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Clearing the fog:

Patenting trends for the treatment of Alzheimer's disease.

What can Network Patent Analysis tell us about developments in the treatment of this crippling condition?

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A unique perspective on Alzheimer's treatments

Alzheimer's is a major disease affecting the elderly

In response, the pharmaceutical industry has invested heavily in developing new treatments. But which treatments are receiving the most attention? More than 48,000 patents filed globally for the treatment of Alzheimer's disease have been analysed using Network Patent Analysis (NPA) to show:

- **What are the most popular innovations in the treatment of Alzheimer's?**
- **Who owns the leading patents?**
- **Who are the leading inventors?**
- **In which direction is the field heading?**

Inside

Shining a new light on Alzheimer's

Patents filed for the treatment of Alzheimer's disease have been analysed by Network Patent Analysis (NPA™). NPA is a unique patent analysis method that maps the 'collective intelligence' of the patent applicants to categorise and rank patents, technologies and patent applicants. By doing so, NPA provides a unique insight on the patent and technology strategies of the companies developing treatments in this area. The purpose of this marketing study was to apply NPA to provide a powerful overview of an otherwise complex area.

Understanding Alzheimer's

Alzheimer's disease refers to a progressive degenerative illness that affects the brain, resulting in memory impairment and other symptoms. While Alzheimer's can occur in people as young as 40, the prevalence increases with age, with up to one in four aged 85 and above suffering from this condition[1]. There are now thought to be more than 35 million sufferers worldwide, and this is expected to increase to 115 million by 2050[2]. Besides affecting sufferers and those who care for them, Alzheimer's also imposes a cost of more than $604 billion worldwide[3]. In the US, Alzheimer's is claimed to be the third most economically important disease[4], and the sixth largest cause of death[5].

Alzheimer's disease is thought to be caused by changes in nerve cells that then cause the death of brain cells. Research into treatment for Alzheimer's[6] tends to be focused on one or both of two proteins. The first of the proteins is *beta amyloid*, which is known to form the main component of deposits found in the brains of Alzheimer's sufferers. The second protein is the *tau* protein, which is an important chemical in the brain.

Unlike the other leading causes of death, no proven cure, prevention or means of slowing Alzheimer's disease has been found to date[7]. Some medicines are thought to reduce the symptoms, and various psychosocial interventions are being considered[8].

The leading first-named inventor in this analysis is Dr Dale B. Schenk, Elan's Chief Scientific Officer, who among other accolades has won an award for being a 'rock star of science' for his work on Alzheimer's. **See page 20.**

What you need to know

A patent search for Alzheimer's patents identified around 48,000 patents. NPA identified the leading 2153 patents in these 48,000 patents, and grouped most of these 2153 patents into 23 subject clusters. The 23 clusters of patents formed into two major groupings:
1) Drugs targeted to the beta amyloid protein ('**Amyloid Grouping**', and comprising 39% of the leading 2153 patents), and
2) Drugs targeted to the Tau and serotonin and other alternative pathways ('**Tau Grouping'**, comprising 33%).

The leading subject clusters in each of these two groupings were 'Peptides and antibodies targeting β amyloid' in the Amyloid Grouping (329 patents), and 'GSK-3 – Tau fibrillation inhibition/Hormonal and kinase inhibitory mechanisms' in the Tau Grouping (304 patents).

Other clusters in these two groupings were connected to either of these two main clusters. There were also 606 'broker patents', namely patents that were not sufficiently similar to other patents to form into any of the clusters, but which may have a role in connecting disparate technologies.

Filing activity for the 2153 strongest patents peaked between the year 2000 and 2005, with a double peak of filing activity for the Amyloid Grouping (around the year 2000 and then around the year 2005). Combined with the broad range of subject matter for the patent clusters, this suggests that Alzheimer's treatments are still undergoing strong development. This seems appropriate when we consider that there is still no proven successful treatment or cure for Alzheimer's.

The highest ranked patent out of the 48,000 patents reviewed was US 7189819, which appeared to protect the stage III (trial) Pfizer/Elan/Johnson & Johnson drug bapineuzumab, and which had been litigated up the US Federal Circuit by the patent applicant to successfully obtain an increase in its patent term. Similarly, the Eli Lilly stage III drug solaneuzumab was protected by the 14th highest ranked patent, US 7195761.

Pfizer has the strongest patent portfolio, combining a range of patents in both the Amyloid and Tau Grouping. Other strong patent owners in the Amyloid Grouping include Irish-based Elan Pharmaceuticals (both alone and together with Pfizer, Johnson & Johnson or Eli Lilly), Merck, and GlaxoSmithKline. The Tau Grouping is led by Pfizer, along with GlaxoSmithKline and Vertex Pharmaceuticals.

Many of the most highly ranked patents revealed in this study referred to the development of drugs for multiple diseases. In many of these patents, treatment of Alzheimer's was claimed or mentioned as only being a possible application or even of secondary importance. This may be because pharmaceutical companies often develop drugs for a particular biological target (rather than a specific disease) whose regulation may be important in the treatment of several disease states.

Why Network Patent Analysis?

The development of a unique tool

A patent offers inventors or their employers a limited monopoly in return for publishing new inventions. Over the years, the patent system has been so successful at encouraging publication of new inventions that there are now tens of millions of patent publications. While the patent publication system is relatively organised and accessible within both public and commercial databases, the sheer quantity of published patents can quickly overwhelm patent analysts. More than 1.9 million patent applications are now added every year to the more than 60 million published patents.

The need to improve the way patents are searched and reviewed has recently led to the development of Network Patent Analysis (NPA) by Ambercite®. NPA is an innovative method of answering the question: *which patents and technologies are the most valuable in a particular area?*

NPA does this by grouping and ranking patents within specific technology areas. NPA can be regarded as a 'popularity contest' for patents, with the 'votes' in this contest being indirectly cast by patent owners and examiners, who should have a reasonable understanding of the field in question. Accordingly, NPA can harness the *collective intelligence* of patent owners and examiners. This collective intelligence should be worth harnessing, as a decision to file a patent is an economic signal by the applicant that they think the invention being patented has value. This is analogous to the housing market, where a large number of individual house-buying decisions combine to form a collective opinion on the most desirable suburbs and houses.

NPA provides valuable patent insight

For a patent to be granted, it needs to be 'novel' and 'inventive'. To determine whether a patent is novel or inventive, patent examiners and applicants identify the most similar and earlier patents (and other publications) to the claimed invention. Earlier patents are known as *backward citations* or *prior art*. Similarly, any later patent that refers to a patent being reviewed is known as a *forward citation*. Backward and forward citations are known to be important in patent analysis, and many leading patent databases carry comprehensive information on backward and forward citations.

NPA applies special algorithms to forward and backward citation data to group patents together into clusters and networks of patents of similar subject matter. Other algorithms are used to calculate the importance of individual patents within these clusters, and this importance is used to determine the relative influence of patents (and by extension the invention disclosed in the patents) compared to similar inventions. Results can be shown in a visually insightful manner as well as presented in spreadsheet form.

See the whole patent landscape: the full Alzheimer's treatment patent landscape map can be found at www.griffithhack.com.au/NetworkPatentAnalysis-Reports

The power of associative searching

Table 1: Distribution of patents analysed in this Alzheimer's NPA study.

Patent kind code	US	EP (European patents)	WO (International patent applications)	Other	All patents
Application (A)	7738	3579	14,106	7977	33,400
Grant (B)	7322	3027	–	1908	12
All other patent kind codes	–	–	–	2482	2500
Total number of patents	15,078	6606	14,111	12,367	48,162
Average filing year	2003	2000	2003	2001	2002

Patent searching

A comprehensive yet focused patent search is the heart of any NPA study. In this study we employed a two-stage search process, as outlined.

Step 1: Traditional patent search

We searched for all patents using a combination of keywords and International Patent Classification (IPC) marks, namely a search for patents that had either:

- The keyword of *Alzheimer** in the title, or
- *Alzheimer** in the title, claims or abstract, and had an IPC[9] mark of A61P 25/28.

Altogether this produced 24,072 patents, which we will call the 'starting patents'.

Step 2: Associative patent search

Experience has taught us that no keyword or IPC patent search is perfect. Technical terms for similar concepts can vary between patent owners, and IPC marks can be imperfectly assigned by patent examiners. This means that relevant patents may be missed by the patent search.

However, any potentially influential patents that have been missed by the IPC class or keyword are likely to be cited by at least one of the examiners or owners of the patents located in the traditional keyword/IPC mark search. For this reason, we include all citationally-linked patents into the patent data set, which we refer to as an 'associative search'.

By using associative searching, we are drawing upon the collective effort of all the patent examiners or owners who have searched for and listed citations for any of the starting patents. When using a combination of traditional and associative searching, the odds of missing an influential patent should be very low.

