



PATENT: A POWERFUL INDICATOR TO MEASURE DRUG INNOVATION

AN EXAMPLE ON ANTI-ALZHEIMER'S DRUGS



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Introduction

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Patent and patent citation

- 90%-95% innovation in the world is embedded in patent
[Liu CY, 2008]
- Patent citation means the innovation is based on the state of art
[Mogee ME, 1998]
- Patent citation can be used as a proxy of technology flows to provide a successional angle to view the interactions of technology and capture the technology evolving process from different dimensions
[Jaffe AB, 1999][Sorenson O, 2006]
- The number of patent citation is also regarded as a powerful indicator to assess patent value
[Harhoff D, 2003][Reitzig M, 2004]

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Patent citation network analysis

- The relationship among patent is similar with interpersonal relationship, thus SNA could be used to analyze the patent citation [Wang Y, 2008]
- SNA, as a new method applied in knowledge management, can make the technology flow visualized and reflect the network circumstance of a particular technology
- A considerable number of studies have been devoted to understand the characteristics of technology flows in a particular domain by applying the patent citation network, which helps identify the core technology cluster and predict technology development
[Li X, 2007][Chang SB, 2009][Érdi P, 2013][Choe H, 2013]

Introduction

A case study with patent citation network analysis

1. To profile technology flows of pharmaceutical R&D for Alzheimer's disease whose pathogenic mechanism is unclear and complex through the patent citation network;
2. To delineate and analyze technology communities with multi-dimensional information attached to patents;
3. To provide recommendations for policymakers, investors and researchers involved in anti-Alzheimer's drug development

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Alzheimer's disease (AD)

- One of the most serious illnesses in the world
- With dramatically increasing incidence
- Complex pathogenic mechanism
- No adequate preventive or curative treatment for AD now



35 million patients now !

One American develops AD every 68s !



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AD pathogenic mechanism and related therapies

- Cholinergic insufficiency theory [Guo YS, 2008][Sun L, 2010]
ChEI ; Cholinergic receptor modulators ; 5-HT
- β -amyloid peptide ($A\beta$) theory [Walsh DM, 2002; 2007]
 $A\beta$ vaccine; $A\beta$ antibody; Anti-inflammatory drug; PPAR γ agonist
- Tau protein theory [Mangialasche F, 2010][Goedert M, 2006]
GSK-3 inhibitor; Methylthioninium chloride
- Others
NMDA antagonist; NGF; calcium antagonists

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Marketed drugs

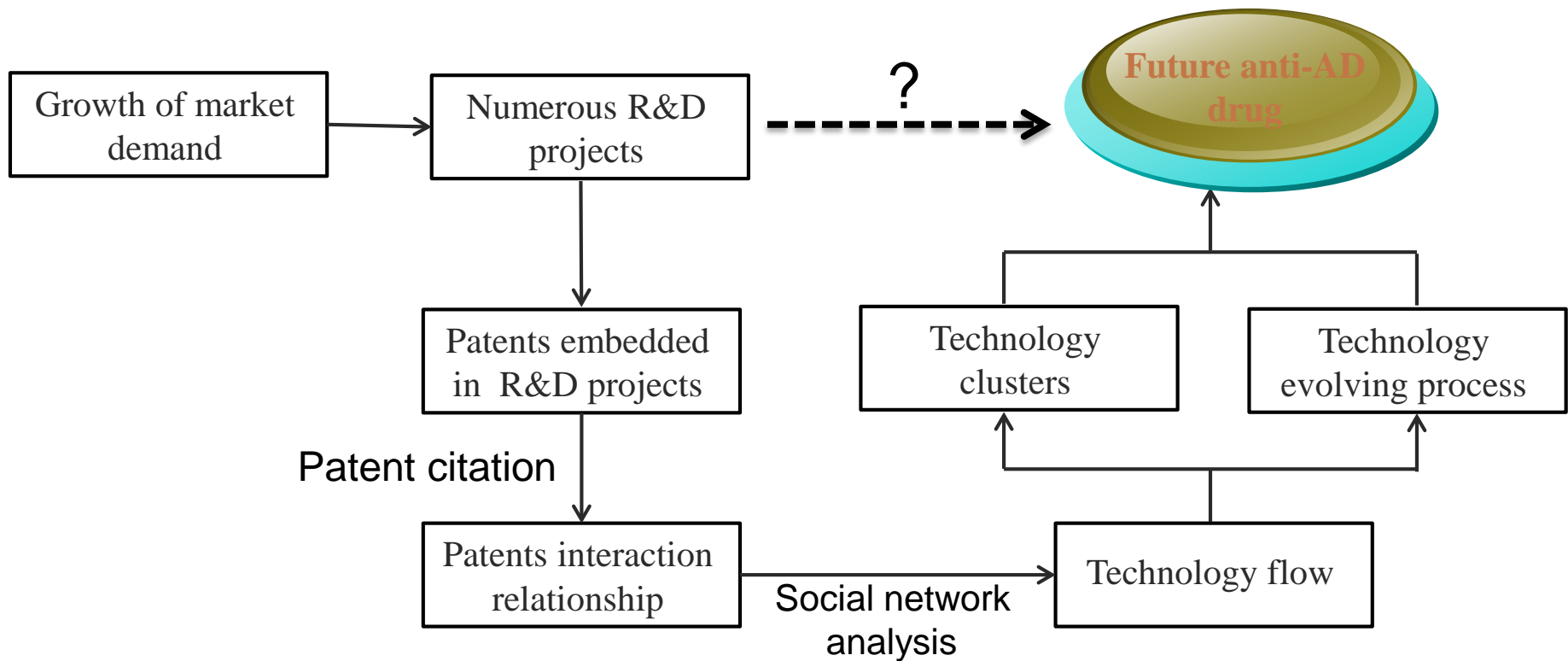
Action	Generic name	Average year of patent grant (STD)	Patentee and country
Cholinesterase inhibitor	Tacrine	1988 (± 2)	Summers.W.K-US Sanofi-France
	Donepezil	2000 (± 7)	Eisai-Japan
	Galantamine	1999 (± 8)	Johnson & Johnson-US Synaptech-US
	Rivastigmine	1998 (± 5)	Novartis-Switzerland Hebrew University of Jerusalem-Israel
NMDA receptor antagonist	Memantine	2000 (± 6)	Children's Medical Center Corporation-US Merz-Germany Forest-US

