β antibody to A β , at least if the clearance had some beneficial effect in reducing amyloid burden. Prof Wisniewski’s evidence on this point does not appear to have been challenged in cross-examination. In any event, I did not find Dr Owen’s evidence persuasive.

An antibody to A β

182. The active ingredient in the pharmaceutical composition of claim 1 is “an antibody to A β ”. Leaving aside the limitation later in the claim to the human IgG1 isotype, JAI contends that this means any antibody which binds to one or more of the naturally occurring forms of A β . JAI argues that this is the plain meaning of the words and confirmed by the statements in the specification at [0030], [0033] and [0036] quoted above.
183. Lilly contends that the skilled team would understand A β in claim 1 to mean multimeric, toxic forms of A β , particularly the forms of A β in plaques. Lilly argues that the skilled team would not understand A β in claim 1 to include monomeric A β for the following reasons:
- i) monomeric A β , unlike multimeric forms, had been found to be a constitutive component of normal fluids throughout the body and was considered to be non-toxic and have a normal role in the neuro-signalling process (even if that role was not understood);
 - ii) there was no understanding that targeting monomeric A β using an antibody would or could be beneficial;
 - iii) monomeric A β cannot be cleared by the mechanism of action disclosed by the Patent, whereas targeting multimeric/toxic forms of A β peptide is consistent with the clearance mechanism of action disclosed by the Patent;
 - iv) the specification states at [0122] that “since the disease pathology is thought to be associated with the insoluble plaque associated form of A β ” image analysis, which “measures only insoluble A β aggregated into plaques”, may have “more

sensitivity to reveal treatment effects” than ELISA, which detects all forms of A β ;

- v) the specification only expressly refers to monomeric AB in [0027] and [0122];
- vi) the specification states at [0104] that immunisation with A β “generated antibodies that recognise and bind *in vivo* to the A β in amyloid plaques”;
- vii) the specification states at [0144] that the lack of effect of immunisation on endogenous A β levels in guinea pigs indicates that “the immune response is focused on pathological formations of A β ”;
- viii) there is no suggestion in the Patent that mere binding to the monomer would be sufficient to achieve the desired effect; and
- ix) there is no suggestion in the Patent that it was intended to block cytokines or their receptors.

184. In my judgment JAI’s construction is the correct one. The claim requires “an antibody to A β ”. Monomeric A β is A β , it is one of the naturally occurring forms mentioned in [0033] and it is specifically referred to in [0027] and [0122]. The claim is not limited to aggregated A β . On the contrary, it is clear from [0008], [0036] and claims 5 and 6 that it embraces “dissociated” A β . As discussed below, I consider that the skilled team would interpret “dissociated” to mean, or at least include, monomeric A β .
185. Lilly’s arguments boil down to three main points. The first is that the skilled team would not expect from their common general knowledge that targeting monomeric A β using an antibody would be beneficial. I accept that that is so, but nor would the skilled team exclude the possibility of targeting monomeric A β based on their common general knowledge. In any event, the Patent discloses and claims a new approach to the prevention and treatment of AD. In that context, the skilled team would appreciate that targeting the non-toxic monomer might prevent formation of the toxic multimers.
186. The second is that the focus of the disclosure in the Patent is on the effect of immunisation on the insoluble plaque-associated form of A β . I accept that that is so, but there is nothing in the specification to suggest to the skilled team that the inventor intended to exclude other effects. That is particularly so given that most of the disclosure is concerned with active immunisation, yet the specification is clear that the claimed invention is directed to passive immunisation.
187. The third is that the skilled team would not think that monomeric A β could be cleared by the mechanism of action proposed in the Patent. I accept that that is so, but as I have already observed, that mechanism is proposed in the context of a specific example involving active immunisation. Claim 1 is not expressly limited to any particular mechanism of action, and there is no reason why the skilled team should understand it implicitly to be so limited.
188. Indeed, claim 1 is not even limited to antibodies which induce an immune response in accordance with the definition at [0022]. Although I acknowledge that the specification states in the summary of the invention at [0007] that the pharmaceutical

composition is for use in methods which “entail inducing an immune response against a peptide component of an amyloid deposit in the patient by administration of an antibody” and at [0008] that “the immune response is induced by administering an antibody to A β ” and states at [0030] that “Therapeutic agents for use in the present invention induce an immune response to A β peptide”, I do not consider that the skilled team would read those words into the claim. Indeed, counsel for Lilly did not argue that the claim was limited to antibodies which induced an immune response in accordance with the definition. On the contrary, he argued that it was not so limited (see the section on added matter below). Rather, his argument was the definition of “immune response” supported the restricted interpretation of “antibody to A β ” for which Lilly contends.

189. My conclusion as to the meaning of the term “immune response” is not necessarily inconsistent with this argument. Although I have not accepted that the definition is limited to Fc-mediated phagocytosis, I have accepted that it is limited to downstream effects such as phagocytosis, complement binding and ADCC. I also accept that the skilled team would not expect from their common general knowledge that antibodies to monomeric A β would induce phagocytosis, complement binding or ADCC. Nevertheless, the fact remains that the wording of the claim covers monomeric A β and it is not limited to a specific mechanism of action or to antibodies that induce an immune response as defined.

For use in preventing or treating a disease characterised by amyloid deposit in a patient

190. It is common ground that these words constitute a functional limitation on the scope of claim 1 and that “for” should be interpreted as meaning “suitable for”. The dispute is as to the criterion for determining whether a pharmaceutical composition, and in particular the antibody to A β , is suitable for use in preventing or treating a disease characterised by amyloid deposit. JAI contends that it is enough for the antibody to be shown to have the potential to treat the amyloidogenic component of the disease and that this can be done by demonstrating in animal models that the antibody has the capacity to reduce the amyloid burden. Lilly contends that the antibody must be shown to be efficacious in humans in clinical trials. It is common ground, however, that it is not necessary for the antibody to cure the disease. It is also common ground that it is enough for the antibody to have an effect on those aspects of the disease associated with amyloid deposits.
191. In order to resolve this dispute it is necessary to consider the law with regard to the interpretation of features of this kind. I was referred to a number of decisions both of the courts of this country and of the Boards of Appeal of the European Patent Office on this point.
192. In *Bristol-Myers Squibb Co v Baker Norton Pharmaceuticals Inc* [2001] RPC 1 the claim was a Swiss-form claim directed to the use of taxol “as a means for treating cancer and simultaneously reducing neutropenia”. Aldous LJ said at [21]:

“I have no doubt that the judge was right. The words ‘for treating cancer’ have to be construed in context. The skilled addressee would realise that drugs which were suitable for treatment would not always be successful. However drugs which had no effect were not suitable. The phrase means

‘suitable for trying to treat cancer’. What is suitable is a question of fact, not one of perception. If the drug has a beneficial effect in the treatment of cancer it will be suitable. If not, it will not be.

193. In *Pfizer Ltd’s Patent* [2001] FSR 16 claim 1 was a Swiss-form claim directed to the use of particular compounds “for the curative or prophylactic treatment of erectile dysfunction”. Laddie J upheld Pfizer’s submission that these words were only fulfilled by the use of a compound which was both for the purpose of trying to treat the target illness and suitable for treating that illness i.e. in relation to at least some individuals the treatment worked. Having cited the above passage from *BMS*, he added at [42]:

“A second medical use claim only survives because the compound is effective to achieve a new treatment. If it is not effective, or not discernibly so, it is not suitable for that treatment. If administration of the compound results in some patients getting better, but the same improvement would be achieved by the administration of any placebo, that is not enough. ...”

194. In *Eli Lilly and Co v Human Genome Sciences Inc* [2012] EWCA Civ 1185 the main issues before the Court of Appeal concerned the sufficiency of claims 13, 18 and 19. Claim 13 was to “An isolated antibody or portion thereof that binds specifically to [effectively neutrokin- α]”. Claim 18 was to “A pharmaceutical composition comprising ... the antibody or portion thereof of any one of claims 13 to 17 ...”. Claim 19 was to “A diagnostic composition comprising ... the antibody or portion thereof of any one of claims 13 to 17”. None of these claims contained a functional limitation of the kind I am presently considering.

195. Sir Robin Jacob construed these claims as follows:

“17. The second answer is one of construction. Mr Waugh’s argument involves reading in the further limitation that the antibody should be ‘useful’ (assuming that this has a sufficiently precise meaning). Such a construction would divide antibodies to neutrokin- α into two classes, those which are ‘useful’ and those which are not. And it would involve undue effort to find out whether a particular antibody was useful or not; to separate the wheat from the chaff.

18. The trouble with that submission is that [claim 13] does not contain any limitation to ‘useful’. One does not read words into patent claims (or other documents for that matter) unless the context compellingly so requires. The context here does not. The skilled reader would know perfectly well that the patentees had discovered neutrokin- α , that it had some biological function similar to other members of the TNF ligand superfamily and that it or its antibodies might be useful. The antibody claim, just like the neutrokin- α claims, are all to things which could be valuable. He would not see from the patent any intention to limit the monopolies claimed to that

which was ‘useful’ for he would well know that the patentee had not limited himself to any particular utility – he was saying no more ‘I know of no particular utility yet, but all these products have potential utility.’ So there is no reason why the skilled reader would read the claim as having a limitation to ‘useful’ antibodies.

...

51. The Judge was not invited to construe [claims 18 and 19] and did not expressly do so. He simply proceeded on the basis that they were limited to the pharmaceutical or diagnostic equivalent of a ‘workable prototype’ (a phrase taken from *Mentor v Hollister*, [1993] RPC 7). If that were right, then the claims would indeed be insufficient on his findings of fact. But before us Mr Thorley contended that the Judge had proceeded on an erroneous construction. He submitted that read in the context of the specification as a whole the skilled reader would not expect the patentee to have intended these claims to be directed to compositions with immediate practical use as a pharmaceutical or diagnostic. On the contrary he would know that no such compositions had been disclosed and that what the patentee had discovered and disclosed is neutrokin- α and its antibodies with a practical use for these purposes yet to be discovered. So there is no reason to suppose that in these claims the patentee intended any specific application for the claimed compositions. They are not tied to any particular application. It follows that all he must have meant is compositions which could be formulated as suitable for administration as a pharmaceutical or suitable for use as a diagnostic. That could be done and so the claims are sufficient.

52. I accept that submission. It is in accordance with the principles of claim construction laid down in *Kirin-Amgen* [2005] RPC 9. The contrary view is not, involving as it does the skilled reader in ignoring the very general high level nature of this invention.”

196. Lewison LJ added:

“62. ... The judge found as a fact that all members of the class could be made. But I cannot see that there is an additional requirement that, once made, all or substantially all members of the class can be ‘put into practice’. That would only be the case if the claim specified some use to which the claimed product had to be put. In this case the judge held that, as a matter of construction, claim 13 did not contain a use limitation.

...

72. HGS argues that the judge's findings are based on the assumption that the claims did claim a medical use. In fact they do not. They claim products. Since claim 1 (to a compound) has been upheld by the Supreme Court both on industrial applicability and sufficiency, and claim 13 (to an antibody) must also be upheld, it must follow that the patentee is entitled to claim a product (manufactured without undue effort and without invention) containing the compounds covered by claims 1 and 13. They, too, point to the decision of the TBA which held that claims 18 and 19 were sufficient. As long as the product is suitable for pharmaceutical or diagnostic use, in the sense that it can be put into a suitable carrier, the claim is sufficient. It does not matter that the claim does not specify a particular condition or disease that such a product could treat or diagnose. It is open to pharmaceutical companies downstream to find specific medical uses for such compositions (in which case a 'Swiss-type' patent for a second medical use could be granted); or to identify specific antibodies which have particular properties."
197. In *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] EWCA Civ 93, the claim was to "Use of a hVEGF antagonist in the preparation of a medicament for the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation ...". Kitchin LJ construed this requirement as follows:
- "39. ... The following points are, I think, material. First, the claim is concerned with non-neoplastic diseases which have, as one of their characteristics, undesirable excessive neovascularisation, that is to say angiogenesis. The angiogenesis must therefore contribute to the pathology of the disease though it need not necessarily be the cause of it. Hence the specification explains in the section to which I have referred at [24] above, angiogenesis is an important component of a variety of diseases of which a number are then identified.
40. Second, the medicament must treat the disease. That is not to say that the medicament must cure the disease; plainly many diseases characterised by angiogenesis cannot be cured. But it must improve the patient's condition, and it must do so by treating the angiogenic component of the disease from which the patient is suffering.
41. Third, the medicament does not have to treat all, or indeed any other, aspects of the disease, of which, in the case of some diseases, such as RA, there may be many. It is only directed at the angiogenic aspect of the disease and its efficacy is derived from its activity as a VEGF antagonist.
42. Against this background, I do not believe the judge's analysis can be faulted. It was not suggested by any party at trial that the claim does not require any therapeutic effect. It clearly

does, and the judge so held. But it does not require a medicament which will cure or even treat all aspects of a disease and, in particular, it does not require treatment of those aspects of a disease which are independent of angiogenesis.”