In this particular study, many of the citationally-linked patents were not directly relevant to Alzheimer's disease and had the potential to expand the subject matter well beyond the treatment of Alzheimer's disease. To maintain our focus on the treatment of Alzheimer's disease, we applied a filter over these additional citationally-linked patents – namely, that to remain in the patent data set, they had to meet either of these conditions:

- Any of the keywords of *Alzheimer*, dementia*, senile, senility or neurodegen** anywhere in the searchable text fields (title, abstract, claims or description), or
- Indexed to the IPC marks A61P 25/28.

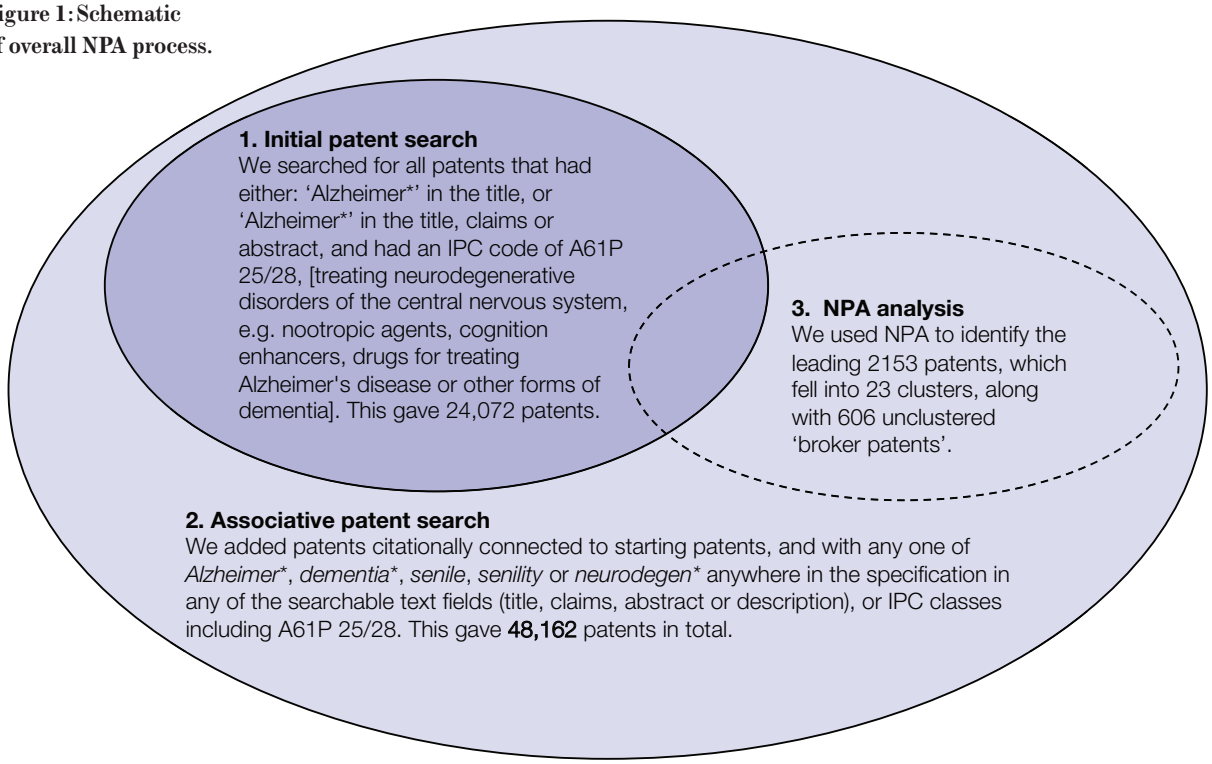
This associative search added 24,090 patents, which brought the total number of patents in the dataset up to 48,162. Table 1 above gives an overview of these patents, and shows that:

- The leading source of patents was from the US (representing 25% of the dataset).
- The average filing year was 2002.
- The US and EP patents were relatively evenly split between patent applications and granted patents.

These 48,162 patents were used to prepare an NPA patent landscape map using the algorithms developed by Ambercite.

Grouping and ranking patents

Figure 1: Schematic of overall NPA process.



Identification of leading patents

While NPA can analyse up to hundreds of thousands of patents, in practice we tend to focus on a limited number of patents for the following reasons:

- Not all patents have strong citation relationships to other patents. This may be because they have been very recently published, or because citation relationships have not been published or recorded in the patent databases that we access.
- Even for those patents with published citation relationships, the degree of interconnectedness with other patents can be low. NPA analyses patents according to their interconnectedness with other patents, working on the assumption that if a patent (or the underlying invention or description) is of high importance, other patent applicants or examiners will file similar patents, and this will be recognised in prior art search reports.
- There is a practical limit to how many patents can be displayed on an NPA map before the map starts to lose definition.

Around 1000 to 3000 patents is about optimal for an NPA patent landscape study. In this study, we focused on the leading 2153 patents, or just under 5% of the 48,162 patents in our dataset. These 2153 patents are the most influential and connected patents within the dataset.

As will be further discussed in the next section, these 2153 leading patents formed into 23 clusters, along with 606 patents that did not fall significantly into any one cluster, which we call *broker patents*. Each cluster contains patents of a common subject matter, typically being related to the mechanism of action (biological target), the class of drug or the disease class being treated.

NPA can group patents into clusters, but cannot by itself identify the common subject matter of the cluster. Instead it is necessary to identify the common subject matter by manually reviewing the title and abstracts of a selection of the highest ranked patents in each cluster, focusing on the highest rated patents in each cluster, and identifying the common themes. This process is performed by subject matter experts in the area of the study.

Schematic of the overall NPA process

The process of firstly forming the patent data to be analysed, and then focusing on the highest ranked patents, is summarised in Figure 1.

Alzheimer's treatments: the big picture

Patent clusters and their subject matter

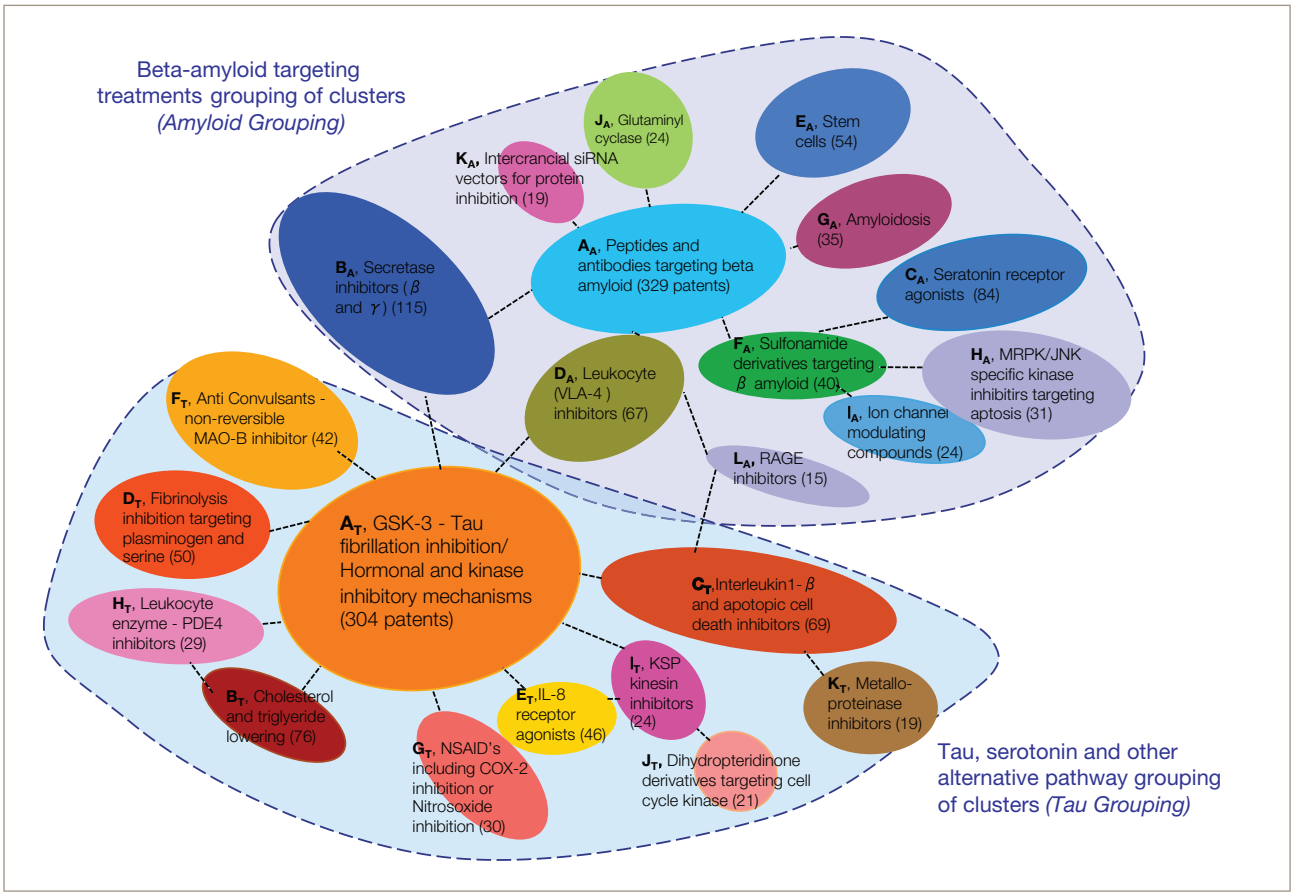
NPA identified 23 clusters of patents, see Figure 2. These clusters in turn (when considering citations between the different clusters) formed into two grouping of clusters. The first grouping targeted beta-amyloid and its associated pathways, with the second groups targeting alternative pathways, including Tau and serotonin pathways. These two groupings appear to substantially represent the different overall approaches to Alzheimer's treatment.