* Data source: IMS Health; USPTO

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Conception framework



Introduction

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Commercial application

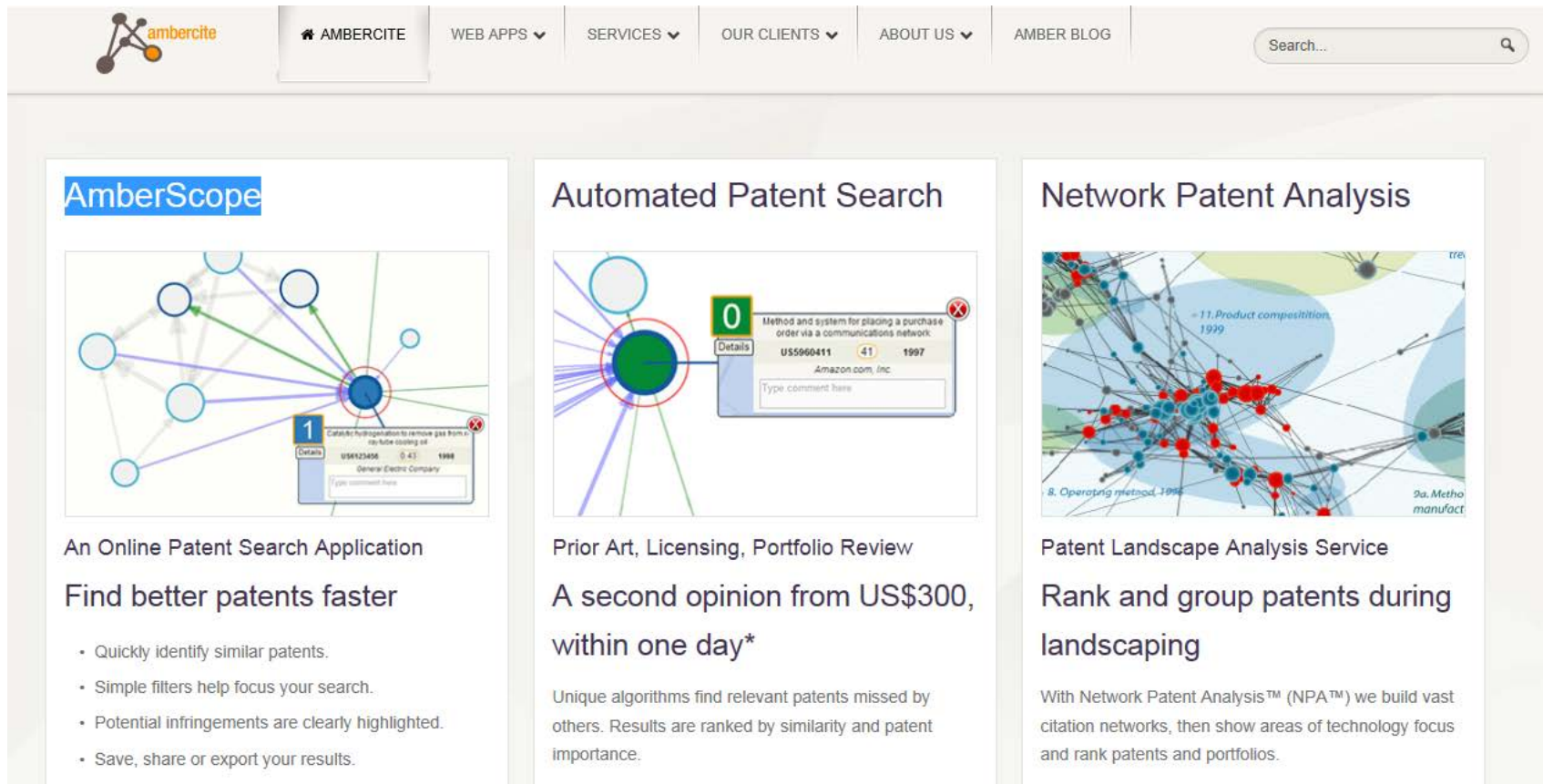
- A business report identified the leading patents, actions, inventors and companies in the field of AD treatment by means of Network Patent Analysis (NPA), a method based on patent citation network and revealed the direction this field was heading. [Ambercite®]



Introduction

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- This method shows great business potential. AmberScope is a product of Ambercite, which was established in 2010 to commercialise NPA



The screenshot shows the Ambercite website with a navigation bar at the top containing the logo and menu items: AMBERCITE, WEB APPS, SERVICES, OUR CLIENTS, ABOUT US, and AMBER BLOG. A search bar is located on the right. Below the navigation bar are three main content panels:

- AmberScope**: An Online Patent Search Application. Find better patents faster. Features include: Quickly identify similar patents, Simple filters help focus your search, Potential infringements are clearly highlighted, and Save, share or export your results. The image shows a network graph with a patent card for US56123456 by General Electric Company.
- Automated Patent Search**: Prior Art, Licensing, Portfolio Review. A second opinion from US\$300, within one day*. Unique algorithms find relevant patents missed by others. Results are ranked by similarity and patent importance. The image shows a network graph with a patent card for US5960411 by Amazon.com, Inc.
- Network Patent Analysis**: Patent Landscape Analysis Service. Rank and group patents during landscaping. With Network Patent Analysis™ (NPA™) we build vast citation networks, then show areas of technology focus and rank patents and portfolios. The image shows a complex network graph with text overlays: "= 11, Product composition, 1999", ".8. Operating method, 1998", and ".9a. Metho manufact".