198. In *Genentech/HIV vaccine* T219/01 (unreported, 15 December 2004) claim 1 of the patentee’s main request was to “Unclipped HIV env for use in the prophylaxis or treatment of AIDS”. The Board of Appeal held at [4] that:

“... For the Board in relation to claim 1 which is drafted in the form of a first medical use claim with the only disclosed medical use specifically mentioned in the claim, a technical feature that requires to be sufficiently described in the patent is how to achieve prophylaxis or effective treatment of AIDS for the whole target group, here, humans, the only known organism developing AIDS after infection with HIV. ...”

199. In *Stryker/Morphogenesis* T699/06 (unreported, 29 June 2010) the Board of Appeal held at [19] that:

“Where a therapeutic application is claimed either in the form of a composition for a specific therapeutic use or in the form allowed by the Enlarged Board of Appeal in its decision G 5/83 (OJ EPO 1985, 64), i.e. in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G decisions 2/88 and 6/88, OJ EPO 1993,93 and 114; point 9 of the reasons, for non-medical applications, see also decision T 158/96 of 28 October 1988; point 3.1 of the reasons). As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the substance or composition for the claimed therapeutic application. Once evidence for this suitability is available from the patent application, then post-published expert evidence may be taken into account, but only to back-up the findings in the patent application in relation to the use of substance or composition, and not to establish sufficiency of disclosure on its own (cf decision T 609/02 of 27 October 2004; point 9 of the reasons).”

200. Counsel for Lilly submitted that this case law established that, where a patent claim stipulated that a product was “for use in preventing or treating a disease”, then the claim was to be construed as requiring that the product did in fact achieve the claimed preventative or therapeutic efficacy. It was different if the claim did not contain such a limitation, as in *Lilly v HGS*. I accept that submission.
201. Counsel for JAI did not really challenge this general proposition. Rather, he argued that the criterion for preventative or therapeutic efficacy depended on the context, and in particular the disclosure of the specification. Again, I accept that submission.

202. The question, therefore, is what the skilled team reading the Patent would understand to be the criterion for preventative or therapeutic efficacy for the purposes of claim 1. Somewhat to my surprise, neither side contended that the criterion was that suggested by Example XI of the Patent, namely success in a Phase 2 trial. Counsel for Lilly submitted that, where available, Phase 3 trial results were the best guide to assessing whether the claimed effect was achieved, but also submitted that the claim did not require a Phase 3 trial to be carried out. It was unclear to me from his submissions what criterion should be applied in the absence of Phase 3 results. Counsel for JAI pointed out that the main evidence of efficacy provided by the Patent was the data contained in Examples I, III and IV, and submitted that the skilled team would therefore take data of that kind as indicative of a sufficient likelihood of efficacy in patients for the purposes of the claim.
203. I do not entirely accept either party's interpretation of this feature of the claim. In my judgment the primary criterion for efficacy indicated by the specification is success in a Phase 2 trial. My reasons are as follows. The specification asserts at [0006] that the invention "fulfils a longstanding need for therapeutic regimes for preventing or ameliorating the neuropathology of Alzheimer's disease". The detailed description of the invention includes discussions of "therapeutic agents", "patients amenable to treatment" and "treatment regimes". The second of these refers at [0041] to diagnosis by MMSE or ADRDA criteria. Thus the skilled team would understand that the object of the invention was to achieve preventative or therapeutic efficacy in patients. Although "patients" is defined in [0026] as "human and other mammalian subjects that receive either prophylactic or therapeutic treatment", the skilled team would appreciate that the MMSE and ADRDA criteria are only applicable to humans beings. While it is true that the headings to Examples I and III refer to "prophylactic efficacy" and "therapeutic efficacy", the skilled team would appreciate that those Examples do not include any cognitive tests even in mice. Thus the skilled team would take these Examples as being, at best, predictive of preventative or therapeutic efficacy, and would interpret the last sentences of [0076] and [0106] accordingly. The skilled team would not regard these Examples as establishing preventative or therapeutic efficacy even in mice. By contrast, the skilled team would note the statement in [0159] that "A phase II trial is performed to determine therapeutic efficacy" using ADRDA and MMSE criteria. To similar effect is the statement in [0161] that a Phase 2 trial is performed to determine preventative efficacy. Thus the skilled team would understand that this is the criterion by which efficacy is to be determined for the purposes of the invention. Tellingly, counsel for JAI accepted in his closing submissions that, if JAI's construction was correct, the whole of Example XI was redundant.
204. Nevertheless, I agree with Lilly that, if they are available, the skilled team would regard Phase 3 trial results as the best guide to assessing whether the claimed effect is achieved. The skilled team, and in particular the clinical member, would be well aware that Phase 3 trials are the gold standard for determining efficacy and are required in order to obtain regulatory approval. The skilled team would also be aware that pharmaceutical compositions that have tested positively in Phase 2 trials frequently fail in Phase 3 trials.

Aggregated A β

205. JAI contends that "aggregated A β " is defined in [0027] to mean "a mixture of oligomers in which the monomeric units are held together by noncovalent bonds".

Lilly contends that “aggregated A β ” would be understood by the skilled team to mean insoluble amyloid deposits or plaques, as indicated by the second sentence of [0029]. In my judgment JAI is correct. The definition in [0027] includes A β in the form of plaques, but is not limited to them. While the skilled team would understand that the invention was particularly targeting A β in the form of plaques, there is nothing in the specification to suggest that the patentee intended to restrict “aggregated A β ” to A β in that form.

Dissociated A β

206. “Dissociated A β ” is not defined in the specification. JAI contends that the skilled team would understand “dissociated A β ” to be a synonym for “disaggregated A β ”, which is defined in [0027] to mean “soluble, monomeric peptide units of A β ”. Lilly contends that the skilled team would understand “dissociated A β ” to mean multimeric A β that is not aggregated into insoluble deposits. In my judgment JAI is again correct. While the skilled team would no doubt think it rather odd that the specification contains a definition of “disaggregated A β ”, and not “dissociated A β ”, I agree with JAI that they would conclude that the two terms were intended to be synonymous. I do not agree with Lilly that the skilled team would think that the definition of “disaggregated A β ” was restricted to A β prepared by the method mentioned in the second sentence of [0027].

Added matter

207. The law with regard to added matter was explained by Jacob LJ in *Vector Corp v Glatt Air Techniques Ltd* [2007] EWCA Civ 805, [2008] RPC 10 at [4]-[9]. As he held in *Napp Pharmaceutical Holdings Ltd v Ratiopharm GmbH* [2009] RPC 18 at [98]-[99], a claim does not add subject matter merely because it is wide enough to cover that subject matter.
208. Lilly contends that the disclosure of the Patent extends beyond that of the application for the Patent, namely WO/99/29944 (“the Application”), in two respects: first, it discloses an antibody which does not induce an immune response; and secondly, it discloses an antibody that is of the human IgG1 isotype.

Disclosure of an antibody which does not induce an immune response

209. Claim 1 of the Application was as follows:

“A pharmaceutical composition comprising an agent effective to induce an immune response against A β in a patient, and a pharmaceutically acceptable adjuvant.”

By contrast, as discussed above, claim 1 of the Patent is not limited to antibodies which induce an immune response. Lilly contends that, as a result, the Patent discloses compositions comprising antibodies which do not induce an immune response which were not disclosed in the Application.

210. Lilly also relies upon a number of amendments which were made to the specification as supporting this objection. It is sufficient to refer to one of these amendments, since the others add nothing of substance. This relates to a passage in the Application

summarising the invention at page 3 lines 2-8 which was amended as shown below in the Patent at [0007]:

“In one aspect, the invention provides a pharmaceutical composition comprising an antibody to A β and a pharmaceutically acceptable non-toxic carrier or diluent, for use in methods of preventing or treating a disease characterized by amyloid deposition in a patient, wherein the isotype of the antibody is human IgG2. Such methods entail inducing an immune response against a peptide component of an amyloid deposit in the patient. ~~Such induction can be active by administration of an immunogen or passive by administration of an antibody that has the human IgG1 isotype or an active fragment or derivative of the antibody.”~~”

211. It is not in dispute that the Application discloses two alternative methods for preventing or treating AD. The first is active immunisation, which involves the administration of A β or another immunogen. The immunogen in turn leads to the generation of antibodies to A β . The second is passive immunisation, which involves the direct administration of antibodies to A β . JAI contends that the effect of the amendments both to claim 1 and to the specification relied on by Lilly was simply to limit the invention claimed in the Patent to the second alternative.
212. JAI disputes that the amendments resulted in the disclosure of antibodies to A β which do not induce an immune response. JAI contends that the binding of an antibody to A β to its antigen will necessarily induce an immune response as defined in both the Application and the Patent.
213. In support of this, JAI points out that the definition of “immune response” in the Application at page 11 line 27 – page 12 line 10 is identical to that in the Patent at [0022]. As discussed above, this includes a passive response induced by the administration of antibody. JAI also points out that in the Application the definition of “antibody” at page 10 lines 24-29 is very broad and expressly includes “both intact antibodies and binding fragments thereof” (whereas the definition in the Patent at [0019] is limited to intact antibodies). As Prof Wisniewski accepted, since the antibody as defined in the Application is not limited to one which has an Fc region, the skilled team would understand that the passive response is not limited to Fc-mediated effector functions such as phagocytosis.
214. Even though I have not accepted JAI’s interpretation of the term “immune response” in the context of passive immunisation in the Patent, I have held that the term is not limited to Fc-mediated phagocytosis, but extends to downstream effects such as phagocytosis, complement binding and ADCC. It appears to me that JAI is probably correct to say that the administration of the claimed antibody and its binding to A β will induce such an immune response.
215. Even if I am wrong about that, however, I consider that the fundamental flaw in Lilly’s argument is that claim 1 of the Patent does not disclose antibodies which do not induce an immune response as defined even though it covers them. Thus the omission of those words from the claim does not add subject matter. As for the other amendments Lilly relies upon, these do not assist its case. If anything, they support

the view that administration of the claimed antibody would be expected to induce an immune response as defined.

Disclosure of an antibody that is of the human IgG1 isotype

216. Claim 1 of the Patent as granted is limited to antibodies of the human IgG1 isotype. The Application discloses use of the IgG1 isotype as follows (at page 19 lines 3-5):

“Human or humanized antibodies can be designed to have IgG, IgD, IgA and IgE constant region, and any isotype, including IgG1, IgG2, IgG3 and IgG4.”

217. Lilly contends that the limitation of claim 1 to human IgG1 adds matter because it amounts to an improper selection of human IgG1 from a list of different antibody types (monoclonal, polyclonal, humanised, human) and isotypes. I disagree. In my judgment the inclusion of this feature in the claim is no more than a restriction of the scope of the claim. It narrows the disclosure of the Application from a range of antibody isotypes down to one.

Novelty

218. As was explained by the House of Lords in *Synthon BV v SmithKline Beecham plc* [2005] UKHL 59, [2006] RPC 10, in order for an item of prior art to deprive a patent claim of novelty, two requirements must be satisfied. First, the prior art must disclose subject matter which, if performed, would necessarily infringe that claim. Secondly, the prior art must disclose that subject matter sufficiently to enable the skilled addressee to perform it. The test for enablement in this context is essentially the same as the test for enablement in the context of insufficiency: see Lord Hoffmann at [27].

219. Lilly contends that claim 1 of the Patent lacks novelty over International Patent Application No. WO96/25435 (“Konig”) which was published on 22 August 1996.

Konig

220. The disclosure of Konig is summarised in the abstract as follows:

“The instant invention provides for monoclonal antibody which is specific for β A4 peptide [i.e. A β], and in particular the free C-terminus of β A4 ‘1-42’ but not ‘1-43’, and stains diffuse and fibrillar amyloid, vascular amyloid, and neurofibrillary tangles. The instant invention further provides for antibody fragments and constructs thereof which have the same binding specificity. The instant invention also provides for methods of diagnosis, screening and therapeutics for treating unique forms of β A4”

221. Konig begins with a background section which discusses AD, the role of A β plaques and the derivation of A β from APP. This notes that A β 1-42 has been implicated as a possible critical factor in sporadic AD, and says that monoclonal antibodies which specifically bind to the A β 1-42 species can be used as a diagnostic indicator of abnormal species present in AD (page 4 lines 20-26). It goes on to state that it would be useful to have a monoclonal antibody specific for the A β 1-42 peptide for

diagnostic tests, therapeutics and for AD monitoring assays. Such an antibody is the subject of Konig (page 6 lines 1-8).

222. In its summary of the invention, Konig states that the invention provides for a monoclonal antibody which is specific for A β , and in particular A β 1-42, specifically an antibody called “Mab369.2B” (page 6 lines 11-16). It goes on (page 7 lines 9-23):

“The instant invention also provides for methods of generating β A4 specific antibodies which recognize the free C-terminal residue 42. The instant invention also provides for methods for detecting the presence of β A4 peptides ending at position 42, in tissue comprising contacting a tissue sample with monoclonal antibody of the instant invention, be detecting the presence of monoclonal antibody in a selective fashion. The instant invention also provides for methods for selective purification of β A4 peptides ending at position 42, comprising contacting a sample to be purified with monoclonal antibody of the instant invention, separating the β A4 peptide from the sample to be purified, and isolating the β A4 peptide. In a further embodiment, the instant invention provides for methods of detection of β A4 peptide associated with Alzheimer’s Disease, comprising a sample to be tested with monoclonal antibody of the instant invention, and detecting the presence of β A4 peptides.