The patent citation connections between the 23 clusters, and between the two groupings, are represented by the dotted lines joining the clusters together.

Further details of these clusters are provided in Table 2 (page 8) and Table 3 (page 9), which also show the leading patent in each cluster.

The first grouping targeted beta-amyloid and its associated pathways, with the second groups targeting alternative pathways, including Tau and serotonin pathways. These two groupings appear to substantially represent the different overall approaches to Alzheimer's treatment.

Figure 2: Patent clusters in Alzheimer's treatments.
Within each grouping, the cluster A has the most patents, followed by the cluster B, and so on.



Leading Amyloid Grouping patents

Table 2: Details of clusters found in the 'Amyloid targeting treatment' grouping of clusters (hereafter *Amyloid Grouping*). Each cluster letter has a suffix 'A' to indicate that it belongs to the Amyloid Grouping.

Cluster name (number of patents in cluster)	Top-ranked patent in cluster (overall NPA position)	Title of top-ranked patent	Current (ultimate) owner(s) of top-ranked patent	Proportion of patents from original query
A_A, Peptides and antibodies targeting β-amyloid (329)	US 7189819 (1)	Humanized antibodies that recognise beta amyloid peptide	Elan Pharmaceuticals / Johnson & Johnson/ Pfizer	37%
B_A, Secretase inhibitors (β and γ) (115)	US 7700603 (84)	Heterocyclic aspartyl protease inhibitors	Merck/Ligand	35%
C_A, Seratonin receptor agonists (84)	US 7402590 (75)	Spiroazacyclic compounds as monoamine receptor modulators	Acadia Pharmaceuticals	17%
D_A, Leukocyte (VLA-4) inhibitors (67)	US 7741328 (230)	Heteroaryl, heterocyclic and aryl compounds which inhibit leukocyte adhesion mediated by VLA-4	Elan Pharmaceuticals / Johnson & Johnson	42%
E_A, Stem cells (54)	US 7604993 (246)	Combined regulation of neural cell production	Stem Cell Therapeutics Inc.	19%
F_A, Sulfonamide derivatives targeting β-amyloid (40)	US 6657070 (154)	Production of chirally pure α-amino acids and N-sulfonyl α-amino acids	Pfizer	30%
G_A, Amyloidosis (35)	US 7598269 (310)	Methods and compositions for treating amyloid-related diseases	Bellus Health (Int.) Ltd	20%
H_A, MRPK/JNK specific kinase inhibitors targeting aptosis (31)	US 7863289 (278)	Compounds and methods for kinase modulation, and indications therefore	Plexxikon Inc.	10%
I_A, Ion channel modulating compounds (24)	WO 2000051981 (437)	Aminocycloalkl cinnamide compounds for arrhythmia and as analgesics and anesthetics	Cardiome Pharma	13%
J_A, Glutaminyl cyclase (24)	WO 2004098591 (387)	Inhibitors of glutaminyl cyclase and their use in the treatment of neurological diseases	Probiodrug AG	25%
K_A, Intercrancial siRNA vectors for protein inhibition (19)	US 7829694 (131)	Treatment of neurodegenerative disease through intracranial delivery of siRNA	Medtronic, Inc	16%
L_A, RAGE inhibitors (15)	US 6613801 (455)	Method for the synthesis of compounds of formula I and their uses thereof	Transtech Pharma	27%
All Amyloid Grouping patents (837 patents, or 39% of the top ranked 2153 patents)	*US 7189819 (1)*	*Humanized antibodies that recognise beta amyloid peptide*	Elan Pharmaceuticals / Johnson & Johnson/ Pfizer	30%

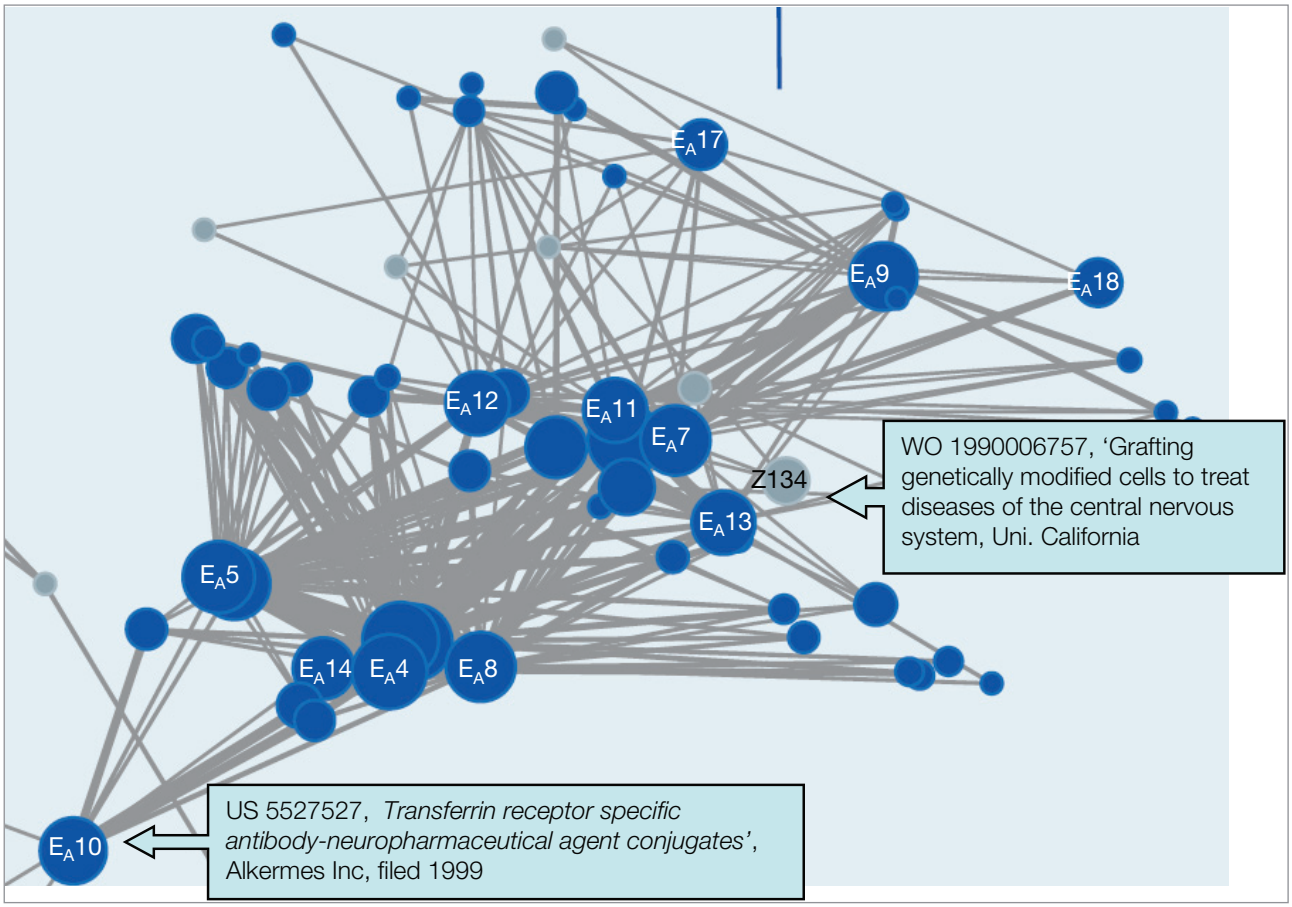
Leading Tau Grouping patents

Table 3: Details of clusters found in the 'Tau, serotonin and other alternative pathways' grouping of clusters (hereafter *Tau Grouping*). Each cluster letter has a suffix 'T' to indicate that it belongs to the Tau Grouping. The top-ranked broker patents are also listed.