Introduction

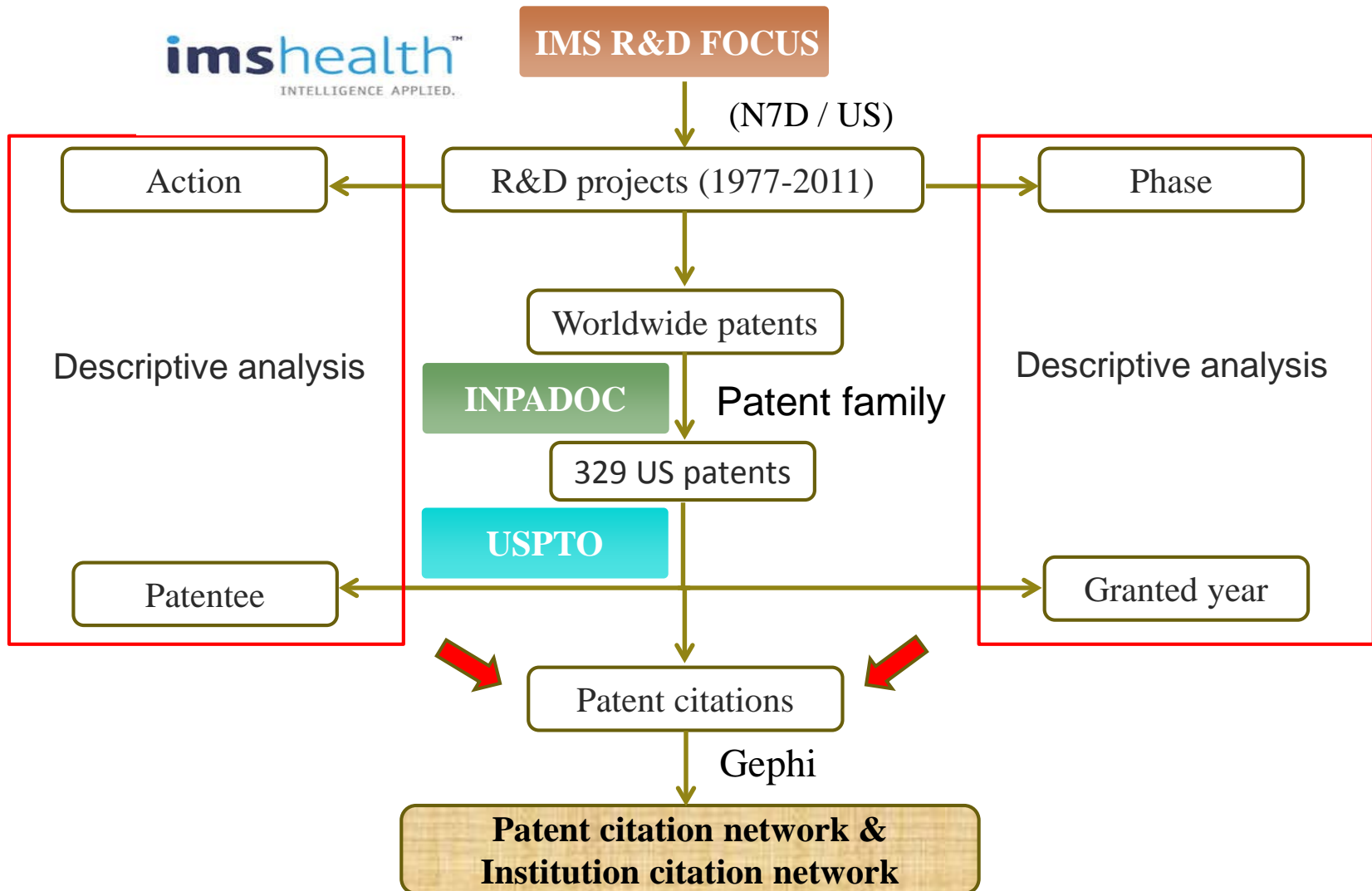
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Compared to this business report, our study has advantages in terms of -

- Focusing on the aspect of technology flows and dynamic development within the R&D of anti-AD drugs
- Collecting the AD-related patents filtered by IMS Health, which is more accurate for our research objects
- Having more detailed pharmacology classification which can be divided into β -amyloid theory, Cholinergic insufficiency theory, Tau theory and others

Data and methods

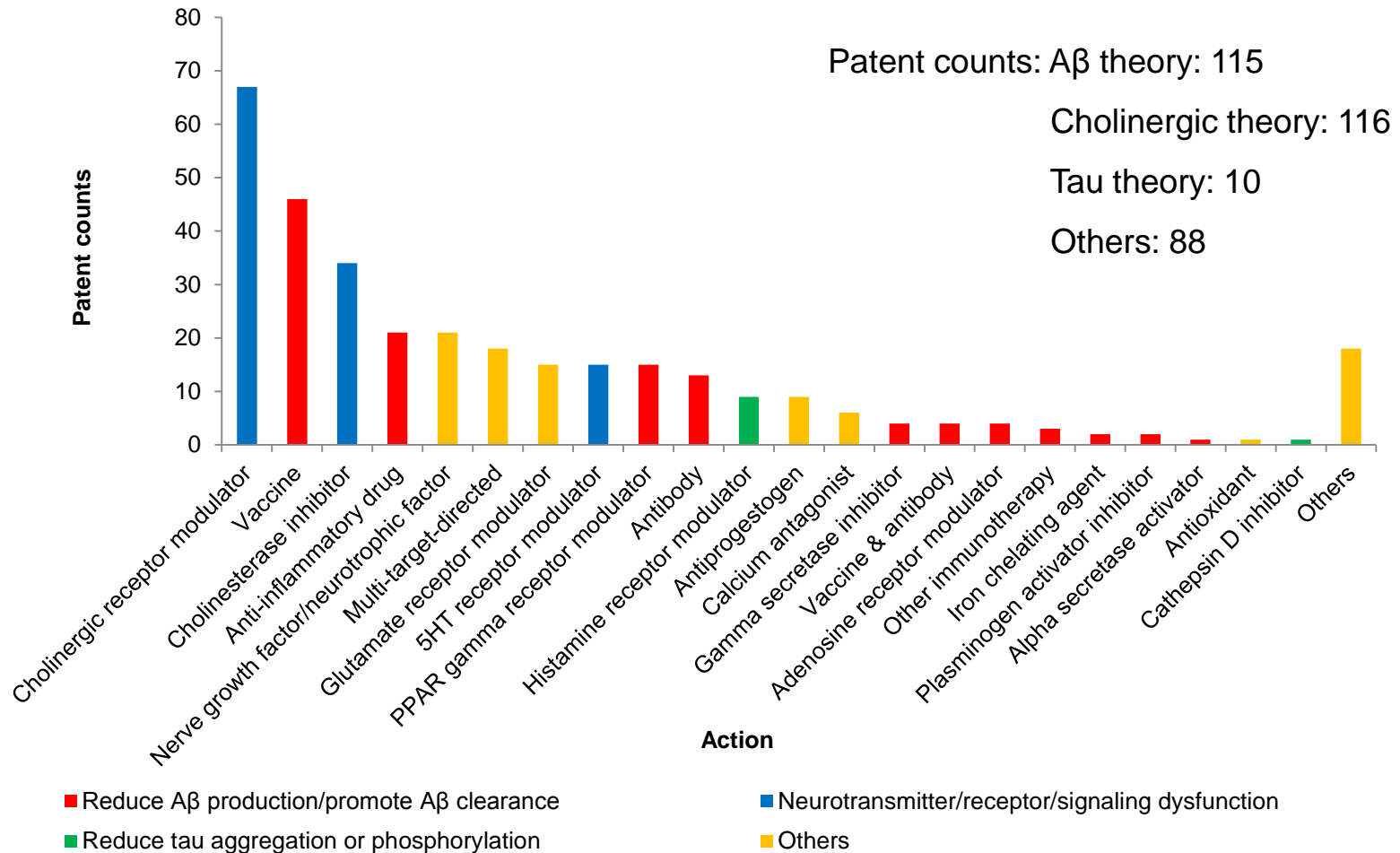
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Patent distribution