Thus the instant invention also provides for methods for the prevention of aggregation of β A4 peptide any administering monoclonal antibody of the instant invention.”

223. In the detailed description of the invention, Konig describes the production of the antibody of the invention, and in particular Mab369.2B. The antibody is stated to differ from the prior art in that it stains diffuse and fibrillar amyloid, NFT and vascular amyloid whilst being specific for A β 1-42 (page 13 lines 21-23).
224. Konig describes a number of examples. Examples 1 and 2 relate to making a peptide expression system and producing synthetic A β peptide by way of *in vitro* transcription and translation respectively. Example 3 details how to make immunogens and screen peptide fragments using, in particular, ELISA protocols. Examples 4 and 5 relate to the immunisation of mice and the subsequent production and screening of hybridoma cell lines to generate monoclonal antibodies. The Mab369.2B antibody is characterised in Example 6. Immunohistochemical studies are performed in Example 7 in order to show its binding properties compared to other monoclonal antibodies which are capable of binding to the A β peptide. The results obtained demonstrate that the Mab369.2B antibody is specific for the C-terminal end of the A β 1-42 peptide.
225. Although Konig states that the antibodies of the invention “provide for methods of preventing aggregation of β A4 [i.e. A β] peptide ... thereby interfering with and disrupting aggregation that may be pathogenic to AD” (page 13 lines 16-20), there is no example of this and no experimental data of any kind (*in vitro* or *in vivo*) are provided to support the contention that the antibodies have this effect. Similarly,

although Konig states that the invention provides for the use of antibodies, fragments and constructs “in diagnostic, analytic, therapeutic and biochemical purification methods which employ the binding specificity of the instant monoclonal antibodies and their use within pharmaceutical formulations” (page 14 lines 9-11), again there are no data in the specification to support the contention that the antibodies of the invention have any therapeutic effect.

226. JAI contends that claim 1 is novel over Konig since (i) Konig does not disclose an antibody to A β of the human IgG1 isotype and (ii) Konig does not disclose use of (a pharmaceutical composition comprising) the antibody in preventing or treating a disease characterised by amyloid deposit.

Disclosure of human IgG1?

227. The only reference to IgG1 in Konig is in Example 4. Table 1 on page 20 lists a number of different mouse cell lines and their isotypes. Cell line 369.1 is said to be of “IgG1/IgG2b” isotype, while cell lines 369.2 and 369.3 are said to have the “IgG1” isotype. Prof Wisniewski accepted that this was mouse IgG1. As is common ground, mouse IgG1 is not the same as human IgG1.
228. Lilly relies on the fact that IgG1 is referred to in claim 4 of Konig. JAI contends that, in the context of Konig, this is a reference to mouse IgG1 and not human IgG1. I agree with JAI.
229. Lilly also relies on the fact that Dr Owen agreed that, in the context of claim 15 (which is to a method of preventing aggregation of A β by administering antibody), the antibody would have to have a human constant region if it was to be administered chronically to humans. As JAI points out, however, claim 15 is dependent on claim 1 (which does not refer to IgG1), but not claim 4 (which does). In my judgment this does not amount to a disclosure of an antibody of human IgG1 isotype.

Disclosure of efficacy?

230. Lilly argues that Konig discloses an antibody for human therapeutic use and thereby satisfies the requirement of claim 1 that it is “for use in preventing or treating a disease”. Lilly does not seriously contend, however, that Konig discloses that the antibody is efficacious in clinical trials of any kind, nor could it. It follows that this feature of the claim is not disclosed as I have construed it. Furthermore, Konig does not even contain data in a mouse model of the kind reported in Examples I, III and IV of the Patent. As Prof Wisniewski accepted, the assertion in Konig that the antibody can be used therapeutically is speculative. Accordingly, Konig does not disclose this feature of the claim even if it is construed as JAI contends it should be.

Obviousness

The law

231. The structured approach to the assessment of allegations of obviousness first articulated by the Court of Appeal in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 was re-stated by Jacob LJ in *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37 at [23] as follows:

- “(1)(a) Identify the notional ‘person skilled in the art’;
- (b) Identify the relevant common general knowledge of that person;
- (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
- (3) Identify what, if any, differences exist between the matter cited as forming part of the ‘state of the art’ and the inventive concept of the claim or the claim as construed;
- (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?”

232. The correct approach to the fourth step in a case such as the present was recently summarised by Kitchin LJ, with whom Lewison and Moore-Bick LJJ agreed, in *MedImmune Ltd v Novartis Pharmaceuticals Ltd* [2012] EWCA Civ 1234 as follows:

- “90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.
91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way.

Lord Hoffmann summarised the position in this way in *Conor* at [42]:

‘In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case.’

92. Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. In *Generics (UK) Ltd v H Lundbeck*, [2008] EWCA Civ 311, [2008] RPC 19, at [24] and in *Conor* [2008] UKHL 49, [2008] RPC 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in *Lundbeck*:

‘The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success.’

93. Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling within the claim....”
233. The primary evidence as to obviousness is that of properly qualified experts and secondary evidence needs to be kept in its place: see *Mölnlycke AB v Procter & Gamble Ltd* [1994] RPC 49 at 112-114 (Sir Donald Nicholls V-C). Nevertheless there are cases in which secondary evidence is important: see *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 at [76]-[85] (Jacob LJ).

Obviousness of claim 1 over König

234. I have identified the skilled team and their common general knowledge and construed claim 1 above. I have also concluded that the differences between König and claim 1 are that König does not disclose an antibody to A β which is of human IgG1 isotype

and does not disclose (a pharmaceutical composition comprising) an antibody to A β “for use in preventing or treating a disease characterised by amyloid deposit”.

235. I do not understand JAI to dispute that it would be obvious to modify Konig to the extent necessary to produce an antibody of the human IgG1 isotype. In any event, I have no doubt that that would be an obvious step to take. The issue is whether it would be obvious in the light of Konig to make an antibody to A β “for use in preventing or treating a disease characterised by amyloid deposit”. As discussed above, Konig expressly proposes using antibodies to A β for the purpose of treating AD, but it contains no data to suggest that the antibodies it discloses (let alone one of human IgG1 isotype) would be efficacious.
236. Lilly contends, and I accept, that the skilled team would have been strongly motivated to find a treatment for AD (and other diseases characterised by amyloid deposit). As discussed above, AD was and remains a major disease, particularly amongst the elderly, with important social and economic consequences.
237. Against this, there were numerous other possible avenues of research (see paragraph 42 above). Furthermore, the effort in pursuing Konig’s proposal would have been considerable, consisting at minimum of mouse model work similar to that undertaken in Examples I, III and IV of the Patent and (on Lilly’s construction of the claim) a great deal more besides.
238. The key question, therefore, is what expectation of success the skilled team would have had if they contemplated implementing Konig’s proposal. JAI contends that the skilled team’s approach to this question would have been coloured by a mindset that (i) antibodies would not cross the BBB in sufficient quantities to have any useful therapeutic effect and (ii) any attempt to transport antibodies to A β across the BBB would be counterproductive since it would exacerbate the inflammation of the brain which was considered to be a cause of AD. Accordingly, JAI says that the skilled team would have discarded any proposal for immunotherapy as a treatment for AD.
239. So far as point (i) is concerned, it is correct that molecules of the size of antibodies were not thought to cross the BBB in therapeutically relevant quantities (see paragraph 46 above). As discussed above, Lilly contend that the skilled team would nevertheless have known from their common general knowledge of methods for assisting the passage of antibodies across the BBB. I have concluded that the clinical member of the team would have been aware of one or two methods that could be tried to assist the passage of antibodies across the BBB, but he would not have regarded such methods as proven, let alone routine (paragraph 159 above).
240. So far as point (ii) is concerned, Prof Wisniewski agreed with Prof Francis that one of the reasons why using antibodies to treat AD had not been widely investigated before December 1997 was because of the potential for an inflammatory reaction in the brain.
241. I do not accept that it follows the skilled team would have discarded any proposal for immunotherapy, but I do consider that the skilled team would have regarded such a proposal with considerable caution, not to say scepticism. Indeed, Dr DeMattos gave evidence that his first reaction to the Schenk Paper itself was one of concern as to the safety implications of initiating an uncontrolled immune response in humans.

242. Lilly contends that, if these points would have been perceived by the skilled team to be “lions in the path”, there is nothing in the Patent to show that they were in fact “paper tigers”. I disagree. For reasons that I will explain when dealing with insufficiency, I consider that the specification of the Patent does contain enough to make it plausible that (pharmaceutical compositions comprising) some antibodies to A β will be effective to prevent and/or treat AD even though the experimental data in Examples I, III and IV relate to active, not passive, immunisation.
243. Would the disclosure of Konig have given the skilled team sufficient encouragement to overcome their caution? As discussed above, Prof Wisniewski accepted that the proposal for therapeutic application in Konig was speculative. Prof Francis said that it might be of interest to an academic lab not concerned with commercial development to investigate the antibodies of Konig in a mouse model, but that a pharmaceutical company would not be interested, as they would not conduct experiments that they did not think were going to lead to a drug. Dr Owen said in cross-examination that it was a reasonable strategy to investigate, but clarified in re-examination that he meant a strategy to determine whether there was any activity in mouse models and whether there was any evidence of any toxicity. Thus he was not suggesting that the skilled team would have expected success. The conclusion which I draw from this evidence is that Konig would not have given the skilled team any real expectation of success.
244. Overall, I conclude that Konig did not make it obvious to make an antibody to A β “for use in preventing or treating a disease characterised by amyloid deposit”.
245. JAI also relies by way of secondary evidence on the contemporaneous reaction in the field to the Schenk Paper. For example, one of the referees for *Nature* said that the data were “very surprising but compelling”. Prof Wisniewski agreed that that was fair comment. In my view this provides some modest support for the conclusion of non-obviousness, although it cannot be pressed very far since there is no evidence that such commentators were aware of Konig.

Obviousness of claim 1 over Becker

246. Lilly also contends that claim 1 is obvious over European Patent Application No. 0 613 007 A2 (“Becker”) published on 31 August 1994. I shall deal with this very briefly, since in my opinion it is manifest that claim 1 cannot be obvious over Becker if it is not obvious over Konig. Becker discloses *inter alia* the preparation of antibodies which have specificity for A β which is predominantly in the β -sheet confirmation (columns 5-7). It also states that the antibodies of the invention “are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations” and “are especially preferred in the diagnosis and/or treatment of Alzheimer’s disease in mammals, preferable humans” (column 7 lines 39-52). These antibodies are described as the “active ingredient” in “pharmaceutical formulations for parenteral administration” (column 8 lines 49-52). As Prof Wisniewski accepted, however, Becker does not disclose any specific antibodies or any *in vivo* data at all. He also accepted that it was again a speculative proposal. Dr Owen’s evidence was similar to his evidence with regard to Konig. In my judgment Becker would not give the skilled team any expectation of success and claim 1 is not obvious over it.

Agrevo obviousness

247. Finally, Lilly contends that the Patent is obvious applying the principles stated by the Board of Appeal in T 939/92 *Agrevo/Triazoles* [1996] EPOR 171. I do not intend to discuss this contention in any detail, because in my view Lilly's real objection is not one of obviousness, but of insufficiency, and I shall consider the matters relied on in that context.

Insufficiency

The law

248. In *Lilly v HGS* Sir Robin Jacob quoted with apparent approval at [11] the following summary of the relevant principles given by Kitchin J (as he then was) at first instance in the same case [2008] EWHC 1903 (Pat), [2008] RPC 29 at [239]:

“The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:

(i) the first step is to identify the invention and that is to be done by reading and construing the claims;

(ii) in the case of a product claim that means making or otherwise obtaining the product;

(iii) in the case of a process claim, it means working the process;

(iv) sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;

(v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;

(vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;

(vii) the specification must be sufficient to allow the invention to be so performed without undue burden.”

249. Failure to enable the invention to be performed without undue burden is often referred to as “classical insufficiency” and failure to enable the invention to be performed over the whole scope of the claim is often referred to as “*Biogen* insufficiency” or “excessive claim breadth”, although these are aspects of the same objection and often shade into one another.