Cluster name (number of patents in cluster)	Top-ranked patent in cluster (overall NPA position)	Title of top-ranked patent	Current owner of top-ranked patent
A_T, GSK-3 – Tau fibrillation inhibition/Hormonal and kinase inhibitory mechanisms (304)	US 7531536 (62)	Pyrazole compounds useful as protein kinase inhibitors	Vertex Pharmaceuticals
B_T, Cholesterol and triglyeride lowering (76)	US 7192944 (98)	Substituted azetidinone compounds, processes for preparing the same, formulations and uses thereof	Merck
C_T, Interleukin1-β and apotopic cell death inhibitors (69)	WO 1995035308 (363)	Inhibitors of interleukin-1 'beta' converting enzyme	Vertex Pharmaceuticals
D_T, Fibrinolysis inhibition targeting plasminogen and serine (50)	US 7163954 (97)	Substituted naphthyl benzothiophene acids	Pfizer
E_T,IL-8 receptor agonists (46)	US 6903131 (166)	3,4-di-substituted maleimide compounds as CXC chemokine receptor antagonists	Merck/Ligand
F_T, Anti Convulsants – non-reversible MAO-B inhibitor (42)	US 5877218 (361)	Compositions containing and methods of using 1-aminoindan and derivatives thereof and process for preparing optically active 1-aminoindan derivatives	Teva Pharmaceuticals
G_T, NSAID's including COX-2 inhibition or Nitrosoxide inhibition (30)	US 6297260 (417)	Nitrosated and nitrosylated nonsteroidal anti-inflammatory compounds, compositions and methods of use	Nicox S.A.
H_T, Leukocyte enzyme – PDE4 inhibitors (29)	US 7405230 (505)	Phosphodiesterase 4 inhibitors, including N-substituted aniline and diphenylamine analogs	Memory Pharmaceuticals
I_T, KSP kinesin inhibitors (24)	US 7009049 (338)	Syntheses of quinazolinones	Cytokinetics, Inc.
J_T, Dihydropteridinone derivatives targeting cell cycle kinase (21)	WO 2003020722 (495)	Novel dihydropteridinones, method for producing the same and the use thereof as medicaments	Boehringer Ingelheim Pharmaceuticals
K_T, Metalloproteinase inhibitors (19)	US 7354940 (410)	2,5-dioxoimidazolidin-4-yl acetamines and analogues as inhibitors of metalloproteinase mmp12	AstraZeneca AB
All Tau Grouping patents (710, or 33% of the 2153 top-ranked Alzheimer's patents)	US 7531536 (62)	Pyrazole compounds useful as protein kinase inhibitors	Vertex Pharmaceuticals
Broker patents (606 patents, 28%)	US 7906625 (71)	Humanized anti-amyloid antibody	Amgen, Inc

Anatomy of a patent cluster

Figure 3: Details of the E_A, stem cells patent cluster.



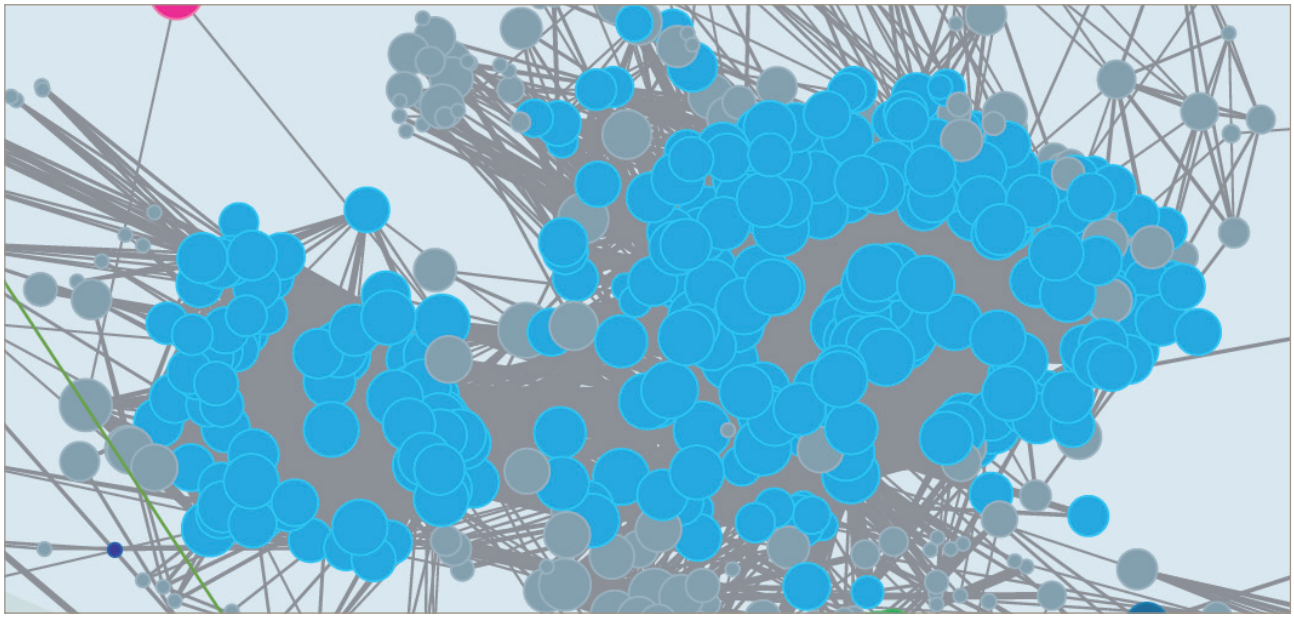
An example of a cluster is shown in Figure 3, which shows the detail of cluster E_A, 'Stem cells'. Some of the patents (blue dots, or 'nodes') are shown with a notation system (such as 'E_A5') that allows their details to be looked up in an accompanying spreadsheet showing the patents analysed in this study.

There are 54 patents in this particular cluster. The larger the node in Figure 3, the higher ranked in the patent. There are also some grey nodes, which show unclustered or 'broker' patents. In the notation system that we use, E_A10 refers to the 10th ranked patent in cluster E_A, while Z134 refers to the 134th ranked broker patent.

Patent E_A10, or US patent 5527527, is of particular interest because it connects this cluster to patents in other clusters.

This is the first NPA study performed by Griffith Hack and Ambercite in which the majority of the clusters have been dominated by patents in the last decade.

Figure 4: Details of the A_A 'Peptides and antibodies' patent cluster.



Patent clusters come in different forms. For example, the largest cluster A_A has its 329 patents spread in a fairly non-structured way (as seen in Figure 4), suggesting that there are no key connecting patents

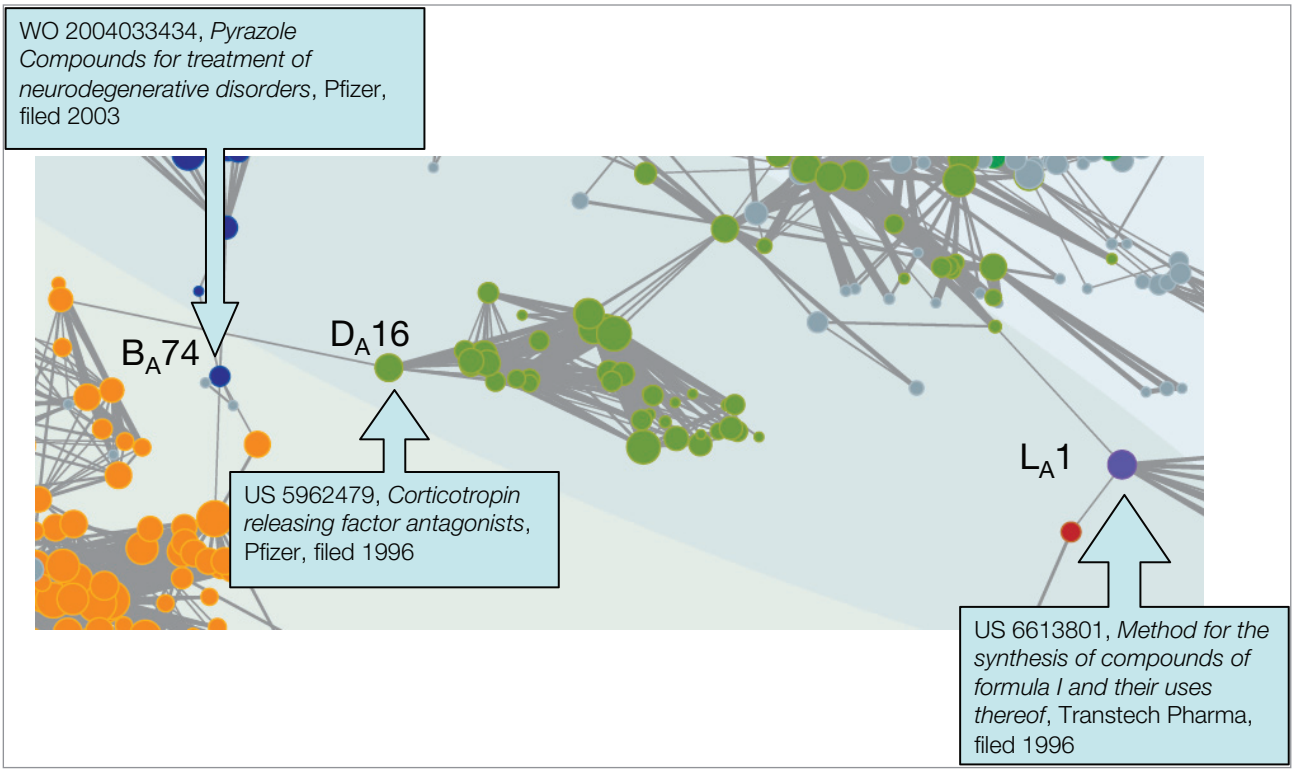
Why are patent clusters important?