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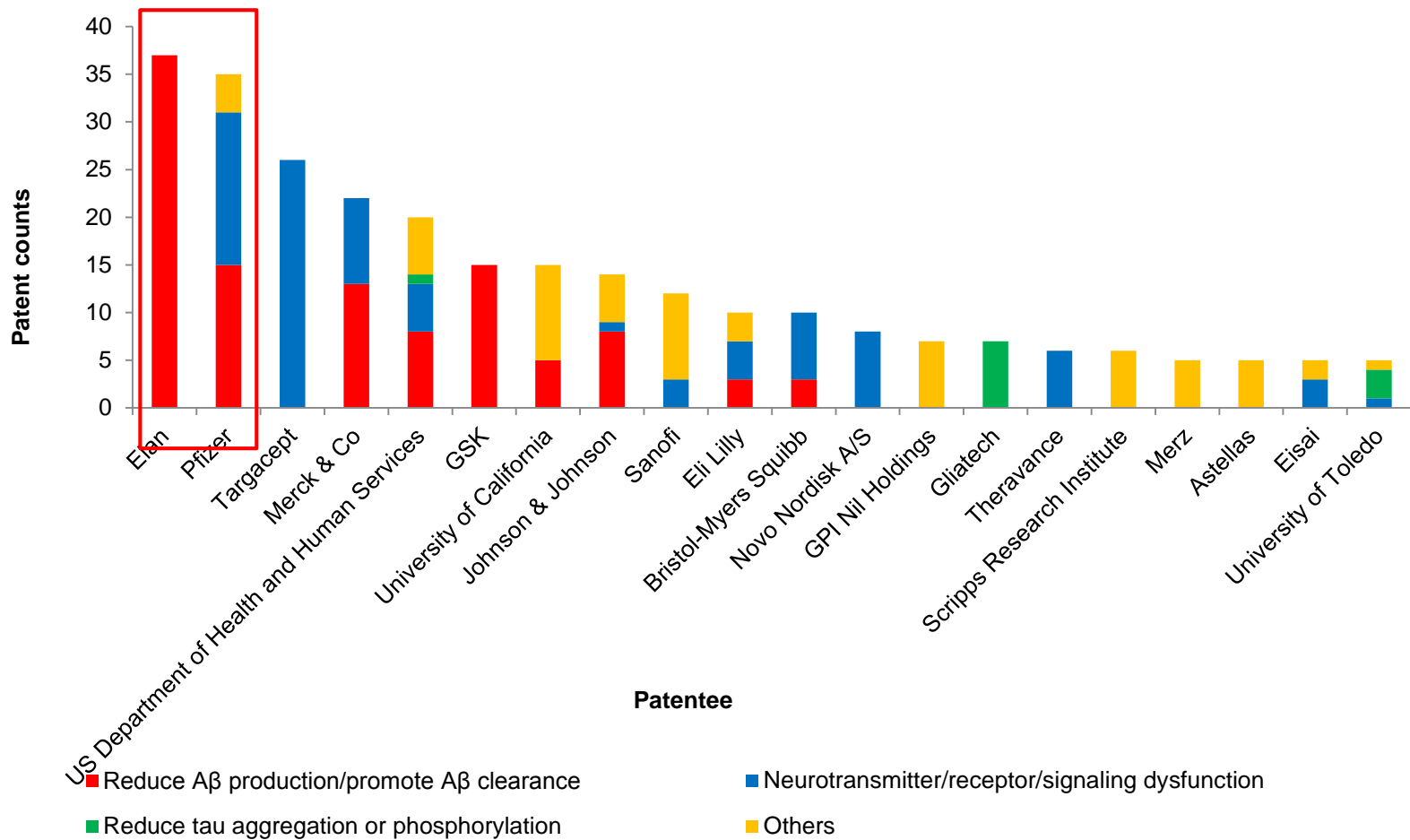
1. Distribution of action mechanisms