250. *Classical insufficiency*. I reviewed the law with regard to classical insufficiency in *Sandvik Intellectual Property AB v Kennametal UK Ltd* [2011] EWHC 3311 (Pat),

[2012] RPC 23 at [106]-[124]. Since then, the Court of Appeal has considered the requirement that the specification enable the skilled person to perform the invention without undue burden in the context of a claim to the use of a product to make a medicine for a particular therapeutic purpose in *Regeneron v Genentech*, where Kitchin LJ stated at [103]:

“... the Boards of Appeal of the EPO have recognised that in the case of a claim to the use of a product to make a medicine for a particular therapeutic purpose it would impose too great a burden on the patentee to require him to provide absolute proof that the compound has approval as a medicine. Further, it is not always necessary to report the results of clinical trials or even animal testing. Nevertheless, he must show, for example by appropriate experiments, that the product has an effect on a disease process so as to make the claimed therapeutic effect plausible. It was put this way in T609/02 *Salk* at [9]:

“... It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a “clear and accepted established relationship” between the shown

physiological activities and the disease (loc. cit.). Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own.”

251. *Excessive claim breadth.* I reviewed the law with regard to excessive claim breadth at some length in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1699 (Pat) at [458]-[484] and summarised that analysis in *Sandvik v Kennametal* at [121]-[124]. As Kitchin LJ stated in *Regeneron v Genentech*:

“100. It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case.

101. On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose.”

252. *Post-dated evidence.* It is common ground that, as Kitchin LJ said in the passage quoted above, “the assertion that the invention will work across the scope of the claim must be plausible” reading the specification as at the application date with the common general knowledge of the skilled person or team. Counsel for JAI submitted that, if the assertion was plausible, then it was not open to a party challenging the validity of the patent on the ground of insufficiency to rely upon evidence which was not available as at the application date, such as the results of subsequent clinical trials, to contradict the assertion.

253. In support of this submission, counsel for JAI relied upon the following passage in my judgment in *Generics (UK) Ltd v Yeda Research and Development Co Ltd* [2012] EWHC 1848 (Pat):

“343. *Evidence which post-dates the patent.* Counsel for Mylan submitted that there was a two-stage enquiry. First, it was necessary to consider the disclosure of the patent itself. If the patent when read with the skilled person’s common general knowledge did not ‘disclose enough

to make the invention plausible', i.e. plausible that the invention solved the technical problem, then that was the end of the matter, and it was not permissible for the patentee to rely upon evidence which post-dated the patent to demonstrate the technical effect. Secondly, even if the patent did make the invention plausible, however, it remained open to the other party to cast doubt on this by post-dated evidence.

343. I did not understand Counsel for the Defendants to dispute the first proposition, which is supported by the decision of the Board of Appeal in T 1329/04 *Johns Hopkins University School of Medicine/Growth differentiation factor-9* [2006] EPOR 8 at [12], which was cited by Lord Hoffmann in *Conor* at [33]-[35] (quoted in *Sandvik* at [182]), although he went on to distinguish *Conor* on the facts. It is also supported by several statements of principle by judges in this jurisdiction. It is sufficient for present purposes to cite three examples.

...

348. Counsel for the Defendants took issue, however, with the second proposition. This raises an important point of principle. If a patent does disclose enough to make the invention plausible at the priority or filing date, can an opposing party come along 20 years later and say that, in the light of subsequently acquired knowledge, in fact the invention does not have the technical benefit that it appeared to have? As a matter of principle, it seems to me that the reasoning of the Board of Appeal in *Johns Hopkins* and of the English judges quoted above applies with equal force: just as a patent which does not make the invention plausible cannot be supported by post-dated evidence, then a patent which does make the invention plausible cannot be shown to be obvious by post-dated evidence. Either way, the fundamental principle is that whether a claimed invention is obvious or not should be judged as at the priority or application date.

349. I acknowledge that it can be seen from the case law of the Boards of Appeal of the EPO that they do sometimes take post-dated evidence into account. Thus in both T 1336/04 *Novozyme/Cellulase* (unreported, 9 March 2006) and T 433/05 *Conjuchem/Fusion peptide inhibitors* (unreported, 14 June 2007), both of which are cited in *Case Law of the Boards of Appeal of the European Patent Office* (6th ed) at 176-177, the Board of Appeal took into account post-dated evidence which supported the disclosure in the patents. As I read those decisions, the Board considered that the disclosure in the patents was plausible and confirmed by the later evidence. The same applies to the decisions in T 898/05 *Zymogenetics/Hematopoietic Cytokine receptor* [2007] EPOR 2, T1452/06 *Bayer/Human epithin-like serine protease* (unreported, 10 May 2007) and T1165/06 *Schering/IL-17 related polypeptide* (unreported, 19 July 2007) cited in the judgment of Lord Neuberger in *HGS v Lilly* at [107(ix)]. I also acknowledge that I took post-dated evidence into account in *Sandvik* as confirming the

conclusion I had reached on the basis of the disclosure of the patent that the invention did not confer any technical advantage.

350. In my judgment, however, these decisions represent the limits to which post-dated evidence may properly be put. In short, post-dated evidence may be relied on to confirm that the disclosure in the patent either does or does not make it plausible that the invention solves the technical problem. Post-dated evidence may not be relied upon either to establish a technical effect which is not made plausible by the specification in order to rebut an allegation of obviousness or to contradict a technical effect which is made plausible by the specification in order to found an allegation of obviousness. In my view it would be bizarre if, as counsel for Mylan submitted, a patent which at the time it was applied for disclosed what everyone thought was a good invention could be revoked 20 years later because subsequent advances in science had revealed that in fact the invention did not solve the technical problem.
351. Furthermore, to return to the first point, if the specification does make it plausible that the invention solves the technical problem, I do not consider that it is open to an applicant for revocation to rely upon post-dated evidence as casting doubt on this so as to place an evidential burden on the patentee to demonstrate affirmatively that the invention does solve the technical problem.”
254. As counsel for JAI acknowledged, those statements were made in the context of dealing with an allegation of obviousness. He argued, however, that as a matter of principle the same approach should be adopted in the context of insufficiency. He accepted that in *Generics v Yeda* itself I had adopted a different approach when dealing with insufficiency at [437], but pointed out correctly that that approach had been common ground in that case. He also accepted that it was open to the party attacking the validity of the patent to adduce expert evidence to show that, even though the disclosure made it plausible that the invention would work, nevertheless putting the invention into effect would involve an undue burden, but sought to distinguish evidence of that kind from evidence derived from later clinical trials.
255. I do not accept this submission. In my judgment it is well established that it is permissible for a party attacking the validity of a patent to rely on post-dated evidence. If domestic authority is required for that proposition, it is not necessary to go further back than Kitchin LJ’s statement in *Regeneron v Genentech* quoted above: “if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then ... the claim will be insufficient”.
256. As counsel for Lilly submitted, the approach of the Boards of Appeal of the EPO is the same. In this regard, he particularly relied on *Genentech/HIV Vaccine*. In that case the patentee relied upon the protection of two chimpanzees as disclosed in the patent as demonstrating that an HIV vaccine comprising unclipped HIV env provided a protective effect against HIV infection *in vivo*. The opponent (appellant II) relied upon the failure of a later Phase 3 trial as demonstrating that the patent was insufficient. The patentee (appellant I) argued that investigations which relied upon

statistical analysis, such as clinical trials, should not be used to judge sufficiency. In the alternative, the patentee argued that the clinical trial data showed that the vaccine afforded statistically significant protection in certain subgroups.

257. The Board of Appeal rejected the patentee's arguments for reasons which merit quotation at some length:

“5. AIDS VAX is a compound falling under the definition of unclipped HIV env of claims 1 and 5, and has been produced with the co-operation of the inventors at a date subsequent to the filing of the patent. The compound was the subject of a clinical trial the results of which were published in February 2003 (document D35). The Board can thus only assume that the results for AIDS VAX are representative of the best of what is achievable according to the teaching of the patent.

...

5.2 Hence, in summary, a large scale clinical trial involving more than five thousand persons whose lifestyle put them at risk of HIV infection, of whom two thirds were given AIDS VAX and the remaining third were a control given a placebo, showed that for the group as a whole there was no statistically significant effect attributable to AIDS VAX. Most of those partaking were white males, and for that subgroup, too, no beneficial effect attributable to AIDS VAX was shown. Prima facie the Board can only conclude that the information in the patent is not sufficient to enable a skilled person to achieve what is claimed in claims 1 and 5.

6. Appellant I has questioned whether results of a statistical analysis of a vaccine trial are appropriate means to challenge sufficiency of disclosure of a patent.

6.1 The statistically evaluated results of a vaccine trial allow predictions on the probability of the efficacy of a compound for prevention of an infection. In effect, the statistical evaluation of large groups is the only way to achieve conclusive results on efficacy in human beings, because of the unavailability for humans of any direct efficacy test such as is done in animals by vaccination with subsequent active infection with, for example, a virus. In this particular case, given that only humans infected with HIV develop AIDS, but chimpanzees infected with HIV do not develop AIDS, the Board considers that the results of the AIDS VAX vaccine trial are much more relevant evidence, than the results in chimpanzees so heavily relied on by the appellant I before the opposition division as evidence of the effectiveness of what is claimed.

- 6.2 The Board is not stating that all vaccine trials or clinical trials are necessarily relevant, as some may relate to issues not relevant to the sufficiency of disclosure of a patent. However, it is common practice in proceedings before the EPO that a decision about the presence or absence of a certain medical effect of a compound is made on the basis of all sorts of evidence, be it in vitro or in vivo experiments provided that they render the intended effect credible.

This includes data filed after the filing date of the application, in particular where the issue is sufficiency of the patent disclosure in relation to medicines or vaccines, since highly relevant evidence concerning actual attempts to put the invention into practice may not be available until many years after the date of the patent, in contrast to in vitro or in vivo preliminary tests carried out to allow an initial assessment of the likelihood of success.

Amongst the available data in a certain case the highest evidential weight is adjudged to those experiments reflecting in the best way the envisaged use.

7. Even if the AIDSVAX clinical trial data were taken into consideration, appellant I argued that an analysis of the results of subsets of participants demonstrated that AIDSVAX was efficient in the prophylaxis of AIDS, in particular in human subgroups, namely women, Asians and Blacks, and this partial success was by itself enough to support the presence of sufficiency of disclosure.

- 7.1 Leaving aside initially the question whether the subset results in fact demonstrated any success, which was in dispute between the parties, this argument for sufficiency fails for the Board because success for part of the area claimed in claims 1 and 5, does not compensate for lack of disclosure how to succeed for humans as a whole. The patent in suit contains no suggestion that the intended vaccine might succeed only for selected human groups, and certainly no identification of such groups. If what is claimed works only for some groups, this suggests that some other (unknown) factors are in play, and raises questions whether for these groups there is any significance in the difference between ‘unclipped’ as claimed and the (partly) clipped env form present in the prior art suggestions.

...

- 7.4 In summary, the Board concludes that the evidence at best shows that it might be worth investigating further whether the results for a larger sample of certain subgroups would still come up with a protective effect, and then to carry out research

to try and explain the cause for any real difference so established. But the evidence does not show that the teaching of the patent will ensure success.”

The facts

258. For the reasons set out above, the court must undertake a two-stage enquiry. The first stage is to determine whether the disclosure of the Patent, read in the light of the common general knowledge of the skilled team, makes it plausible that the invention will work across the scope of the claim. If the disclosure does make it plausible, the second stage is to consider whether the later evidence establishes that in fact the invention cannot be performed across the scope of the claim without undue burden. For convenience, I shall divide the second stage into two, first considering whether the invention can be performed without undue burden at all and then whether the claim is of excessive breadth. It is only necessary to consider claim 1 for this purpose: although JAI formally asserted independent validity of a number of the subsidiary claims, including claims 4-6, counsel for JAI did not suggest in his closing submissions that any of the subsidiary claims would survive if claim 1 was invalid on the grounds contended for by Lilly.
259. *Is it plausible?* Lilly contends that the disclosure of the Patent does not make it plausible that any antibody to A β can be used in preventing or treating a disease characterised by amyloid deposit. JAI contends that it does, because the specification contains extensive *in vivo* data generated from an established mouse model of AD. Whilst the data concerns active immunisation, JAI contends that the skilled team would consider the data to make the claim in the Patent regarding passive administration plausible.
260. It is convenient to begin by summarising the aspects of the disclosure which are particularly relied on by JAI in this respect:
- i) Examples III and IV show that the plaques were coated with endogenous IgG which, together with data showing reductions in A β levels and amyloid burden, indicates that therapeutic quantities of antibody were getting into the brain.
 - ii) Example IV contains data which demonstrates that an antigen-specific T-cell response is not necessary to reduce total A β and A β 1-42 in the brain. As discussed above, a T-cell response is normally generated as part of an active immunisation, but not as part of a passive approach. On this basis, it is stated at [0127] of the Patent that “the key effector immune response induced by immunization with this peptide appears to be antibody”.
 - iii) Together, JAI says that these points demonstrate that the reduction in amyloid burden in these Examples is caused by therapeutically relevant levels of antibody entering the brain. As this does not require a T cell response, it is plausible that the same effect can be achieved with passive administration. Furthermore, it is plausible that, as a result, a preventative and/or therapeutic effect can be achieved in humans.