A cluster shows an area of significant patent filing focus. Patents cost money to file, and the research and development needed to come up with new inventions can be costly as well. Hence a decision to file even just a single patent can be a costly investment. A number of patents filed in an area can show:

- This particular area has economic value, something to justify the expenditure in research and development and then patent filing.
- The problem that each patent (and underlying invention) is trying to solve hasn't been solved yet. If it had, there wouldn't be significant investment in these areas.

Connecting Amyloid and Tau

Figure 5: Three key patents that connect the Amyloid and Tau groupings of drug patents.



The distinct difference between the two main groupings suggests there are very few treatments that work on both the Amyloid and Tau mechanisms.

How were the two groupings of clusters connected?

The overall cluster diagram shown in Figure 2 revealed that there are only three connections between the Amyloid and Tau groupings. When we look at these connections in detail, each connection comes down to a single and potentially influential patent.

These patents are shown in Figure 5. These patents are important because they imply treatment options that cover one or multiple treatment pathways. These patents may have a closer affinity to a particular treatment by mechanism of action or class of compound or both.

For early development molecules or where the treatment pathway may cover more than one disease state, the patent may not fit into a particular cluster. These can become the broker patents or the main connecting patents within a cluster.

Clustering knowledge

What does NPA cluster analysis tell us about Alzheimer's treatments?

- There is a wide range of treatments being patented. Each of the 23 discrete clusters appeared to be related to a different treatment pathway.
- The leading cluster in the Amyloid Grouping was *Peptides and antibodies targeting beta amyloid*. This cluster was dominated with patents associated assigned to Elan, either by itself or together with one or more of the subsidiaries of Pfizer, Johnson & Johnson and Eli Lilly for monoclonal antibody therapies.
- The leading cluster in the Tau Grouping was *GSK-3 – Tau fibrillation inhibition/Hormonal and kinase inhibitory mechanisms*.
- These two dominant groups were joined via smaller clusters, such as the clusters B_A: *Secretase inhibitors* (β and γ), D_A: *Leukocyte (VLA-4) inhibitors*, and L_A: *RAGE inhibitors*.
- The majority of clusters had average filing years later than 2000, indicating that many key patents have only been filed recently. This is the first NPA study performed by Griffith Hack and Ambercite in which the majority of the clusters have been dominated by patents in the last decade. This suggests a lot of recent activity in the area of Alzheimer's treatments. However, it may take many years for these inventions to achieve regulatory approval.
- There were also 606 *broker patents*. Broker patents are those that were not sufficiently similar to other patents to form into any of the clusters, but which may have a role in connecting disparate technologies, hence their title. Broker patents should be considered in the light of the technologies that they join.
- The dominance of an NPA patent map by large and central clusters tends to be a typical outcome for an NPA study. Most areas of technology are dominated by a pivotal collection of inventions around a technology platform. However, this is the first study in which we have seen two such groupings, suggesting that there is still no dominant treatment mechanism.
- The distinct difference between the two main groupings suggests there are very few treatments that work on both the Amyloid and Tau mechanisms. Conversely, this also suggests that there may be scope to develop treatments that work on both mechanisms.

Which patents led the Amyloid and Tau Groupings?

Amyloid Grouping

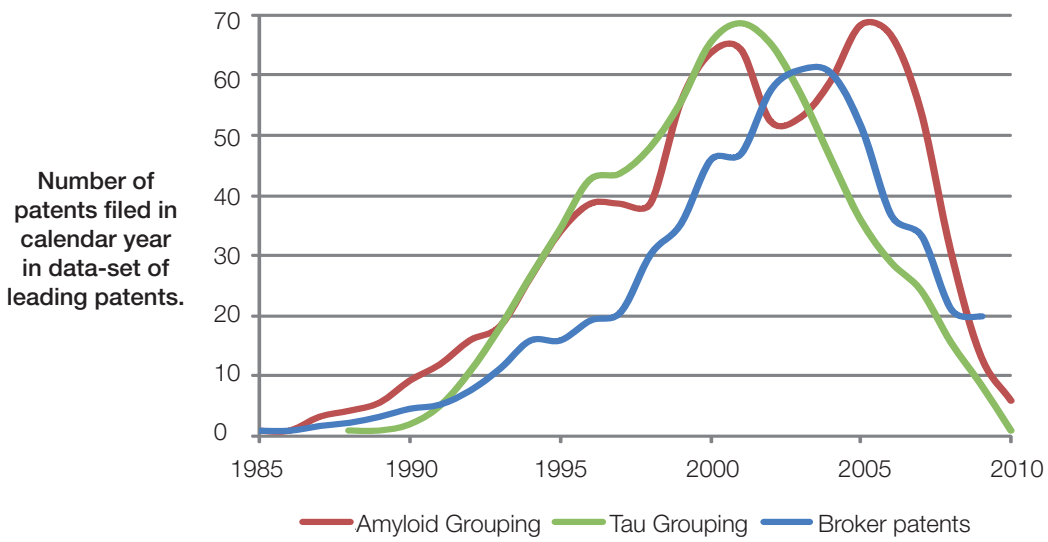
The very top-ranked patent in this grouping of clusters was US 7189819 'Humanized Anti-bodies that recognise beta amyloid peptide' filed in the year 2000, and jointly owned by Elan Pharmaceuticals, Johnson & Johnson and Pfizer (or these companies' subsidiaries). But did this patent deserve to be the top-ranked patent?

There are some clues that combine to support the potential importance of this patent:

- This patent has been litigated up to the Federal Circuit level. Listed patent applicants Wyeth (now owned by Pfizer) and Elan Pharmaceutical sued the US patent office to obtain an extension of the patent term for this patent[10] (and also US 7179892, the fifth equal ranked patent in our analysis). Wyeth and Pfizer were able to obtain an extension in the term of these two patents to compensate for delays caused by the United States Patent and Trademark Office (USPTO) during examination of this patent, and forced the USPTO to recalculate in general how these delays are calculated.
- The patent discloses 'the identification and characterisation of two monoclonal antibodies that specifically bind to (the beta-amyloid) peptide'. One of these antibodies has been modified by the inclusion of amino acid residues from the mouse 3D6 monoclonal antibody, but the combined antibody is claimed to be 'humanized' because it features components from both mice and humans.
- There is substantial prior art for this patent application, 304 backward citations in total, plus 124 non-patent references. While some may say that this is a sign of a weaker patent, other authors[11] have correlated a high backward citation count with more valuable patents in the life sciences and other technical areas, possibly because a granted patent with a wider prior art base may disclose a broader invention that was examined very carefully.
- The patent appears to be related to the drug bapineuzumab, which is in stage III trials being run by Elan and Johnson & Johnson, and which is thought to be one of the most promising Alzheimer's treatments[12].

Strong patent activity in the last decade

Figure 6: Filing year distribution of leading 2153 Alzheimer's patents[14].



Another promising drug is thought to be the Eli Lilly marketed drug solenezumab, which is protected by US 719576 – the 14th highest ranked patent in our NPA patent listing.

It should be noted that NPA patent rankings are all relative, and it would be unwise to say that the highest ranked patent is significantly more important than the second ranked patent, and so on. However, we would expect a significant difference in the value of the first and say, for example, the 1000th ranked patent. In this case, there appears to be a suggestion that the top-ranked patent is an important patent that discloses what may be an important invention in the treatment of Alzheimer's.

Tau Grouping

The highest ranked patents in the anti-inflammatory grouping of patent clusters were filed by Vertex Pharmaceuticals, based in Cambridge, Massachusetts, but which also has laboratories in the UK and Canada. These patents were filed by compounds targeting GSK-3. GSK-3 is believed to be the key protein kinase involved in Tau fibrillation, which is a key secondary target of Alzheimer's research.

When were the leading 2153 patents filed?

Despite the fact that Alzheimer's has been an identified disease for more than 100 years, the majority of the leading 2153 patents have been filed in the last 10 years, see Figure 6.

Figure 6 also shows:

- The increase in the filing activity for Amyloid and Tau Grouping patents was similar up to the year 2000.
- However, the Amyloid Grouping filing activity appeared to have a double peak, with a first peak of activity in around the year 2000, and a second peak of activity in around the year 2005.