Patent distribution

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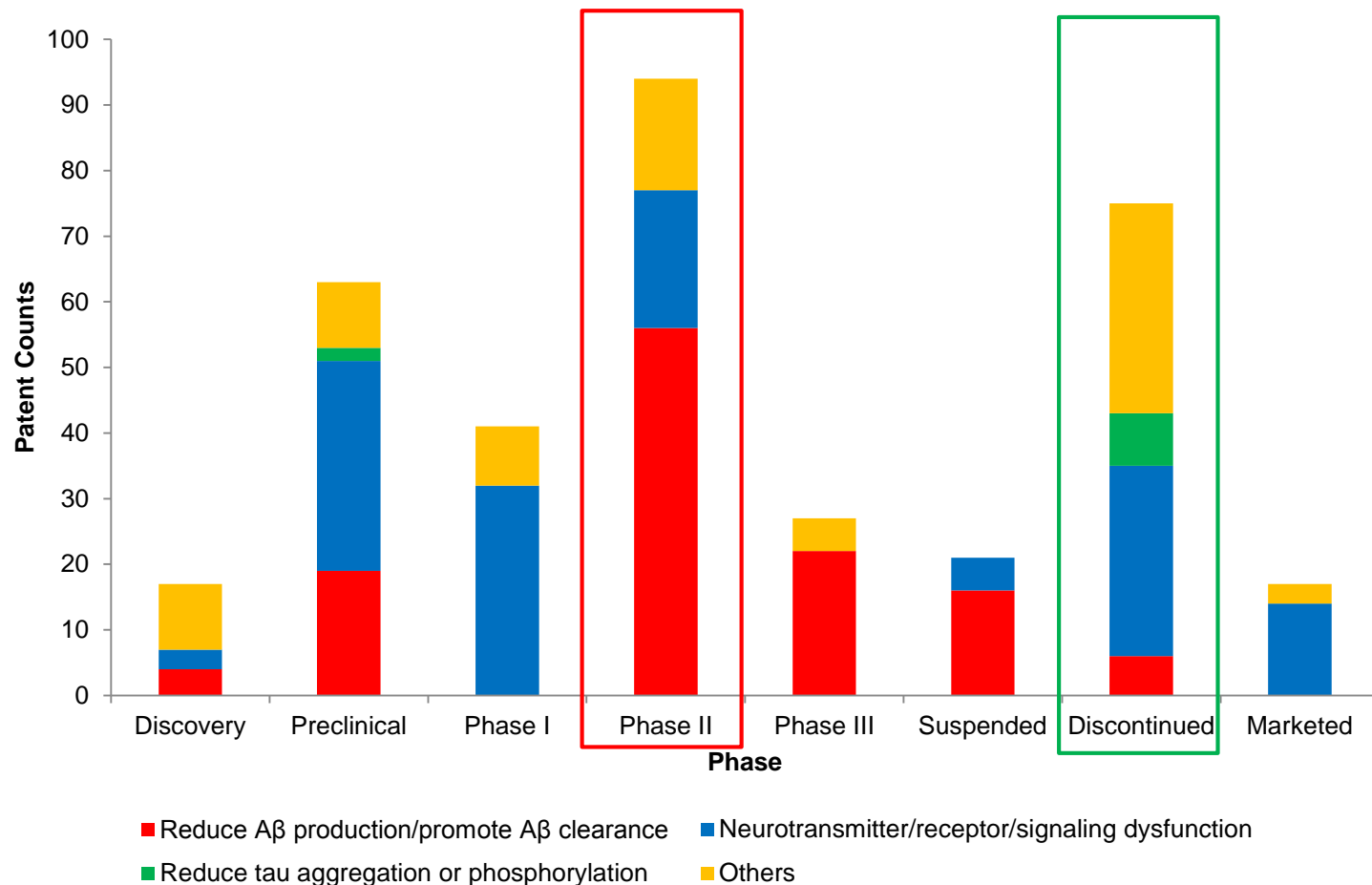
2. Distribution of patentees



Patent distribution

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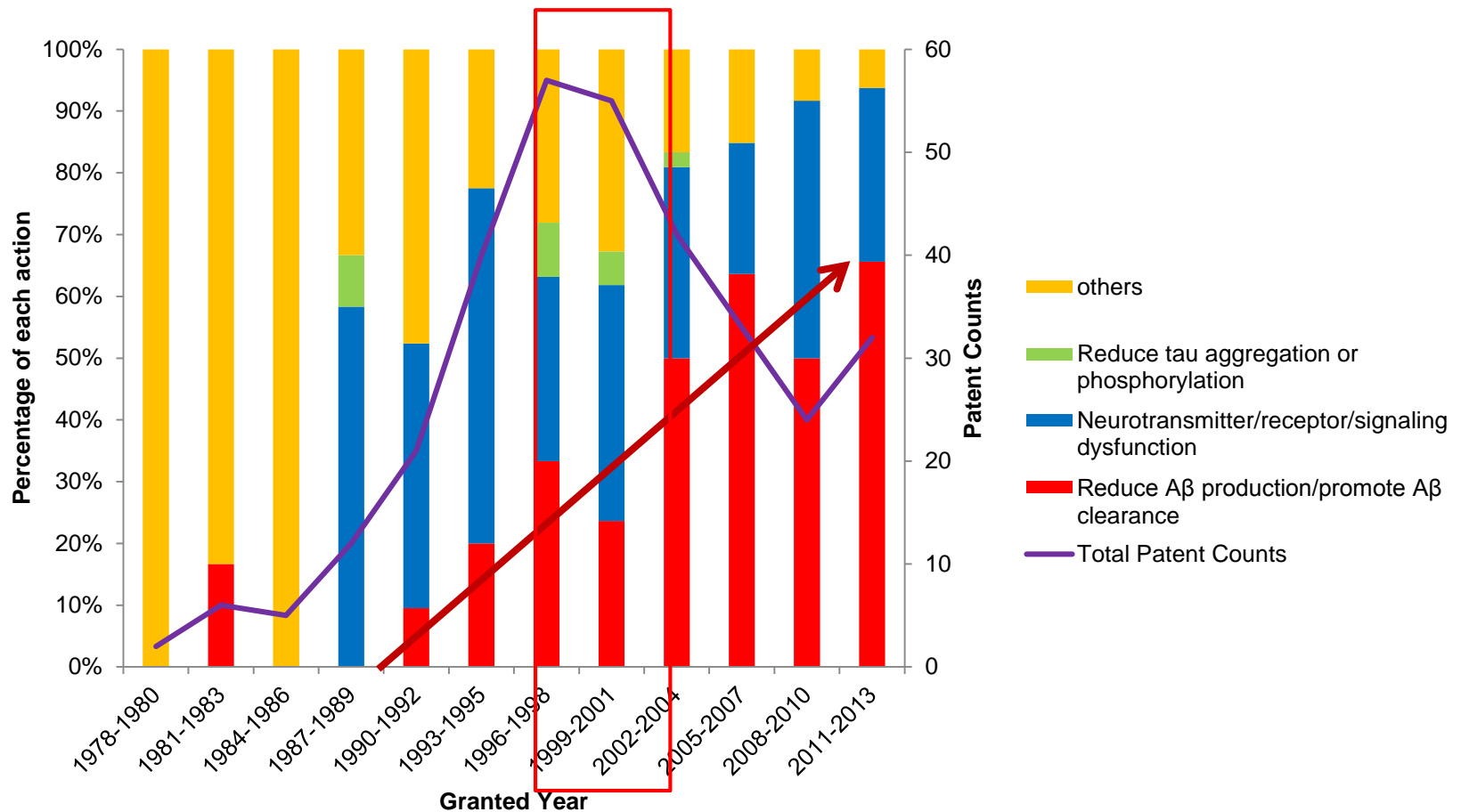
3. Distribution of phases of the drug pipeline