261. In addition, JAI relies on the evidence of Dr Owen and Prof Wisniewski. Dr Owen accepted that one could not extrapolate from active to passive with certainty, but his view was that, given the data on active immunisation disclosed in the Patent, one could be reasonably confident that passive administration of a monoclonal antibody would work. Prof Wisniewski expressed the view in his reports that a monoclonal antibody was unlikely to reproduce the effect of the active polyclonal response. In cross-examination, it became apparent that what he meant was that the active data was no guarantee of success with passive administration. In re-examination, he said that selecting an appropriate monoclonal antibody would introduce an extra layer of complexity, but that is a different point which I shall consider below.
262. Against this, Lilly relies on three matters as casting doubt on the plausibility of the claim. The first is that all the Examples used CFA. As discussed above, CFA is not a mere adjuvant, but includes an antigen. Accordingly, it strongly stimulates the innate immune system. Dr Owen accepted that, as a result, there would be higher levels of activated macrophages in the periphery at the site of the injection, but he did not know what would happen in the CNS. He also accepted that the stimulation of the innate immune system could not be replicated by passive immunisation alone. Whether this matters, however, depends on what happens in the CNS, and specifically in the context of the experiments reported in the Patent. So far as that is concerned, Dr Owen's evidence was that, if CFA stimulated the macrophages of the innate immune system to phagocytose A β plaques, one would expect this effect to be observed in the controls which used CFA/PBS alone. Given that significant reductions of amyloid burden were only observed in the groups treated with A β , however, this suggests that the clearance of A β reported in Example IV was antigen-specific and not due to the activity of macrophages which were non-specifically activated by CFA. Prof Wisniewski agreed with this.
263. The second point concerns the BBB. As discussed above, I am not satisfied that it was part of the common general knowledge of the skilled team that CFA would compromise the BBB and thereby facilitate the passage of antibodies across the BBB. Counsel for Lilly nevertheless submitted that the skilled reader would appreciate that the active immunisation approach used in the Examples of the Patent might depend upon some impairment of the BBB which might not be replicated by passive immunisation. In support of this submission, he relied in particular on the following passage from the cross-examination of Dr Owen:
- “Q. ... Would you go this far, doctor, that the data in the patent suggests that the antibodies have crossed the blood-brain barrier?
- A. Yes, I would.
- Q. One explanation is that the blood-brain barrier has been compromised in some way.
- A. Yes, that would be one.
- Q. And that could have happened as a consequence of inflammatory events associated with active immunisation.

A. Yes, it could.

Q. It could have been triggered either by the aggregated immunogen themselves.

A. Yes.

Q. Or it could have been, we do not know, because the control was not done, the immunogen plus the adjuvant used in the examples?

A. Yes, it could.

Q. If that is right, then higher amounts of antibody would be expected to cross the blood-brain barrier if you are using an active immunisation approach?

A. If that were right.

Q. Now, you agree that there is no basis in the patent to assume that antibodies are able to cross the blood-brain barrier in the absence of impairment in some way?

A. There is no basis in the patent for that, that is correct.”

264. Counsel also relied on the fact that Dr Owen accepted that, in the context of treating human disease, one of the things one would want to investigate in the light of the data in the Patent was the extent to which the BBB was compromised or not and that one would want to build into a safety study ways to assess the potential toxicity of initiating an immune response.
265. I accept that for these reasons the skilled team would not be confident of success using passive administration and would proceed with caution before administering antibodies to humans. It does not follow, however, that the skilled team would not regard the claim made in the Patent as plausible.
266. The third, and to my mind most important, point is that the Patent does not enable any prediction to be made that the reduction in amyloid burden occasioned by active immunisation, let alone passive administration of an antibody, will produce a cognitive benefit in patients (whether in terms of preventing, reducing or slowing cognitive deterioration or in terms of alleviating cognitive deficit). Thus, as I have already noted, the Patent contains no data from any cognitive tests in mice, let alone humans.
267. Prof Francis gave some quite telling evidence in this regard concerning a conversation he had had with Dr Schenk at some point after the publication of the Schenk Paper:

“Q. Do you see the last sentence: ‘I asked whether the vaccination improved cognitive performance in the mice, but as far as I recall he did not answer this point.’ Why did you ask the question?

A. Because I believed that was an important factor. My research effort was around cognition and behaviour in dementia. I would be interested in any new medication or approach, whether it would improve or potentially improve cognition.

Q. The fact that it might have affected the amyloid burden, okay, but you would have wanted to know whether in fact it was accompanied by some improved cognition in mice.

A. Yes, I would.

Q. What was your reaction to the fact that he did not tell you?

A. I said, ‘When are you going to tell me?’ Well, I could not tell whether he just was not telling me because it was confidential or that he had not done it or there was a problem with the mice. I had no way of knowing, and he gave an enigmatic smile.”

268. Nevertheless, I did not understand any of the experts to disagree that the conclusion in the Schenk Paper that “the results suggest that amyloid- β immunization may prove beneficial for both the treatment and prevention of Alzheimer’s disease” was a fair statement in the light of the data contained in the Examples of the Patent. This is consistent with the fact that it was generally thought at the time that reducing amyloid burden would be a key to the prevention and treatment of AD. Thus the Patent makes it plausible that active immunisation will be beneficial in such prevention and treatment even though it contains no cognitive data. By extension, it also makes it plausible that passive immunisation will be beneficial unless the skilled team would have had some reason to think otherwise. For the reasons I have given, I do not think that they would have done.
269. Thus I conclude that the disclosure in the Patent does make it plausible that passive immunisation of a suitable antibody to A β will be effective to prevent and/or treat a disease characterised by amyloid deposit.
270. That is not the end of the enquiry, however. It remains to be considered whether the Patent makes it plausible that *any* antibody to A β (provided it is of IgG1 isotype) will be effective to prevent and/or treat a disease characterised by amyloid deposit. Lilly contends that the skilled team would conclude from the data in Example IV summarised in paragraph 137 above that this was not the case, and that on the contrary antibodies to the mid-region and C-terminal end of A β would be unlikely to work. Thus whereas the A β 1-5 fragment both reduced total cortical A β and reduced the burden of plaque A β in the brain, the A β 1-12 and A β 13-28 fragments had neither effect while the A β 32-42 fragment had no effect on total cortical A β and was not tested on plaque A β . This data relates to active administration, but the thesis upon which the Patent is based is that such data provide a plausible basis for predicting what will happen with passive administration. Thus all the experts agreed that the teaching of the Patent suggests selecting an antibody to an epitope at the N-terminal end of A β .

271. Accordingly, I conclude that the disclosure of the Patent does not make it plausible that any antibody to A β (provided it is of IgG1 isotype) will be effective to prevent and/or treat a disease characterised by amyloid deposit. It only makes it plausible that N-terminal antibodies will be effective. It follows that the Patent is insufficient. In case I am wrong on the question of plausibility, however, I shall go on to consider the additional grounds relied on by Lilly.
272. *Can the invention be performed without undue burden?* There are two main aspects to this question. The first is how burdensome it would be to produce an appropriate antibody to A β . Lilly contends that this would be a lengthy and complex task. JAI contends that, while it would take some time, effort and expense, it would be routine work for the skilled immunologist. The second aspect is whether the antibody would be efficacious applying the criterion I have discussed above (see paragraphs 203-204). Lilly relies upon evidence as to JAI's own attempts to perform the invention as showing very clearly that achieving success would be very difficult and uncertain. JAI's main answers to this contention are (i) its argument as to the construction of the words "for preventing or treating a disease characterised by amyloid deposit" and (ii) its argument that post-dated evidence cannot be relied on, both of which I have already rejected. Nevertheless, I must consider the evidence and make the appropriate findings in case I am wrong on construction.
273. So far as the first aspect is concerned, Prof Wisniewski's evidence was that, before starting work on passive immunisation at all, the skilled team would first experiment with active immunisation. Even though the Patent only claims passive immunisation, the skilled team would first want to verify that active immunisation worked, to get a better idea of what the mechanism was and to ensure that there was no toxicity because of the uncertainty associated with moving from active to passive given the absence of data in the Patent. Dr Owen disagreed with this. In my judgment, however, Prof Francis' evidence (see in particular the passage quoted in paragraph 267 above) confirms that the skilled team would want to see some cognitive data in mice from active immunisation, in order to satisfy themselves that there was a sufficient likelihood of therapeutic benefit before embarking on the effort and cost of developing and testing monoclonal antibodies. This in itself would take some time, effort and money.
274. Turning to the development of monoclonal antibodies, the obvious starting point would be to try and obtain or make the four monoclonal antibodies listed in Table 6 in Example VI, namely 2H3, 10D5, 266 and 21F12. The Patent does not enable the skilled team to do that, however, since, as noted above, it does not give any deposit, sequence information, reference or other source of those antibodies. Dr Owen agreed that it would not be possible for the skilled team to produce a structurally identical antibody to any of those listed, although he considered it likely that functionally equivalent antibodies could be produced.
275. As noted above, it was Prof Wisniewski's evidence that in going from active to passive immunisation and hence from a polyclonal response to monoclonal antibodies, the skilled team would face an extra level of complexity in making and testing appropriate monoclonal antibodies.
276. Dr Owen's evidence was that making monoclonal antibodies was routine, albeit time-consuming, work for the skilled immunologist in December 1997. He described the

steps involved in making a humanised antibody and the time involved in his second report as follows:

- i) *Generating hybridomas*: this involves active immunisation of mice with A β peptide and an appropriate adjuvant. This would require an initial “priming”, followed by subsequent boosting to obtain a high antibody titer. He estimated that this would take four months, but would only require a few days’ work during this period. The B cells would then be harvested from the spleens of the mice, fused with cells from a myeloma cell line and clones selected. He estimated that these steps would take up to two months’ full-time work, so that this stage would take up to six months in total.
- ii) *Biophysical characterisation of the antibodies*: this involves growing the hybridoma cells in large amounts so that a large quantity (tens of milligrams) of a single antibody can be purified. He estimated that this would take about one month, but there would be very little work. The antibodies would then be purified and the binding properties of the antibody investigated (using, for example, surface plasmon resonance). He estimated that this would take up to two months’ full-time work, so that this stage would take up to three months in total.
- iii) *Biological assays of antibodies*: during the two months’ work on biophysical analysis, larger quantities of antibody (e.g. 500 milligrams) would be prepared for biological testing. He estimated that biological testing would comprise passive administration of the monoclonal antibodies, as described in Example VI of the Patent and subsequent biochemical and histological analysis, which would take about six months.
- iv) *Generation of a chimaeric antibody*: this involves isolating the DNA encoding the V_H and V_L regions of the mouse monoclonal antibodies of interest (using a technique known as the polymerase chain reaction or PCR), cloning them into an expression vector expressing the constant region of a human antibody, preparing stably-expressing cell lines and purifying antibody for analysis. He estimated that these steps would take up to four months, depending on the amount of antibody required. The biophysical properties of the antibodies would be characterised as described above, which would again take about two months, so that this stage would take up to six months in total.
- v) *Generation of humanised antibodies*: this involves transplanting the CDR regions from the mouse monoclonal antibody into the equivalent region of V region framework of a human antibody using recombinant DNA technology. This humanised V region is then cloned upstream of a fully human constant region in order to express an antibody heavy or light chain. He estimated that this step would typically take about nine months. Thus the total time taken for all five steps would be around 30 months.

277. Prof Wisniewski considered that Dr Owen’s time estimates were optimistic, but in the right ballpark. Moreover, he agreed that these time periods were not unusual or burdensome for making a humanised antibody. As he made clear, however, his view was that the difficulty lay in ensuring that the antibody was therapeutically effective

without having adverse effects. Thus the key stage of this phase of the work would be stage (iii).