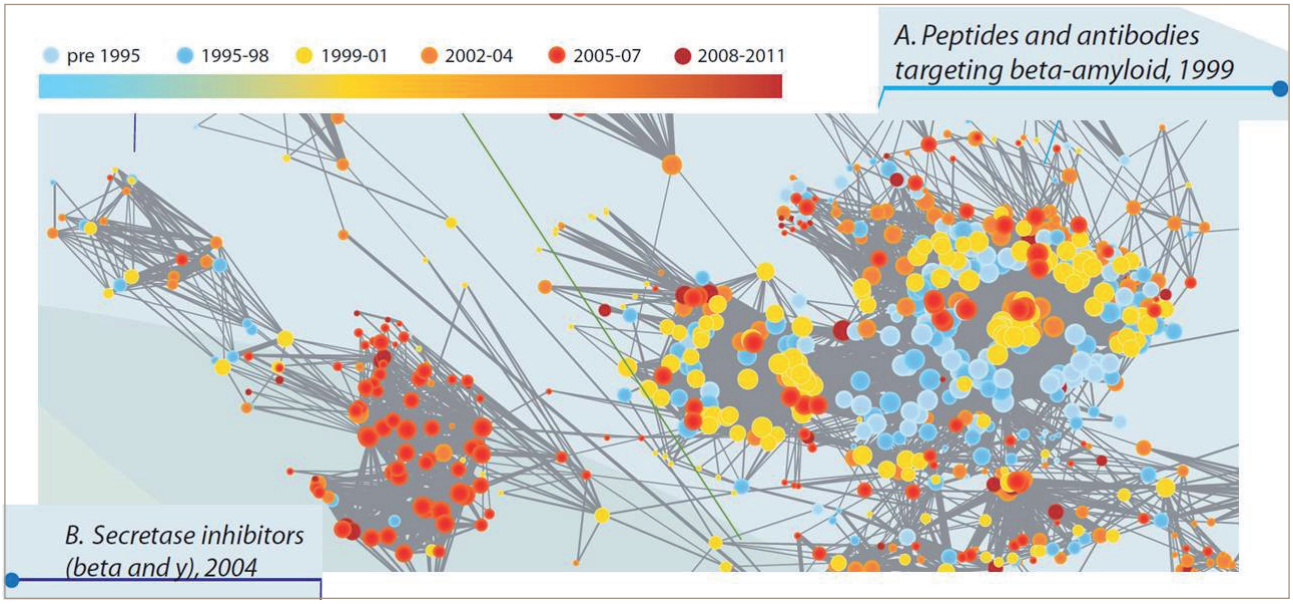
The double peak in the Amyloid Grouping filing activity was interesting, and we investigated further:

- The highest ranked (most 'popular' patent) during the 1999 to 2001 period being the previously discussed number one ranked patent overall, US 7189819 (see page 13).
- Patent filings in the 2004 to 2006 period were led by the related patent US 6972127, which claimed the use of the beta amyloid peptide or its antibody as a vaccine.

The later approach appears to be different to the earlier approach, and this may have catalysed a number of similar patents.

A rapidly changing field

Figure 7: Time Map Amyloid cluster



Another way of considering the technology development in Alzheimer's research is to show an NPA map where the patents are coloured by filing years. This is shown in Figure 7, which compares the filing dates for the two largest clusters in the Amyloid Grouping. The B_A: Secretase Inhibitors cluster had mostly recently filed patents, in contrast to cluster A_A, Peptides and antibodies targeting β-amyloid (329).

"As a patent attorney working on Alzheimer's patents, it was interesting to see that there is scope for researchers to explore the subject areas covered by the leading patents and move closer to treating this debilitating illness."

Debbie Beadle, Principal, Patent Attorney, Griffith Hack
debbie.beadle@griffithhack.com.au

"Having watched a family member suffer from Alzheimer's, I was pleased to see the depth and breadth of new treatments uncovered in this study."

Mike Lloyd, IP Consultant, Griffith Hack
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Building on foundation patents

Table 4: Top three 'foundation patents' in the two groupings of clusters.

Patent (filing year)	Indexed relationship strength (top-ranked patent in grouping = 100)	Forward citations in NPA study	Patent owner (inventors)	Patent rank in cluster grouping	Cluster
Amyloid Grouping					
US 4666829 (1985)	100	94	University of California (Glenner, George, and Wong, Caine W)	65	A_b, Peptides and antibodies targeting β amyloid
US 7189819 (2001)	76	23	Elan/Johnson & Johnson/Pfizer (Basi, Guriq)	1	"
WO 1999027944 (1998)	67	71	Elan (Schenk, Dale B)	21	"
Tau Grouping					
US 7265148 (2004)	100	29	Pfizer (Hu, Baihua)	19	D_T, Fibrinolysis inhibition targeting plasminogen and serine
US 7332521 (2004)	91	27	Pfizer (Hu, Baihua)	17	"
US 7056943 (2003)	88	30	Pfizer (Elokdah, Hassan)	23	"

Can NPA be used to identify the 'foundation patents' in the current foci of Alzheimer's patent filings?

Invention never happens in a vacuum, and instead tends to build on earlier work done by either the inventor or other inventors. It is possible to track this 'knowledge flow' by looking at patent citations. While some other patent analysis techniques also analyse patent citations, NPA adds two improvements to this process:

- Only citations between patents in the study of interest are considered. Some broad patents have disclosures that may be relevant to a number of different fields. However, NPA is focused on finding the strongest patents within a specific field of interest, and so only takes relevant patent citations into account.
- In any case, Patent citations are not treated equally. NPA has a process for weighting patent citations, and these weighted patent citations are used when assessing the relative importance of patents.

There are many other potential applications for knowledge flow analysis, including patent litigation[15], but in this report we only consider one possible application, namely determining which patents have had the strongest influence on other patents in this field. This should not be confused with the general NPA patent ranking process, which also takes into account other measures of patent 'popularity'.

The top three foundation patents, or most influential, in each grouping of clusters is shown in Table 4.

Table 4 shows some interesting results. The most influential patent in the Amyloid Grouping, the now expired US 4666829 filed by the University of California, discloses the Alzheimer's Amyloid Polypeptide (AAP) which is the precursor of beta amyloid, and had 94 forward citations in the dataset. The next most influential patent was the number one ranked NPA patent of all.

In the Tau Grouping, the two most influential patents were both invented by Baihua Hu, a principle scientist at Pfizer, and refer to substituted pyrrole-indoles.

Looking forward

Table 5: The top two NPA ranked patents in each of the last five years.

Filing year Age band	Top-ranked patent filed in that year (regardless of grouping)	2nd top-ranked patent filed in that year
2006	**US 7635473**, 'Anti Aβ antibody formulation', Elan/ Johnson & Johnson/Pfizer, NPA ranking = 22, Peptides and antibodies targeting beta amyloid cluster	**US 7557106**, 'Substituted pyrimidines useful as protein kinase inhibitors', Vertex Pharma, NPA ranking = 70, *GSK-3 – Tau fibrillation inhibition/ Hormonal and kinase inhibitory mechanisms* cluster
2007	**US 7678760**, 'Inhibitors of Memapsin 2 and use thereof', Oklahoma Medical Research Foundation, NPA ranking = 94, *Peptides and antibodies targeting beta amyloid cluster*	**US 7893214**, 'Humanized antibodies that recognize beta amyloid peptide', Elan/Johnson & Johnson/Pfizer, NPA ranking = 97, *Peptides and antibodies targeting beta amyloid cluster*
2008	**US 7906625**, 'Humanized anti-amyloid antibody', Amgen Inc, NPA ranking = 71, Broker patent	**US 78293035**, 'Ligand screening method using a crystal of beta secretase', Elan Pharam, NPA ranking = 213, *Peptides and antibodies targeting beta amyloid* cluster
2009	**US 7727999**, 'Spiroazacyclic compounds as monoamine receptor modulators', Acadia Pharmaceutical Inc, NPA ranking = 143, *Seratonin receptor agonists cluster*	**US 7875632**, 'Selective serotonin receptor inverse agonists as therapeutics for disease', Acadia Pharmaceutical Inc, NPA ranking = 167, *Seratonin receptor agonists* cluster
2010	**US 7875632**, Synthesis of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy) phenylmethyl)carbamide and its tartrate salt and crystalline forms', Acadia Pharmaceutical Inc, NPA ranking = 165, *Seratonin receptor agonists* cluster	**US 7910333**, 'Antibodies to alpha-synuclein', Elan Pharmaceuticals, NPA ranking = 195, *Peptides and antibodies targeting beta amyloid cluster*

Can NPA be used to identify the potential future high-ranking patents?

NPA can also be used to identify recently filed patents that may become important in future years. This is based on the principle of association – that many future important patents may share backward citation linkages with important current patents.

This can be done by considering the highest ranked patents for any filing year. The highest ranked patents for each of the last five years is shown in Table 5.

Who were the leading patent applicants?

NPA can be used to identify the leading patent applicants. Unlike other patent analysis methods, NPA does not merely count the number of patents filed by an applicant, but instead weights the patents based on the NPA rankings of the patents.

Many future important patents may share backward citation linkages with important current patents.

Leading the field

Table 6: Top-ranked by NPA patent applicants.