Patent distribution

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4. Distribution of patent granted year



Patent distribution

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Findings

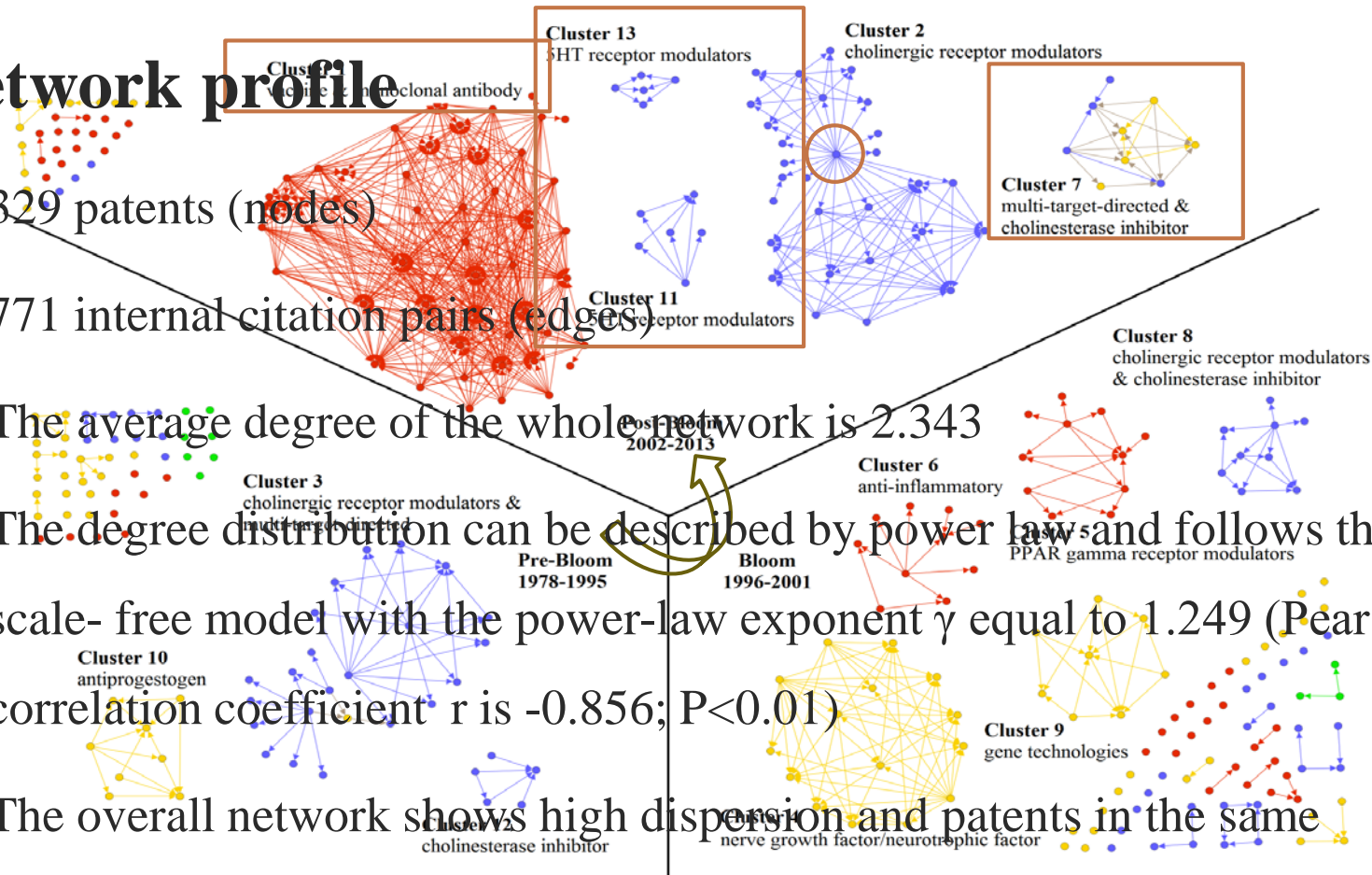
- The patent distribution shows feature of asymmetry
- A β theory and cholinergic theory makeup over one-third of the total patent counts respectively, with a notable difference from tau protein theory
- Patentees can be mainly divided into technologically diversified type and technologically concentrated type
- A β theory shows increasing importance within the development of anti-AD drugs