278. As counsel for Lilly submitted, the best evidence of what would be involved at that stage is provided by the work of JAI's predecessor Elan (JAI is a subsidiary of Johnson & Johnson which acquired the AD immunotherapy business of Elan in September 2009).
279. As noted above, it was common ground between the experts that the Patent suggests that one should select an antibody to an epitope at the N-terminal region of A β . As Prof Wisniewski explained, however, the skilled team would select several suitable candidates identified on the basis of their ability to bind A β *in vitro* for testing in a transgenic mouse model, rather than put all their eggs in one basket. This is precisely what Elan did: see Bard *et al*, "Peripherally administered antibodies against amyloid β -peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease", *Nature Medicine*, 8, 916-919 (2000) ("Bard 1"). As reported in this paper, Dr Schenk and his colleagues first tested two mouse monoclonals against A β , 10D5 and 21F12, in PDAPP mice. The mice received weekly injections for six months, after which quantitative image analysis was used to determine amyloid burden and ELISA to determine A β 1-42 levels in the cortex. 10D5 reduced plaque burden and cortical A β 1-42, whereas 21F12 had less effect on plaque burden and none on cortical A β 1-42. In a second study the Elan team repeated the 10D5 treatment and also tested two additional antibodies referred to as 3D6 and 16C11. Both 10D5 and 3D6 were effective in reducing plaque burden, whereas 16C11 was not. In addition, the authors established an *ex vivo* assay which was found to be predictive of *in vivo* efficacy. Using the *ex vivo* assay, they found that F(ab') fragments of 3D6 were unable to trigger microglial cell phagocytosis, while phagocytosis induced by the whole 3D6 antibody was inhibited by antibodies specific for Fc receptors on microglial cells. From this, they concluded that *in vivo* clearance of A β occurred through Fc receptor-mediated phagocytosis.
280. Prof Wisniewski's evidence was that the approach adopted by the Elan group and published in Bard 1 was the most likely one the skilled team would have taken based on the teaching of the Patent. Dr Owen agreed that it was a reasonable strategy to adopt. Dr Owen went on to accept that the Bard 1 work represented an extensive research programme and that it amounted to the patentee's best shot at making it work. He also agreed that, in carrying out the *ex vivo* assays, the authors were seeking to produce a system that replicated the mechanism of action suggested in the Patent and in the Schenk Paper.
281. It was common ground between the experts that, based on the results reported in Bard 1, the skilled team would have progressed 3D6. An alternative would have been 10D5. The 21F12 and 16C11 antibodies would have been found to be inactive, and so would not have been progressed.
282. The Elan team next did further work to try to define the optimal antibody response for reducing neuropathology by examining the influence of different antibody epitopes and isotypes on plaque clearance and neuronal protection. This work was published in Bard *et al*, "Epitope and isotype specificities of antibodies to β -amyloid peptide for protection against Alzheimer's disease-like neuropathology", *PNAS*, 100, 2023-2028 (2003) ("Bard 2"). In this paper the authors tested 3D6 (an antibody directed against

the 1-5 epitope of A β 1-42), 10D5 (directed against the 3-7 epitope), 22D12 (directed against the 18-21 epitope), 266 (directed against the 16-24 epitope), 16C11 (directed against the 33-42 epitope) and 21F12 (directed against the 34-42 epitope), for binding to plaques in PDAPP mice and *ex vivo* phagocytosis. While 3D6 and 10D5 gave positive results in both tests, 22D12, 266, 16C11 and 21F12 gave negative results in both tests (see Table 1). The authors also tested a number of fragments of A β . In this regard, the authors commented that “The internal peptide A β 15-24 encompasses the epitope of antibody 266, which exhibits high affinity for soluble A β ..., but as shown above it does not recognize plaques in sections of unfixed AD or PDAPP tissue” (page 2024 right-hand column). In addition, the authors did some work on different antibody isotypes. Their conclusion was that their results “indicate that antibody Fc-mediated plaque clearance is a highly efficient and effective process for protection against neuropathology in an animal model of Alzheimer’s disease” (abstract on page 2023).

283. Prof Wisniewski’s unchallenged evidence was that, based on the data in Bard 2, the skilled team would not have progressed 266. Dr Owen agreed that the skilled team would have focused on N-terminal antibodies and taken forward 3D6, consistently with the hypothesis advanced in the Schenk Paper. As discussed below, this is in fact what Elan did: bapineuzumab is a humanised version of 3D6.
284. Prof Wisniewski’s evidence was that it would take the skilled team around three to five years to complete the experiments described above and to reach the stage of selecting the best candidate antibody to take forward. Leaving aside the fact that Prof Wisniewski thought that Dr Owen’s timescales were on the optimistic side, as I understand it, the main reason for the discrepancy between this estimate and Dr Owen’s estimate of 15 months to reach this stage is that Prof Wisniewski took into account the need for the skilled team to do experiments of the kind performed by the Elan team to identify the best candidate antibody to progress. In my judgment Prof Wisniewski’s evidence is to be preferred, supported as it is by reference to what Elan actually did.
285. As for the second aspect, this work would involve two stages. The first would be cognitive tests in mice. The second, following humanisation of the candidate antibody and toxicology, would be clinical trials in humans.
286. So far as cognitive tests in mice are concerned, Prof Wisniewski explained that these were complicated and time-consuming to carry out and interpret. As Prof Francis explained, even deciding what mouse to use for this purpose would not have been simple. In principle either the PDAPP or the Tg2576 mouse could be used, but he did not know whether there was a cognitive deficit in PDAPP mice the amelioration of which could be tested. He also said that there were significant limitations with the mouse models being used in 1997, which only became clear subsequently. Thus the mouse models failed to pick up both inflammation and a failure to improve cognition, and these problems only became apparent in the clinical trials in humans.
287. Evidence as to the results that would have been obtained is provided by a presentation by Steve Jacobsen of Wyeth Neuroscience to a joint meeting of Wyeth and Elan (as I understand it, at that time Elan was collaborating with Wyeth) dated 27 April 2004 (“Jacobsen”). This shows the results of cognitive tests that had been carried out to evaluate the efficacy of a number of antibodies targeting N-terminal, central A β and

C-terminal epitopes. Of the N-terminal antibodies, 3D6 and 10D5 were found to be the most efficacious, 12A11 was found to be somewhat effective and 2H3 and two others were found not to be efficacious. Of the central region antibodies, an antibody called 15C11 was found to be most efficacious, 266 was found to be somewhat effective, two antibodies were found to be partially effective, one was found not to be effective and results were apparently awaited for four. All four of the C-terminal antibodies, including 21F12, were found to be ineffective.

288. As to toxicology, Prof Wisniewski explained that there were a number of reasons why both the immune response and toxicity might well be greater in humans than in mice. These included that the facts that both PDAPP mice and Tg2576 mice lacked two of the four main lesions of AD and hence were more resistant to amyloid-related pathology, that transgenic mice were less likely to have auto-immune complications and low levels of toxicity were more easily missed in mice. Thus there would be a great deal of work involved in order to verify that the chosen product could be put into humans.
289. The next steps would be humanisation and formulation. Although humanisation is usually achievable, it can, in the process, alter the properties of the antibodies and destroy efficacy. Thus an effective outcome would not be guaranteed. Formulation is a routine process but would take about another three to six months.
290. Turning to clinical trials in humans, as noted above the antibody which Elan took forward was bapineuzumab, a humanised version of 3D6. A multi-centre, randomised, double-blind, placebo-controlled, multiple ascending dose Phase 2 trial of bapineuzumab was conducted by JAI in collaboration with Pfizer at 30 sites in the USA between April 2005 and March 2008. 234 patients received either bapineuzumab or placebo, in an 8:7 ratio, in one of four sequential dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg).
291. The trial did not show statistical significance for the primary efficacy endpoint in the study population as whole. In the subgroup of non-apoE4 carriers, however, clinically significant benefits were documented with a number of scales over the 18-month trial period. In addition among non-apoE4 carriers, evaluation of magnetic resonance imaging (“MRI”) results showed less loss of brain volume in treated patients versus control patients. On other hand, it was reported that an adverse effect, namely vasogenic edema (now called ARIA-E), was detected using MRI in 12/124 patients (9.7%) treated with bapineuzumab and in 0/110 (0%) with placebo. These findings were considered to support continued evaluation of bapineuzumab for AD in Phase 3 trials with consideration to possible treatment differences by apoE4 carrier status.
292. A Phase 3 trial of bapineuzumab was carried out by JAI and Pfizer between December 2007 and June 2012. This essentially repeated the design of the Phase 2 trial on a larger scale, this time with a total of 2452 patients, except that the trial was split into two arms, one for apoE4 carriers and one for non-carriers. Administration of the 2 mg/kg dose was terminated early due to amyloid-related imaging abnormalities or ARIAs.
293. The results of the Phase 3 trial were presented by Dr Reisa Sperling at the Annual Meeting of the American Neurological Association in Boston in October 2012. Dr Sperling reported that the Phase 3 study had failed to show any effect in either mild or

moderate AD patients clinically. Dr Sperling also reported the results on safety including vasogenic edema (ARIA-E) and micro-hemorrhages (ARIA-H). In the apoE4 carriers, who only received a low dose of bapineuzumab (0.5 mg/kg), the vasogenic edema rate (ARIA-E) was 15.3% (compared to 1% for controls). In the apoE4 non-carriers it was 4.2 and 9.4% in the 0.5 and 1mg/kg dosages respectively (in the control group for the non-carriers it was 0.2%). In terms of biomarkers, there was a statistically significant reduction in amyloid burden, but the effect was very small (in the order of 0.05 to 0.1%) and not likely to be physiologically significant. Slight reductions in phosphorylated tau were also noted, which looked more promising in the higher dosage group; but this group had the high complication rate.

294. Prof Wisniewski expressed the opinion that the adverse side effects, in particular the ARIA-E and ARIA-H, seen in the bapineuzumab trials were in part the result of clearance of vascular amyloid plaques by the proposed mechanism of action for bapineuzumab, namely binding of deposited amyloid leading to clearance via cell-mediated phagocytosis. This clearance may damage the already delicate vasculature suffering from CAA, causing leakiness and hence edema and haemorrhaging.
295. Be that as it may, there is no doubt that the Phase 3 trial was a failure. As a result, JAI and Pfizer announced in October 2012 that they had abandoned the development of bapineuzumab. There is no evidence before the court as to precisely how much Elan, JAI and their partners had spent on getting to that point, but there is no dispute that the sum will have run into hundreds of millions of dollars.
296. Counsel for Lilly submitted that the bapineuzumab Phase 3 trial demonstrated that the Patent was classically insufficient: despite the best efforts of the patentee and its collaborators, despite the application of a very great deal of effort for over a decade (and many person years) and despite huge expenditure, the patentee had not succeeded in making an antibody to A β which was “for use in preventing or treating a disease characterised by amyloid deposit”. As the Phase 3 trial proved, bapineuzumab was not suitable for preventing or treating AD (or any other disease characterised by amyloid deposit), because it was not efficacious (and also had unacceptable adverse effects). Accordingly, he submitted that the present case was on all fours with *Genentech/HIV vaccine*. I accept that submission.
297. Counsel for Lilly also submitted that the bapineuzumab Phase 2 trial did not support any different conclusion, for a number of reasons. First, because the Phase 2 trial did not establish efficacy with regard to the primary endpoint. Secondly, because although the Phase 2 results suggested a beneficial effect in one sub-group of patients, the claim was not confined to that sub-group but extended to the whole population of patients. Thirdly, because the subsequent Phase 3 trials were a better guide to efficacy. I accept each of these submissions.
298. *Is the claim of excessive breadth?* Lilly also contends that the Patent does not enable the skilled team to perform the invention over the whole scope of the claim. In this regard, Lilly advances two main contentions. The first is that the specification does not enable the skilled team to make suitable antibodies to A β without undue burden. The second is that some antibodies to A β are not efficacious even in mice, and indeed even in tests of the kind reported in the Patent, let alone in cognitive tests such as those in Jacobsen. For good measure, counsel for Lilly also submitted that, if the claims were construed as contended for by JAI, the claims were of excessive breadth

because the Patent covers antibodies which do not function by the mechanism proposed in the Patent and the Schenk Paper.

299. So far as the first point is concerned, JAI contends that making humanised antibodies was routine, albeit time-consuming, work for a skilled immunologist in December 1997. As discussed above, however, in order to perform the invention the skilled team needs to make a number of candidate antibodies for testing *in vivo* initially in a mouse model and ultimately in humans. It is clear from the evidence that this requires a very substantial, lengthy and costly programme of work. If substantially all the candidate antibodies proved to be efficacious, I might nevertheless conclude that the burden was not an undue one. As I shall discuss, however, that is not the case.
300. As for the second point, I have already considered the data relating to active administration of A β fragments in Example IV of the Patent. Despite this, JAI contends that there is evidence that various different antibodies to A β have an effect on the amyloidogenic component of AD by affecting total A β levels in the brain and/or reducing amyloid burden in mouse model tests. Lilly disputes this, and also disputes that this necessarily translates into any cognitive improvement in mice (as shown by Jacobsen) or humans (as shown by the clinical trials of bapineuzumab).
301. There is little dispute that N-terminal antibodies, and in particular 3D6 and 10D5, have been demonstrated to bind A β and to reduce amyloid burden in PDAPP mice. This is shown not only by Bard 1 and Bard 2, but also by two internal reports by Elan scientists. The first is a report by Peter Seubert and Dora Games dated 22 July 2003 entitled “Comparison of Immunization with AN1792 and A β 1-7MAP and Passive Immunization of 3D6 and 266” (“Seubert and Games”). As the title indicates, the authors compared active immunisation with AN1792 and an A β 1-7 immunogen with passive administration of 3D6 and 22. A significant reduction in amyloid plaque burden was found after six months’ administration of 3D6 to PDAPP mice, whereas a slight increase was found with 266.
302. The second is a report by Robin Barbour and five others dated May 2007 entitled “Efficacy of Passively Administered N-Terminal and Midregion Anti-Abeta Antibodies Alone and in Combination in the PDAPP Mouse” (“Barbour”). The authors compared the effect of administering three N-terminal antibodies, namely 3D6 (epitope A β 1-5), 12A11 (epitope A β 3-6) and 10D5 (epitope A β 3-7) with one mid-region antibody, namely 266 (epitope A β 16-23). Both 3D6 and 10D5 reduced amyloidosis as assessed by ELISA values of total cortical A β substantially in PDAPP mice. 12A11 reduced total cortical A β , but the reduction was not statistically significant. Treatment with 266 resulted in a slight increase in total cortical A β . All three N-terminal antibodies significantly decreased the amyloid burden as assessed by immunohistochemical analysis, whereas 266 did not. A similar result was obtained for neuritic burden. In addition, vascular deposits of A β were found to be cleared by 3D6, partially by 12A11 and 10D5 and not by 266.
303. The dispute concerns C-terminal and mid-region antibodies. JAI accepts that the work published in Bard 1 and Bard 2 suggests that such antibodies are not effective to reduce amyloid burden (consistently with Example IV of the Patent). JAI contends, however, that (i) the conclusions drawn in Bard 1 and Bard 2 are not supported by the underlying data and (ii) in any event those conclusions are contradicted by later work, and in particular work contained in a confidential unpublished patent application

entitled “C-Terminal and Central Epitope A-Beta Antibodies” filed by JAI (I assume in the USA) on 3 July 2012 (“the CUPA”).