Ranking in grouping	Top-ranked patent portfolios in Amyloid Grouping	Indexed patent portfolio strength, where the leading company in grouping = 100 (number of patents in leading 2153 patents)	Top-ranked patent portfolios in Tau Grouping	Indexed patent portfolio strength, where the leading company = 100 (number of patents in leading 2153 patents)
1	Elan Pharmaceuticals (Ireland)	100 (55)	Pfizer (US)	100 (94)
2	Pfizer (US)	96 (58)	GlaxoSmithKline (UK)	72 (99)
3	Acadia Pharmaceuticals (US)	81 (39)	Vertex Pharmaceuticals (US)	68 (84)
4	Elan/Johnson & Johnson	76 (27)	Merck (US)	24 (38)
5	Elan/Pfizer	76 (44)	Boehringer Ingelheim (Germany)	20 (34)
6	Merck (US)	58 (53)	Teva Pharmaceutical (Israel)	15 (28)
7	GlaxoSmithKline (UK)	52 (35)	GliaMed (US)	14 (33)
8	Elan/Eli Lilly (US/US)	45 (24)	Cytokinetics (US)	13 (13)
9	US Government agencies	34 (22)	Merck/Ligand (US/US)	12 (14)
10	Eisai Company Ltd (Japan)	33 (27)	OSI Pharmaceuticals (US)	11 (11)
11	Elan/Johnson & Johnson/ Pfizer	30 (11)	Bayer (Germany)	8 (11)
12	AstraZeneca (UK)	28 (31)	AstraZeneca (UK)	8 (16)
13	Bellus Health (Switzerland)	26 (23)	Nicox (France)	7 (20)
14	Stem Cell Therapeutics (Canada)	16 (13)	Mitsubishi (Japan)	5 (9)
15	Cardiome Pharma (Canada)	15 (15)	Cytovia (Maxim Pharmaceuticals, US)	5 (9)
16	Merck/Ligand (US/US)	14 (10)	Bristol-Myers Squibb (US)	5 (9)
17	Milkhaus Laboratory Inc (US)	14 (6)	Technion (Israel)	4 (5)
18	Eli Lilly (US)	13 (9)	Sanofi (France)	4 (10)
19	Johnson & Johnson (US)	13 (12)	Johnson & Johnson (US)	4 (5)
20	University of California	13 (6)	Takeda Pharmaceutical (JP)	4 (4)

Table 6 shows the top applicants in each of the Amyloid and Tau groupings. While many of the patent owners are large and well-known pharmaceutical companies, some are smaller and lesser known.

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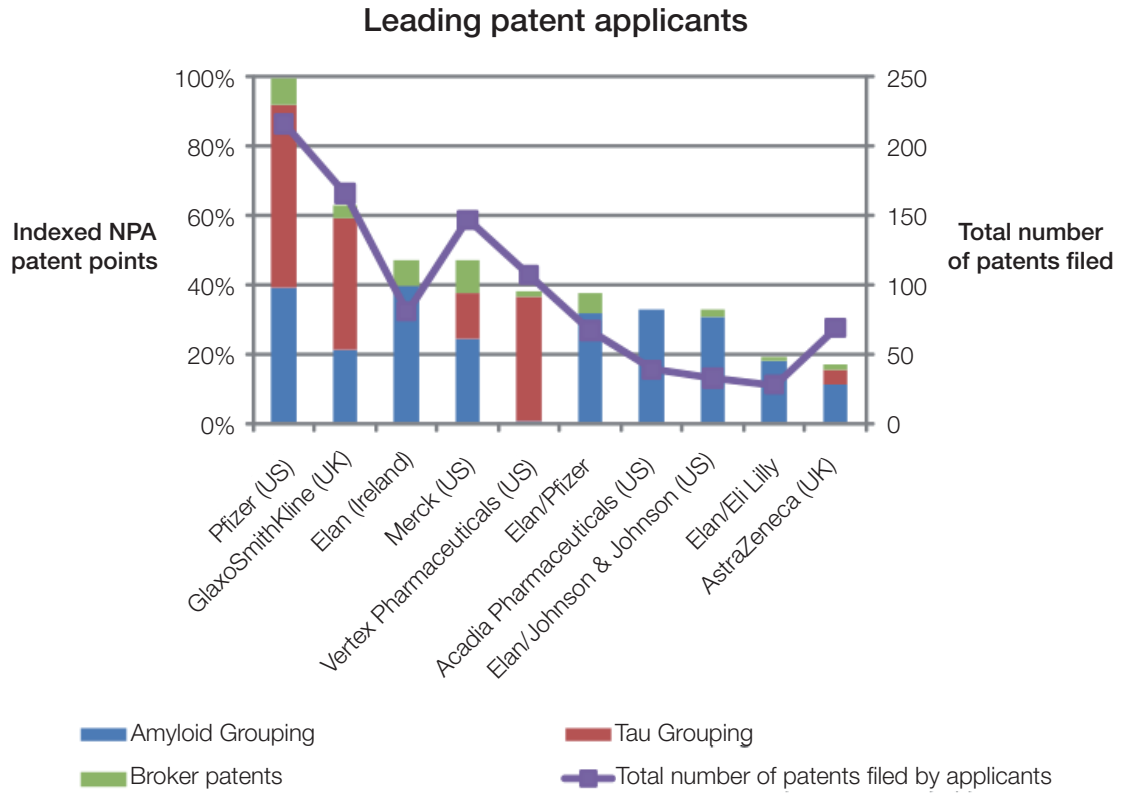
Figure 8: Leading applicants for patents for the treatment of Alzheimer's, as determined by NPA.



Leading the Amyloid Grouping is Elan Pharmaceuticals of Ireland. Elan describes itself as 'a neuroscience-based biotechnology company headquartered in Dublin, Ireland', and has been in business since 1996. In recent years, Elan has had a range of collaborations, including with Johnson & Johnson (through the Johnson & Johnson subsidiary Janssen Alzheimer Immunotherapy), Pfizer (through its acquisition of Wyeth) and Eli Lilly.

Given that some of the companies listed are strong in both groupings of clusters, it is also worth combining the results in the two clusters. Figure 8 shows that:

- Pfizer was the single largest applicant, ahead of GlaxoSmithKline and Elan Pharmaceuticals;
- However, Elan Pharmaceuticals is also represented by patents filed in conjunction with its partners, such as Pfizer and Johnson & Johnson;
- The Amyloid Grouping of patent clusters were dominated by Elan Pharmaceuticals, and its partnership patent filings. Other strong contenders are Pfizer by itself, Johnson & Johnson by itself, Acadia Pharmaceuticals and Merck;
- The leading applicants in the Tau Grouping were Pfizer, GlaxoSmithKline and Vertex Pharmaceuticals.

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How we prepared Table 6 and Figure 8

- Figure 8 was prepared by assigning 'patent points' to patents based on the overall ranking of the patent.
- The highest ranked patent got 915 patent points, with the lowest ranked patents gaining one point (NPA allows for an equal ranking of patents, so there were only 915 unique rankings in the 2153 leading Alzheimer's patents).
- The patent points earned by each applicant were then added, including patent points for known subsidiaries of these applicants.
- The International Patent Documentation Center (INPADOC) was used to update patent ownership records.
- Patents assigned companies that were known subsidiaries or acquisitions of larger companies were attributed to the larger company (for example, all patents with Wyeth listed as an owner were attributed to Pfizer as Pfizer now owns Wyeth).
- The patent points earned by each applicant were then indexed to the patent points earned by the highest scoring applicants, namely Pfizer in this case. By indexing patent points to the leading applicant, the relative influence of each patent applicant can be easily seen.
- The total number of patents filed by each applicant (and known subsidiaries) was also shown.

Who were the leading inventors?

A similar technique used to find the leading patent owners was used to rank the leading first named inventors on the patent applications. The top two inventors were:

Dale B. Schenk (pictured top, far right): with an Indexed NPA patent score of 100%, and 48 patents naming him as the leading 2153 patents. Schenk is the Chief Scientific Officer at Elan Pharmaceuticals, which has been profiled elsewhere in this paper. Schenk won the Pomtakin Prize in 2001 for 'Research in Picks, Alzheimer's and related research', and was also named as a 'Rock star of Science' in 2009 by the Geoffrey Beene Foundation for his work as 'the inventor of beta amyloid immunotherapy, which seeks to use the body's own immune system to rid the brain of the plaque that is the hallmark of Alzheimer's'[16]. The highest ranked of his patents was US 6743427 'Prevention and treatment of amyloidogenic disease' which was the second highest ranked patent overall, and has been discussed earlier in this paper.

Mark Gurney (pictured bottom): former Director of Genomics Research in Pharmacia and now a venture capitalist, was first-named inventor in 28 patents in the top 2153 patents, for an Indexed NPA Patent Score of 55 per cent (of the Dale B. Schenk score). The highest ranked of these 28 patents was US 6420534 (filed in the year 2000) 'Alzheimer's disease secretase, APP substrates therefore, and uses thereof', which was the 30th ranked patent both overall and in the Peptides and Antibodies cluster. This patent discloses a beta secretes enzyme, which is thought to be associated with the development of Alzheimer's, and which thereby may be important in the control of Alzheimer's once methods are developed to control this enzyme.