Patent citation network

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Network profile

- 329 patents (nodes)
- 771 internal citation pairs (edges)
- The average degree of the whole network is 2.343
- The degree distribution can be described by power law and follows the scale-free model with the power-law exponent γ equal to 1.249 (Pearson correlation coefficient r is -0.856; $P < 0.01$)
- The overall network shows high dispersion and patents in the same community show a similar mechanism of action



- Neurotransmitter/receptor/signaling dysfunction
- Reducing tau aggregation or phosphorylation
- Reducing beta-amyloid peptide (A β) production/promote A β clearance
- Others

Patent citation network

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Cluster number	Node	Edge	Average degree	Density	Main action	Phase	Average year of patent grant (STD)	Patentee with largest Si	Patentee with largest So
Cluster1	51	443	8.69	0.35	vaccine & monoclonal antibody	Preclinical; Phase II; III	2008 (± 3)	J&J (44.92%)	Elan (92.55%)
Cluster2	29	86	3.00	0.21	cholinergic receptor modulators	Preclinical; Phase I; II	2006 (± 5)	Targacept (96.51%)	Targacept (98.83%)
Cluster3	23	36	1.56	0.14	cholinergic receptor modulators & multi-target-directed	Discontinued; Preclinical; Phase I	1994 (± 3)	Novo Nordisk A/S (47.22%)	Novo Nordisk A/S (66.67%)
Cluster4	15	55	3.67	0.52	nerve growth factor / neurotrophic factor	Discontinued; Preclinical	2001 (± 6)	GPI Nil Holdings (50.91%)	Vertex Pharmaceuticals (56.36%)
Cluster5	11	16	1.46	0.29	PPAR gamma receptor modulators	Phase III	1997 (± 4)	GlaxoSmithKline (100%)	GlaxoSmithKline (100%)
Cluster6	10	10	1.00	0.22	anti-inflammatory	Suspended	1998 (± 2)	Merck Frosst Canada (80%)	Merck Frosst Canada (80%)
Cluster7	9	21	2.33	0.58	multi-target-directed & cholinesterase inhibitor	Preclinical; Phase III	2002 (± 7)	Department of Health and Human Services (38.10%) & Raptor (38.10%)	Department of Health and Human Services (85.71%)
Cluster8	9	14	1.56	0.39	cholinergic receptor modulators & cholinesterase inhibitor	Discontinued; Marketed	1998 (± 4)	Merck & Co (92.86%)	Eisai (71.43%)
Cluster9	8	16	2.00	0.57	others (gene technologies)	Discovery	2000 (± 3)	The Scripps Research Institute (100%)	The Scripps Research Institute (81.25%)
Cluster10	8	14	1.75	0.50	antiprogesterone	Phase II	1986 (± 3)	Sanofi-Aventis (100%)	Sanofi-Aventis (100%)
Cluster11	6	8	1.33	0.53	5HT receptor modulators	Phase I	2010 (± 2)	Theravance (100%)	Theravance (100%)
Cluster12	5	6	1.20	0.60	cholinesterase inhibitor	Discontinued	1994 (± 4)	Bristol-Myers Squibb (100%)	Bristol-Myers Squibb (100%)
Cluster13	5	5	1.00	0.50	5HT receptor modulators	Suspended	2006 (± 3)	Pfizer (100%)	Pfizer (100%)

Institution citation network

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Top 15 technology flows

Rank	Technology outputting	Technology inputting	Citation counts
1	Elan	J&J	208
2	Elan	Elan	179
3	Elan	Pfizer	125
4	Targacept	Targacept	83
5	Elan	University of California	56
6	Pfizer	Pfizer	20
7	US Health & Human Services Dept.	US Health & Human Services Dept.	20
8	Vertex	GPI	18
9	Pfizer	J&J	16
10	NovoNordisk A/S	NovoNordisk A/S	16
11	GSK	GSK	16
12	Sanofi-aventis	Sanofi-aventis	14
13	S Health & Human Services Dept.	Raptor	14
14	Scripps	Scripps	13
15	Merck & Co	Merck & Co	11

Institution citation network

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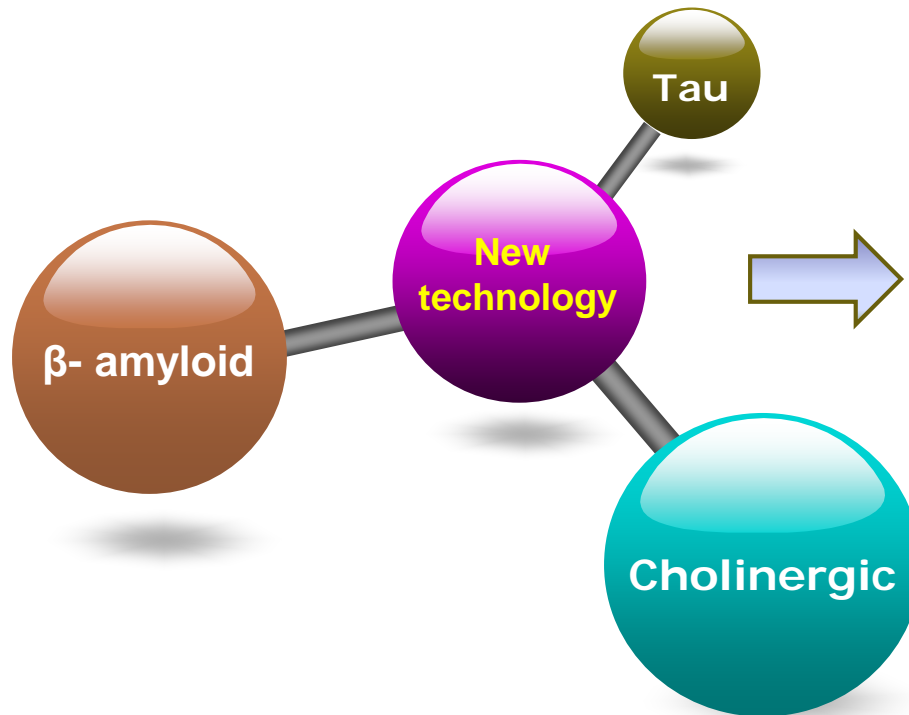
Patentee classification