304. I do not accept the first of these contentions. In my judgment the data in Bard 1 and Bard 2 is of equivalent quality to that contained in Examples I, III and IV of the Patent; the conclusions which the authors drew from that data were the patentee’s own conclusions; and those conclusions are supported by Seubert and Games and by Barbour. I turn, therefore, to consider the more recent work relied upon by JAI.
305. In relation to central region antibodies, JAI relies firstly upon Deane *et al*, “IgG-Assisted Age-Dependent Clearance of Alzheimer’s Amyloid β Peptide by the Blood-Brain Barrier Neonatal Fc Receptor”, *J. Neuroscience*, 25(50), 11495-11503 (2005) (“Deane”). This paper, which concerns an antibody called 4G8 raised to the 17-24 residues of A β , is problematic for reasons discussed below, however. In addition, there is no evidence that the 4G8 antibody has been progressed further. Dr Owen accepted that, if it has afforded an effective treatment of AD, he would have expected to have seen something about it.
306. Secondly, JAI relies upon the CUPA. Counsel for Lilly made some general submissions as the weight to be attached to this which it is more convenient to address in the context of infringement. JAI particularly relies upon the data in the CUPA relating to 266, which I shall also consider in the context of infringement. For the reasons I shall explain, I consider that less weight should be given to this than the earlier work, and in particular Elan’s own peer-reviewed publications. JAI also relies on similar data in Examples 5, 6 and 8 relating to 15C11 and 22D12, but the same applies to this data. In any event, at best, this data shows an effect in PSAPP mice, but not PDAPP mice.
307. In relation to C-terminal antibodies, JAI relies firstly on Wilcock *et al*, “Passive Amyloid Immunotherapy Clears Amyloid and Transiently Activates Microglia in a Transgenic Mouse Model of Amyloid Deposition”, *J. Neuroscience*, 24(27), 6144-6151 (2004). In this study the authors injected Tg2576 with antibody called 2286 for one, two or three months. They found that amyloid deposits were reduced after two months and Fcy expression on microglia was increased after one month. A humanised version of 2286 called ponezumab was developed by Rinat Neuroscience, which was acquired by Pfizer in 2006. Ponezumab was progressed to two Phase 2 trials which were carried out between 2008 and 2011. In November 2011, Pfizer announced that it had abandoned development of ponezumab. As counsel for JAI pointed out, ponezumab was an antibody of IgG2 isotype, and for that reason did not fall within claim 1 of the Patent. As counsel for Lilly pointed out, if the only problem with ponezumab was that it was not IgG1, it would have been a relatively straightforward matter to re-engineer it to change it from IgG2 to IgG1.
308. Secondly, JAI again relies upon the CUPA. Examples 2 and 4 purport to show that three C-terminal antibodies, 2G4, 14C2 and 21F12, bind to A β plaques in PSAPP and Line 41 mice, but not PDAPP mice, and promote microglial phagocytosis of A β plaques from such mice in an *ex vivo* assay.
309. Thirdly, JAI relies upon a paper by Stoltzner *et al*, “Temporal Accrual of Complement Proteins in Amyloid Plaques in Down’s Syndrome with Amyloid Disease”, *Am. J. Pathology*, 156(2) (2000) as supporting the CUPA in relation to

21F12. Prof Wisniewski was one of the authors of this paper, and he accepted that it was consistent with the CUPA.

310. The conclusion that I draw from the evidence as a whole is that it is not the case that all antibodies to A β are effective to reduce amyloid burden or to reduce total cortical A β levels even in the kind of tests performed in the Patent. On the contrary, at least some mid-region and C-terminal antibodies are ineffective at least in PDAPP mice. While there is some evidence to show that mid-region and C-terminal antibodies have an effect on A β plaques in PSAPP mice, which are not used in the examples in the Patent, that would simply present the skilled team with the conundrum of which tests to rely on. Still less do all antibodies to A β produce cognitive benefits even in mice. Still less are all antibodies to A β effective to prevent or treat AD (or any other disease characterised by amyloid deposit).
311. It follows, of course, that such antibodies fall outside the claim because they do not satisfy the functional requirement of being “for use in preventing or treating a disease characterised by amyloid deposit”. Furthermore, I accept that Elan discovered that 21F12, 16C11, 22D12 and 266 were ineffective in PDAPP mice before proceeding to cognition tests in mice, let alone tests in humans. By then, however, Elan had already done a considerable, and burdensome, amount of work. Furthermore, it is clear from what happened subsequently that demonstration of plaque clearance in a mouse model is no guarantee of effective prevention or treatment in humans.
312. The upshot is that the Patent does no more than invite the skilled team to perform what Prof Wisniewski rightly described as a “very significant research project with a high prospect of failure” and, if they succeed, claims the fruits of their research. It is therefore insufficient: see *Novartis AG v Johnson & Johnson Medical Ltd* [2010] EWCA Civ 1039, [2011] ECC 10 at [77].
313. In those circumstances, it is not necessary to consider Lilly’s third point, but for completeness I will do so. JAI contends that the Patent discloses a principle of general application, namely the passive administration of antibodies to A β “for use in preventing or treating a disease characterised by amyloid deposit”. Accordingly, JAI contends that it is immaterial that the claims cover antibodies that function by different mechanisms to that proposed by the Patent. If the specification enabled the skilled team to produce antibodies to A β that were effective without undue burden, I would agree with this. As discussed above, claim 1 is not limited to antibodies that function by any specific mechanism. Rather, it is limited to antibodies that are efficacious. If the specification enabled the skilled person to make efficacious antibodies without undue burden, it would be immaterial that some of those antibodies functioned by a different mechanism to that postulated in the Patent.

Infringement

314. I do not understand there to be any dispute that, if claims 1 and 5 are construed as I have construed them, then (a pharmaceutical composition comprising) solanezumab falls within them. In particular, Lilly does not dispute that (pharmaceutical compositions comprising) solanezumab are “for use in preventing or treating a disease characterised by amyloid deposit”. Lilly contends, however, that, if the expression “antibody to A β ” is construed as it contends, solanezumab is not an “antibody to A β ”. In case I am wrong on the issues of construction, I must find the necessary facts.

315. Solanezumab is described in Lilly's product description. Unusually, JAI also served a product description. Both product descriptions addressed the mechanism(s) of action of solanezumab.
316. The history of the development of solanezumab is set out in the unchallenged evidence of Dr DeMattos. Solanezumab is a humanised form of the murine 266 antibody (also referred to as "m266" and "m266.2"), the development of which goes back to before publication of the Schenk Paper. 266 was raised against residues 13-28 of the central domain of A β .
317. It is common ground that the vast majority of solanezumab in the body (about 99.88%) is found in the plasma, but a small proportion (about 0.12%) crosses the BBB. It is also common ground that that solanezumab in the plasma appears to act by binding monomeric A β , thereby altering the equilibrium of A β between the plasma and the CNS and hence reducing the amyloid burden in the brain (i.e. by the peripheral sink mechanism). This explains why administration of solanezumab causes rapid changes in plasma levels of A β (i.e. before it could have crossed the BBB).
318. The dispute is as to what effect, if any, the 0.12% of solanezumab which crosses the BBB has.

Is solanezumab specific for monomeric A β ?

319. The principal issue in this regard is whether, as Lilly contends, solanezumab is specific for monomeric A β or whether, as JAI, contends, it also binds multimeric A β including A β deposited in plaques. Between them, the parties have relied on a considerable number of published papers and other documents. I will consider first the documents relied on by Lilly in chronological order.
320. DeMattos (2001) reported that, when fixed brain sections of PDAPP mice to which 266 had been administered for five months by intraperitoneal injection were stained with an antibody that binds to mouse IgG, no staining of A β deposits was observed (page 8851 left—hand column). This suggests that either 266 does not cross the blood-brain barrier at all or it does not bind to A β plaques. Although DeMattos 2001 suggests elsewhere that 266 probably binds to dimers of A β (pages 8851-8852 and Figure 2B), Dr DeMattos explained in his second witness statement, however, that he and his colleagues had subsequently discovered that this result was an artefact of the experimental technique they had used after they had improved the technique. Prof Francis accepted that this explanation was perfectly reasonable, and in any event Dr DeMattos' evidence was not challenged.
321. As mentioned above, Bard 2 reported that 266 does not bind to A β plaques in PDAPP mice or trigger plaque clearance in the *ex vivo* phagocytosis assay. JAI's experts criticised the lack of data in this paper to support the conclusions stated, but Dr Owen agreed that the conclusions were unqualified and Prof Francis accepted that the authors would have had the data. If Elan's data did not support the conclusions, I am confident that JAI would have disclosed it but no such disclosure was given.
322. Racke *et al*, "Exacerbation of Cerebral Amyloid Angiopathy-Associated Microhemorrhage in Amyloid Precursor Protein Transgenic Mice by Immunotherapy Is Dependent on Antibody Recognition of Deposited Forms of Amyloid β ", *J.*

Neuroscience, 25(3), 629-636 (2005) (“Racke”) is a paper published by Dr DeMattos and colleagues from Lilly together with some academic collaborators. It reported that 266 does not bind to deposited A β in fixed brain sections from PDAPP mice or unfixed human AD sections (page 631 right-hand column, Figures 3 and 4). It also stated that 266 lacks the potential to localise to these sites of vessel amyloid (page 632 right-hand column). The authors concluded that “266 is a conformation-specific antibody that solely recognises soluble A β ” (page 633 right-hand column). Dr Owen agreed that these results from Lilly were consistent with those from the Elan group in Bard 2.

323. Barbour reported that “266 does not react with aggregated A β ” (page 14). Prof Francis agreed that that would have been the view that Elan’s scientists took in the light of the data they held at the time.
324. Siemers *et al*, “Role of biochemical Alzheimer’s disease biomarkers as end points in clinical trials”, *Biomarkers Med.*, 4(1), 81-89 (2010) is an article by Dr DeMattos and colleagues at Lilly. It states that 266 “is specific for soluble monomer A β ” and “the mechanism of action for m266 or solanezumab must be through changes in soluble equilibria since this antibody does not bind to the deposited forms of the peptide present in plaque” (page 83, left-hand column). Dr Owen agreed that this was a reasonable statement to make on the basis of data that he had seen.
325. Finally, Lilly relied on a report by Jirong Lu of Lilly dated April 2012 entitled “In Vitro Binding Analysis of LY2062430: Surface Plasmon Resonance and FACS Analysis” (“Lu”). Lu was produced in response to a request from the United States Food and Drug Administration to demonstrate that solanezumab (also referred to as “LY2062430”, “hu266” and “LA300A”) does not have an effector function, although the underlying data was pre-existing data. Dr Owen agreed that such requests are treated with utmost seriousness. Effector function is thought to be the cause of the vasogenic edemas and micro-haemorrhages that contributed to bapineuzumab failing, and Lu was therefore of considerable clinical and regulatory importance.
326. Lu measured the binding affinity of antibody to antigen using a technique called surface plasmon resonance (“SPR”), a widely used technique for this purpose. By calculating the ratio of antibody to antigen (ideally 1:2 for an antibody binding only monomeric antigen – a “1:1 binding model”) the specificity of the antibody for different species can be assessed. Lu showed that, in the presence of soluble monomeric A β solution, the ratio of solanezumab to soluble monomeric A β is 1:1.9, which corresponds to two monomeric A β peptides binding to a single antibody. Further, even when solanezumab is incubated with aggregated A β , it binds only to monomeric A β with a ratio of 1:1.7. Had it bound to aggregated A β to any significant degree, the ratio would have gone up above 1:2.
327. It was common ground between Prof Wisniewski and Dr Owen that there is no evidence in Lu’s data to suggest that solanezumab binds to anything other than monomeric A β . The dispute between them was whether Lu’s data excluded the possibility of solanezumab binding to oligomeric A β .
328. In his first report Dr Owen disagreed with the conclusion drawn by Lu for a number of reasons. One of these was that, if an antibody bound to multiple species with varying affinities within the sample, the software would generally fit the data to a 1:1

binding model, thus generating one stoichiometry for the species with the highest affinity. Accordingly, a species with lower binding affinity would be “ignored”. In response to this, Lilly disclosed the underlying laboratory notebooks which showed the “goodness of the fit” of the data to the binding models. As Prof Wisniewski explained in his second report, it can be seen from the curves that the solanezumab data fits well to a 1:1 binding model, and thus the antibodies are not binding to a second species. By contrast, this is not the case with hu10D5.