Limitations of this NPA study

While relying on the collective intelligence of patent owners can provide powerful and unique insights, there are some natural limitations that need to be understood:

a. NPA rankings are based on patenting activity, and not on invention outcomes.

For example, as part of this study we looked at well-known drug candidates for the treatments of Alzheimer's disease. Some of these drugs (or more specifically patents protecting these drugs) were very highly ranked (for example, patents for the drugs bapineuzumab and solenezumab), while other drugs were not highly ranked by this analysis, such as patents for the drug latrepridine. When we investigated the most likely patents for these 'lower ranked' drugs, we discovered that these patents had relatively weak citation connections to other patents in this study[17]. This implies that both the original developer of these drugs, as well as other pharmaceutical companies, had not filed many patents for similar or variations of these drugs.

It is unclear what the lack of patents for similar drugs says about a drug. Currently, there are no clinical proven cures for Alzheimer's, and so it is not possible to say for sure where a pharmaceutical company should be filing patents. But we do assume that the decision to file and prosecute patents for Alzheimer's treatments are rational decisions made by informed patent applicants, and so their opinions on what patent areas are important (as summarised by their patent filings) should carry some weight.

It is also worth considering that NPA summarises what can be hundreds of thousands of individual decisions by either patent applicants or examiners, and so any individual errors made by these applicants or examiners should have a negligible effect on the final outcomes.

b. NPA patent rankings are affected by large patent families.

If a company has a large patent family, for example lots of continuation and continuation-in-part (CIP) patents as are commonly used in the US, these individual patents tend to heavily refer to each other and can boost their own NPA rankings.

While some might argue that this leads to a distortion of the results, others might suggest that a large patent family by itself is an indication of a valuable patent. The company filing this patent obviously believes that subject matter is important enough to file multiple patents, and is prepared to invest what can be hundreds of thousands of dollars doing so. A large patent family may contain many variations of the underlying invention family, allowing the patent owner to spread the risk of a given variation of a drug failing in drug trials or the marketplace.

One effect of large patent families is that it can bias NPA patent and patent owner rankings towards larger pharmaceutical companies, which can afford both the extended research and development and patent filing costs required to build a large patent family. We do not believe that it is a true 'bias' as this is simply reflecting commercial reality, but it can make it harder, for example, to identify smaller companies that may be of interest as licensing or acquisition targets, or their individual patents.

In practice, this bias towards larger companies can be very easy to get around. A knowledgeable industry observer can review an NPA ranking list of patents or companies and filter out those companies that are not of interest because of its size or other factors. >

A knowledgeable industry observer can review an NPA ranking list of patents or companies and filter out those companies that are not of interest because of their size or other factors.

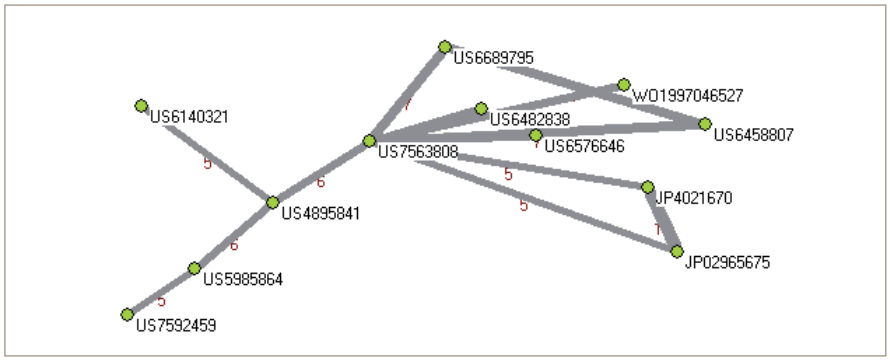

Figure 9: Citation connections between US patent 4895841 and other well-connected patents within the 48,000 patent starting set.

c. An overly broad search can paradoxically limit the patents found. This particular marketing oriented study was very broad in scope, intended to identify the most popular patenting area for Alzheimer's. A consequence of this is that some of the niche areas for Alzheimer's treatments may be missed. As a simple analogy, a map showing the whole of the city of New York will not give you much detail of Central Park.

In a commercial study reviewing patents for Alzheimer's treatments, we might instead narrow the focus of the patent search, for example to beta amyloid-targeting drugs, or to patents related to acetylcholinesterase inhibitors.

d. More recent patents and research areas were given much greater weight due to an apparent acceleration of patent filings for the treatment of Alzheimer's disease.

As an example, the patent for the drug donepezil was not highly rated in this study. Donepezil, developed by Eisai and marketed by Pfizer under the name Aricept®, is a reversible acetylcholinesterase inhibitor[18] and the world's biggest selling treatment[19] for Alzheimer's. However, the evidence for its effectiveness is mixed[20][21].

The primary US patent for donepezil is US 4895841, which expired on 25 November 2010, although some family members are still valid in other countries[22]. Given the commercial value of donepezil, we might have expected US patent 4895841 to be highly rated by NPA (and from a pathway perspective to be connected to the A_A: *Peptides and antibodies targeting* β*-amyloid* cluster). In fact, US 4895841 was not ranked within the leading 2153 patents in this study, although it was found in the 48,000 starting patents. This was initially surprising, although the reasons behind this help show how NPA ranks patents.

US 4895841 has 85 forward citations, which is a significant amount and suggests that it should be well connected. Not all of these citations were to other patents within our study (meaning that these citations were instead to other patents that fell outside the scope of our study), and hence the number of forward citations to other patents in our study was 54. There were also no backward citations to other patents within our study.

However, US 4895841 was only citationally-connected to a group of other patents that collectively were not connected to the main patent clusters seen in this study. The leading patents in this 'satellite cluster' are shown in Figure 9, with US 4895841 shown in the left of this cluster. In practical terms, this means that the main emphasis of Alzheimer's patenting has moved on from patents related to donepezil, possibly in response for the need to identify alternative treatments.

Get in touch for the full set of results

This white paper provides an overview and some of the information that is available from an NPA analysis of patents filed for Alzheimer's treatments. However, this is only a snapshot of the overall results. The full set of results, including further details of each of the 23 identified patent clusters, are available upon request from Griffith Hack.

Acknowledgements

Daniel Ash, Paul Hamilton-Brown and Ewan Driver from Griffith Hack are all gratefully acknowledged for their significant contributions to this paper.

Our search was conducted through the Thomson Innovation platform (provided by Thomson Reuters) and the details of the patent records located were obtained from the national collection available through this platform.

What else can we do with NPA results?

In this particular study we have focused on the use of an NPA analysis to provide a unique overview of an otherwise very complicated area of patent filings, and to show how the technology is progressing in this area. Besides providing these types of high level insights, NPA results can have other applications, which include:

- **Litigation analysis:** NPA can provide new insights on litigation, including predicting and showing litigation risks, as well as illuminating possible outcomes. NPA can also help uncover prior art that may be missed by other patent analysis techniques.
- **Reducing research and development costs and risks**: by comprehensively reviewing what has been done before, as expressed by the patent landscape.
- **Valuing patents**: by providing a relative indication of the importance of individual patents.
- **Benchmarking patent portfolios**: either your own portfolio or portfolios belonging to competitors or potential acquisition targets.
- **Finding under-valued patent 'gems'**: which could be defined as patents that rank higher in NPA analyses, or in their ability to connect other patents, than anybody expected, including the patent owners.
- **Showing technology progression.**
- **Identifying licensing opportunities.**
- **Marketing patent portfolios.**

And there are probably many more opportunities for applying NPA that will become clearer as NPA is developed.

About NPA and Ambercite

Network Patent Analysis (NPA) applies the wealth of information in patent citation data to group and rank patents, and provides a numerical analysis of patent litigation. NPA is being developed by patent analysts Ambercite, in conjunction with Griffith Hack.

Need to know more?

Please visit www.griffithhack.com/networkpatentanalysis or www.ambercite.com to learn more about NPA in general. If you are interested in a more detailed discussion of this paper, please contact the authors:

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NPA: Mike Lloyd, IP Consultant, Griffith Hack (mike.lloyd@griffithhack.com.au)

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About Griffith Hack

Griffith Hack is the leading Australian intellectual property (IP) law firm comprising patent and trade marks attorneys, IP lawyers (commercial and litigation), information services, IP portfolio management consultants, and R&D tax experts. One of the largest Australian IP firms with 270+ staff operating from offices in Melbourne, Sydney, Perth and Brisbane, its clients include many of Australia's leading companies as well as an enviable international client base and an extensive network of associate firms throughout the world. A major IP force in Australia, Griffith Hack is the leading filer of Australian originating patent applications, Madrid international trade marks applications, Australian design applications and IP related actions in the Australian Federal Court.

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- Ranked the top firm in 2010 and 2011 for **Patent Cooperation Treaty (PCT) filings in Australia** by *Managing Intellectual Property* (*MIP*)
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