Patentee	Total degree	Proportion of other-citation	Proportion of citation by others	Proportion of self-citation	Type
Sanofi-aventis	31	0.18	0.00	0.82	Closed
NovoNordisk A/S	41	0.04	0.32	0.64	Closed
Targacept	168	0.00	0.02	0.98	Closed
Theravance	16	0.00	0.00	1.00	Closed
Bristol-MyersSquibb	12	0.00	0.00	1.00	Closed
GSK	32	0.00	0.00	1.00	Closed
Scripps	29	0.19	0.00	0.81	Closed
Lilly	30	0.35	0.50	0.15	Balanced
Merck & Co	36	0.40	0.16	0.44	Balanced
US Health & Human Services Dept.	65	0.13	0.42	0.44	Balanced
Eisai	26	0.32	0.64	0.04	Outputting
Vertex	31	0.00	1.00	0.00	Outputting
Elan	766	0.03	0.66	0.30	Outputting
University of Washington	16	0.07	0.87	0.07	Outputting
Pfizer	201	0.73	0.16	0.11	Inputting
J&J	253	0.96	0.03	0.02	Inputting
GliaMed	20	0.95	0.00	0.05	Inputting
GPI	44	0.57	0.24	0.19	Inputting
Raptor	30	0.56	0.24	0.20	Inputting
University of California	76	0.86	0.04	0.10	Inputting

Discussion

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1. Technology distribution



◆ Pure birth

◆ Recombination
(Based on technology flows)

Multi-target-directed

ChEI	~	ChEI
NMDA	~	ChEI
ChEI	~	anti-A β

Discussion

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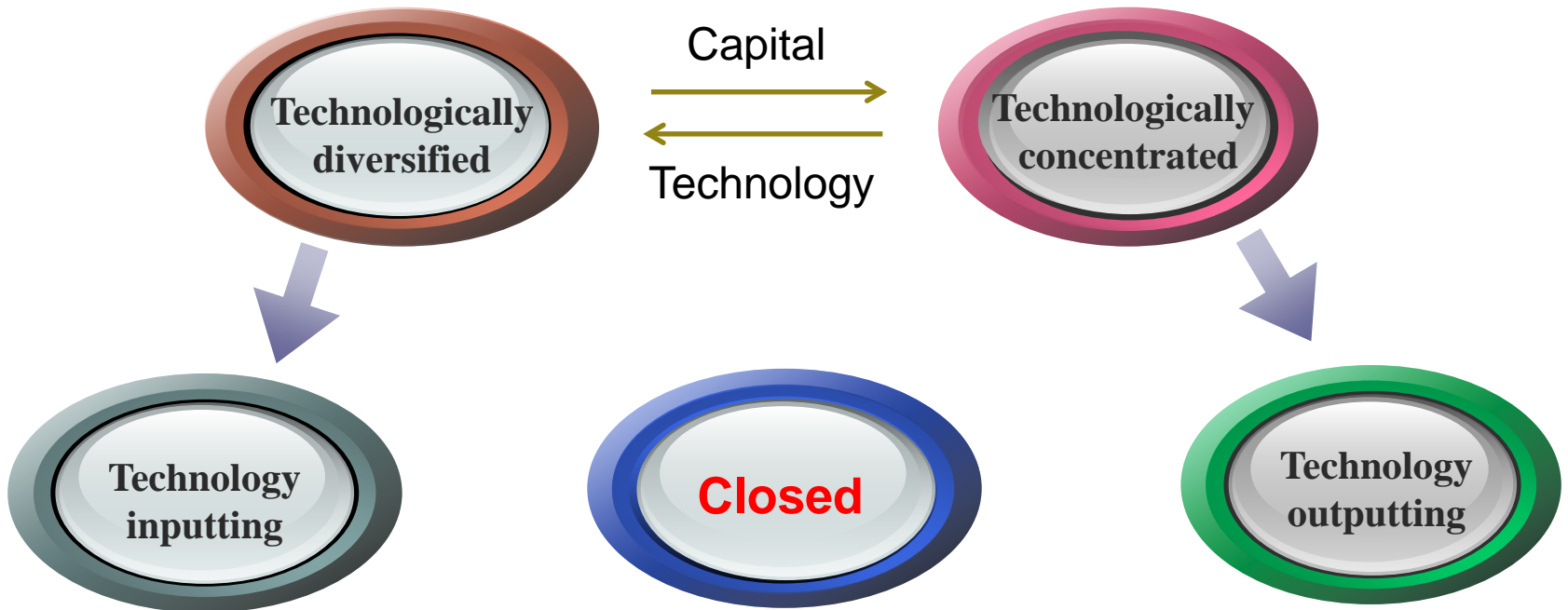
2. Development of different hypothesis

- Cholinergic insufficiency theory
 - mature stage
 - decline
 - marketed drugs
- A β theory
 - growth stage
 - great potential
 - Phase II , III
- Tau theory
 - Great importance
 - Develop slowly
 - High cost of the technological procedure

Discussion

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3. Analysis based on patentees



- Technology self-diffusion
- Leader in a specific technology domain

Discussion

4. Recommendations

- The government can guide to **pay more attention to prophylaxis and treatment of AD** and **promote basic research** for anti-AD drug development at the policy level.
- The researchers should identify unambiguous therapeutic drugs with **more stable clinical results**. Some **new theories and targets for AD** must be noted. Further, mature technology should be **protected by patents timely**.
- For investors, technologies that **have a huge potential** and that are **protected by a mature patent** are worth investing in , and companies that **concentrate on a single therapeutic mechanism that performs well** need to receive investments to market their products.

Discussion

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Navigation Map

Knowledge Position System

Publication

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Xu Jiachen, Kong Xiangjun, Qiu Lan, Geng Xiaomei, Hu Yuanjia*, Wang Yitao*. Research and development of anti-Alzheimer's drugs: an analysis based on technology flows measured by patent citations. *Expert Opinion on Therapeutic Patents*, 2014. [doi:10.1517/13543776.2014.915943].





Thank You !