329. Prof Wisniewski’s evidence in cross-examination was that Lu excludes the possibility of solanezumab binding oligomers of A β beyond a reasonable doubt. He accepted that it was theoretically possible that Lu had failed to detect the antibody binding to other species with lower affinity and at low concentration, but unlikely. For his part, Dr Owen maintained that Lu did not exclude this possibility.
330. On this point I prefer the evidence of Prof Wisniewski for a number of reasons. First, he had more experience of both SPR and A β than Dr Owen. Secondly, the principal point made by Dr Owen in his evidence which counsel for JAI relied on his closing submissions was that Dr Owen had pointed out in paragraph 272 of his first report that Lu did not state whether monomeric A β was isolated from a size exclusion column for the purpose of the experiments and therefore it was possible that Lu’s “soluble monomeric A β ” had contained multimeric A β . Prof Wisniewski explained in paragraph 213 of his second report why he disagreed with this. Dr Owen did not respond to this in his third report and Prof Wisniewski’s explanation was not challenged in cross-examination. Nor was Dr Owen’s original point about the size exclusion column put to Prof Wisniewski, although Dr Owen repeated it when he was cross-examined. Thirdly, I find Prof Wisniewski’s evidence more convincing overall.
331. JAI relies on three documents. Again I shall consider these in chronological order.
332. First, DeMattos (2001) stated that, when 266 was applied to brain sections from PDAPP mice in an *ex vivo* assay, A β deposits were detected. The paper does not include any experimental data to support this statement. Dr DeMattos accepted that the statement must have been correct in the sense that exogenous staining of A β plaques was seen. He did not recall whether appropriate controls were used, however, and no longer had access to the relevant laboratory notebooks. More importantly, the exogenous staining was used as a control for the peripheral administration experiments. In those experiments Dr DeMattos and his colleagues found no evidence of 266 binding to A β in peripherally treated mice. Still more importantly, Dr DeMattos said that this was a very limited study in relation to binding of A β deposits by 266 and that his team’s later binding studies reported in Racke were significantly more rigorous, with appropriate positive and negative controls. In those studies the binding of 266 to deposited forms of A β was indistinguishable from the negative controls.
333. The second document is an internal JAI presentation by a JAI scientist called Chris Nishioka in November 2011 entitled “Anti-A β antibody panel test: Potency in oligomer binding assay” together with some laboratory notebook pages evidencing Mr Nishioka’s work (“Nishioka”). This study used the same method as a paper which was published subsequently, Zago *et al*, “Neutralization of Soluble, Synaptotoxic Amyloid β Species is Epitope Specific”, *J. Neuroscience*, 32(8), 2696-2702 (2012).

334. It is common ground that Nishioka shows that 266 blocks the binding of soluble oligomeric A β to rat hippocampal neurons. The question is whether it shows that 266 binds to oligomeric A β . It is known that soluble oligomeric A β binds to neurons. The experiment proceeds on the theory that, if the binding of soluble A β oligomers to neurons decreases on addition of 266, that must be due to 266 blocking the binding of the oligomers. As is common ground, however, the experiment is an indirect one. It was also common ground between Prof Wisniewski and Prof Francis that, due to the method of preparation, there would be monomer present in the oligomer mixture.
335. Prof Wisniewski's evidence was that Nishioka does not indicate that there is any direct interaction between 266 and oligomers because 266 could equally be binding to monomers and shifting the equilibrium so as to reduce the presence of oligomers. Prof Francis accepted that the results could be explained by a shift in equilibrium if the kinetics of the dissociation were such that oligomers could dissociate in the time available, and admitted that he did not know whether that was so or not. Again, I prefer Prof Wisniewski's evidence on this point.
336. The third document is the CUPA. Counsel for Lilly submitted that the CUPA was effectively an unwitnessed experiment, and accordingly it should be given no weight. I do not accept this submission. There is no reason to doubt that the CUPA is what it appears to be, namely, a patent application filed by JAI in the ordinary course of its business as a result of research carried out by JAI's scientists. It follows that the experiments it records are not subject to constraints imposed on experiments conducted for the purposes of litigation. Counsel for Lilly also submitted that the weight to be attached to the experiments was affected by the fact that, unlike in the case of Lu and Nishioka, JAI had not disclosed the relevant laboratory notebooks. This submission has particular relevance for reasons that will appear, and I accept it. It is immaterial that Lilly did not specifically request such disclosure.
337. Example 5 and Figure 6 of the CUPA are said to show that 266 binds to A β plaques in unfixed AD brain sections. Example 6 and Figure 7 are said to show that 266 binds to A β in PSAPP mice (another type of transgenic mouse), but not in PDAPP mice. Example 8 and Figures 9 and 10 are said to show that 266 promotes microglial phagocytosis of A β plaques from PSAPP mice, but not PDAPP mice, in an *ex vivo* assay.
338. Prof Wisniewski's evidence was that the results presented in the CUPA were not reliable for three main reasons: there was no quantitative data, but only individual images; there was a lack of negative controls in Examples 5 and 8; and accordingly the results might be due to non-specific sticking of the antibodies to amyloid deposits.
339. So far as the first point is concerned, Prof Wisniewski explained in his first report that sequential sections (Figure 9) and a full Z stack of images (Figure 10) were required to enable proper conclusions to be drawn. If JAI had further images which demonstrated that Prof Wisniewski's criticisms were unfounded, it would have been a simple matter for JAI to produce them. It did not. I can only conclude that either it did not have the images or they did not assist its case. Counsel for JAI submitted that Prof Wisniewski had applied an inconsistent approach to Racke, but Racke did include some sequential sections and negative controls. Furthermore, Racke was a peer-reviewed paper and it is likely that the reviewers would have been given access to more images than were included in the paper.

340. I do not understand the second point to be disputed. Rather, JAI contends that the lack of negative controls would only be a concern if the other two points were well-founded.
341. As for the third point, Prof Wisniewski's evidence was that A β plaques were notoriously sticky, something that he not only had personal experience of, but also was mentioned in the literature. He explained that this could give rise to misleading results unless extra caution was taken. Somewhat surprisingly, Prof Francis was not aware that A β plaques were sticky.
342. Overall, Prof Wisniewski's opinion was that he would not approve the publication of this data in peer-reviewed journal and that it was not possible to draw any conclusions from it. Prof Francis said that he would like more information to be confident of the interpretation placed on the data by the authors and agreed it would be required for publication in a high-impact journal. Accordingly, I consider that less weight should be given to the CUPA than the earlier work, and in particular Elan's own peer-reviewed publications.
343. Taking all the evidence into account, my conclusion is that solanezumab is specific for monomeric A β and does not bind to any appreciable extent to A β plaques.

Does solanezumab which crosses the BBB induce any downstream effects?

344. The next question is whether solanezumab which crosses the BBB induces any downstream effects, and in particular Fc-mediated phagocytosis. Dr Owen accepted that, if solanezumab is specific for monomeric A β , then monomers of solanezumab would have no effector function, and in particular would be very unlikely to activate Fc receptor- or complement-mediated phagocytosis. He nevertheless suggested that aggregated solanezumab could be present in small quantities which would have such functions. He accepted, however, that he had no evidence that aggregated solanezumab was present (let alone that it crossed the BBB). Although information about this would be contained in the chemistry manufacturing control package for solanezumab, he had not asked to see that package. Furthermore, he accepted that he had no idea whether aggregated solanezumab would have any therapeutic effect. Accordingly, I conclude that solanezumab which crosses the BBB does not induce any downstream effects.

Does solanezumab affect the equilibrium in the brain?

345. JAI contends that solanezumab which crosses the BBB binds to monomeric A β so as to affect the equilibrium between monomeric A β and plaque A β in the brain. In support of this contention, JAI relies on Yamada *et al*, "A β Immunotherapy: Intracerebral Sequestration of A β by an Anti-A β Monoclonal Antibody 266 with High Affinity to Soluble A β ", *J. Neuroscience*, 29(36), 11393-11398 (2009) ("Yamada"), a paper by Dr Schenk and a colleague from Elan with some academic collaborators. In order to test the peripheral sink hypothesis, the authors studied the clearance of radio-labelled A β 1-40 microinjected into mouse brains after intraperitoneal administration of 266. Radio-labelled A β 1-40 was rapidly eliminated from brains with a half-life of about 30 minutes in control mice, whereas 266 significantly retarded the elimination of radio-labelled A β 1-40. The authors also found evidence that 266 entered the brain and bound radio-labelled A β .

346. Prof Wisniewski's evidence was that Yamada could not be relied on to show what would normally happen, because the authors had microinjected the A β into the brain and therefore compromised the BBB. Prof Francis relied on Kakee *et al*, "Brain Efflux Index as a Novel Method of Analyzing Efflux Transport at the Blood-Brain Barrier", *J. P. E. T.*, 277(3), 1550-1559 (1996) ("Kakee") as suggesting that microinjection would not have this effect. Prof Wisniewski said that it was not clear whether Yamada had faithfully followed the technique of Kakee, but accepted that if it had this was less of an issue. On the other hand, he said that there was evidence of excessive breakdown of the BBB in Yamada. Prof Francis agreed that the extent of breach of the BBB caused by the microinjection technique used in Yamada depends on the precision with which it is carried out, and will vary from injection to injection, investigator to investigator, and with the speed and volume of injection and size of animal. Accordingly, he agreed that it was possible that the results in the paper were an artefact of the experimental technique.
347. Even if the results in Yamada are reliable, there was a dispute as to whether the amount of solanezumab which crosses the BBB would be sufficient to have a significant effect on monomeric A β in the brain. Prof Francis calculated that the amount of A β monomer bound to 266 as about 35% of A β 1-40 monomer in the brain or about 70% of total monomeric A β 1-42. By contrast, Prof Wisniewski calculated that about 6.4% of total A β 1-40 in the brain and about 20% of total A β 1-42 was bound. Prof Wisniewski said that the fraction of the total pool was the most physiologically relevant figure because it was the total pool that was potentially available for binding even though 266 only bound monomers. Prof Francis disagreed with this. Although at first blush Prof Francis's calculation appears more logical, I find Prof Wisniewski's reasoning more persuasive, because the question is not whether solanezumab can bind to monomeric A β . The question is whether it can thereby affect the equilibrium between monomeric and multimeric A β , and thereby A β plaques. For that purpose, it seems to me that the proportion calculated by Prof Wisniewski is more relevant.
348. The conclusion I reach is that solanezumab does not have a significant effect by virtue of binding monomeric A β in the brain.

Does solanezumab induce FcRn-mediated clearance?

349. JAI relied on Deane as showing that clearance of 4G8/A β complexes from the brain was mediated by the FcRn, and hence as showing that the same mechanism could occur with solanezumab. Like Yamada *et al*, Deane *et al* injected radio-labelled A β and antibody into the brains of mice. The authors found that 120 hours after administration of 4G8 the efflux of radio-labelled A β 1-40 was substantially increased compared to 1 hour after administration. They also investigated the possible mechanisms for this using transgenic mice that did not express FcRn. They concluded that there were two possible mechanisms in play, the peripheral sink mechanism and FcRn-mediated clearance.
350. Prof Wisniewski's evidence was that this conclusion was not reliable because the experiments were flawed in a number of respects: they used direct injection techniques which compromised the BBB and knockout mice which might have compensation mechanisms. Most importantly, the experiments depended upon the comparison between the efflux rate at 1 hour and 120 hours, but the authors had used

different amounts of 4G8 in the two runs. Dr Owen accepted that there were flaws in the experiment, and in particular that it was difficult to compare the position at 1 hour and 120 hours because of the different amounts used.

351. In addition, it was Prof Wisniewski's evidence that a later paper by Abuqayyas and Balthasar, "Investigation of the Role of Fc γ R and FcRn in mAb Distribution to the Brain", *Mol. Pharmaceutics* (2012) contradicted the conclusion reached in Deane, although as he acknowledged these authors also used knockout mice. Dr Owen's answer to this was to say that there was additional data in Deane from an *in vitro* experiment, but he accepted that that was not quantitative and provided no basis for saying that there was a significant mechanism *in vivo*.
352. In any event, as Dr Owen accepted, unlike 266, 4G8 is directed to a different epitope which is visible when A β is in multimeric form. It follows that 4G8 may have effects that 266 and solanezumab do not.
353. I conclude that there is no reliable evidence that solanezumab induces FcRn-mediated clearance of A β from the brain.

Summary of main conclusions

354. For the reasons given above, I conclude that:
- i) the Patent is not invalid on the ground of added matter;
 - ii) claim 1 is novel over Konig;
 - iii) claim 1 is not obvious over Konig or Becker or on *Agrevo* grounds;
 - iv) the Patent is invalid on the ground of insufficiency; and
 - v) if the Patent were valid, Lilly would infringe claims 1 and 5.