IP Overview

HIV Therapy

2009

FRINNOV

www.frinnov.fr

FRINNOV
83 Boulevard Exelmans
75016 PARIS
Tél. : +33 (0)1 40 51 00 90
Fax : +33 (0)1 40 51 78 58
www.frinnov.fr

IP OVERVIEW
Competitive Panorama

Patent mapping - A new tool to decipher market trends

IP Overview

MULTI-CLIENT PATENT LANDSCAPE ANALYSIS

IP Overview is a report that analyses all patent families filed on a given thematic
Available reports in life sciences are HIV Therapy, Malaria, CDK inhibitors, Nanoparticles for bio-imaging, Monoclonal antibodies against digestive system cancers

ON DEMAND IP Overview

TAILOR-MADE PATENT LANDSCAPE ANALYSIS

IP Overview On Demand is similar to IP Overview but 100% tailored to your needs
Ask your questions and we will answer by **a specific analysis of the patent landscape** of your area of interest

IP Portfolio

CUSTOMIZED STUDIES OF PATENT PORTFOLIOS

Position your patent portfolio or the one of your competitors

IP First step

PRIOR-ART SEARCH

Need more information? ***Free access to the interactive database is provided for studies published since 2010***

Contact us at ipoverview@fist.fr

FIST

HIV Therapy

Summary

Figures and tables

Methodology

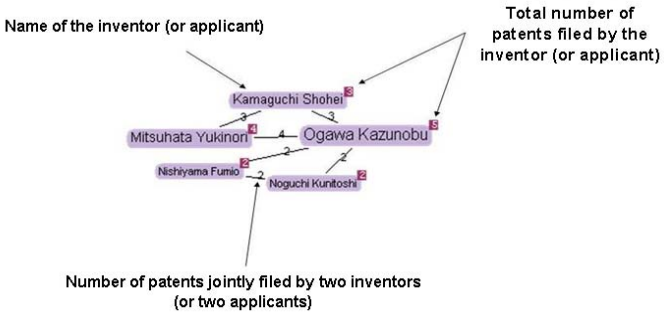
The different patents and patent applications were extracted from the data bases FamPat (Questel), espacenet, USPTO or other data bases. In particular, with these bases it is possible to group patents and patent applications into patent families and to cover all the domains found in the documents published by 77 patent offices.

The search methodology used in this study associated Boolean operators (AND, OR and AND NOT) but also more complex search operators such as word truncation (in the middle or the end of a word), series of words or searching for words in the same sentence or paragraph. The search for key words can be made in titles, abstracts or the main claims.

The search for patents can be limited by IPC or ECLA codes or by the US classification, as well as by filing or priority dates.

Raw data and global statistics were processed with Intellixir software (www.intellixir.com).

How to read the maps of inventors or collaborations among applicants:



Introduction

The Human Immunodeficiency Virus (HIV) is a double-stranded RNA virus from the Retroviridae family. Discovered in 1983, HIV is responsible for the Acquired Immune Deficiency Syndrome (AIDS). Its mechanisms of action and transmission were described in the years following its discovery, and the first treatment, called azidothymidine or azidovudine, was marketed in 1987 as a monotherapy. A new antiretroviral has been marketed nearly every year since 1992. Tritherapies associating several antiretrovirals were marketed in 1996.

Even if tritherapies have significantly reduced mortality from AIDS in the developed countries, worldwide mortality is still high because treatment is not readily available in the developing countries. In 2007, an estimated 2.1 million people died of AIDS worldwide and there were 2.5 million new infections. The prevalence of the disease is 33.2 million people. The figure below shows the distribution of seropositive individuals throughout the world.

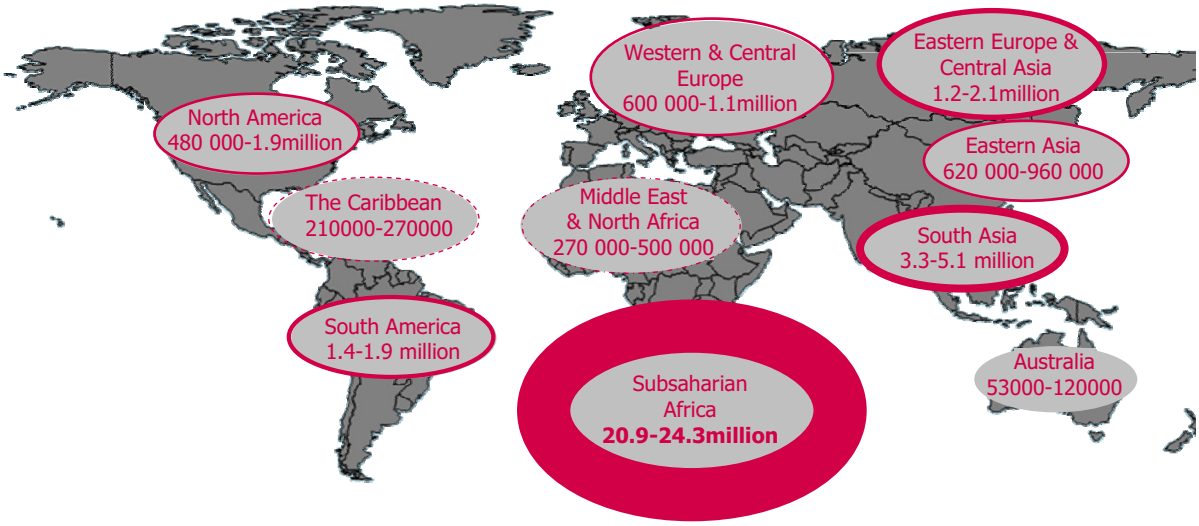


Figure 1: Number of people living with HIV (2007) [1]

Most of the antiretroviral drugs being marketed today target inhibition of two types of enzymes that are crucial to the HIV replication cycle: reverse transcriptase and protease. Recently new therapeutic classes have been developed to inhibit other steps in the cycle. Indeed, as seen in the figure and table below, the life cycle of the virus is complex and involves many steps, each of which is a new potential target for therapy.

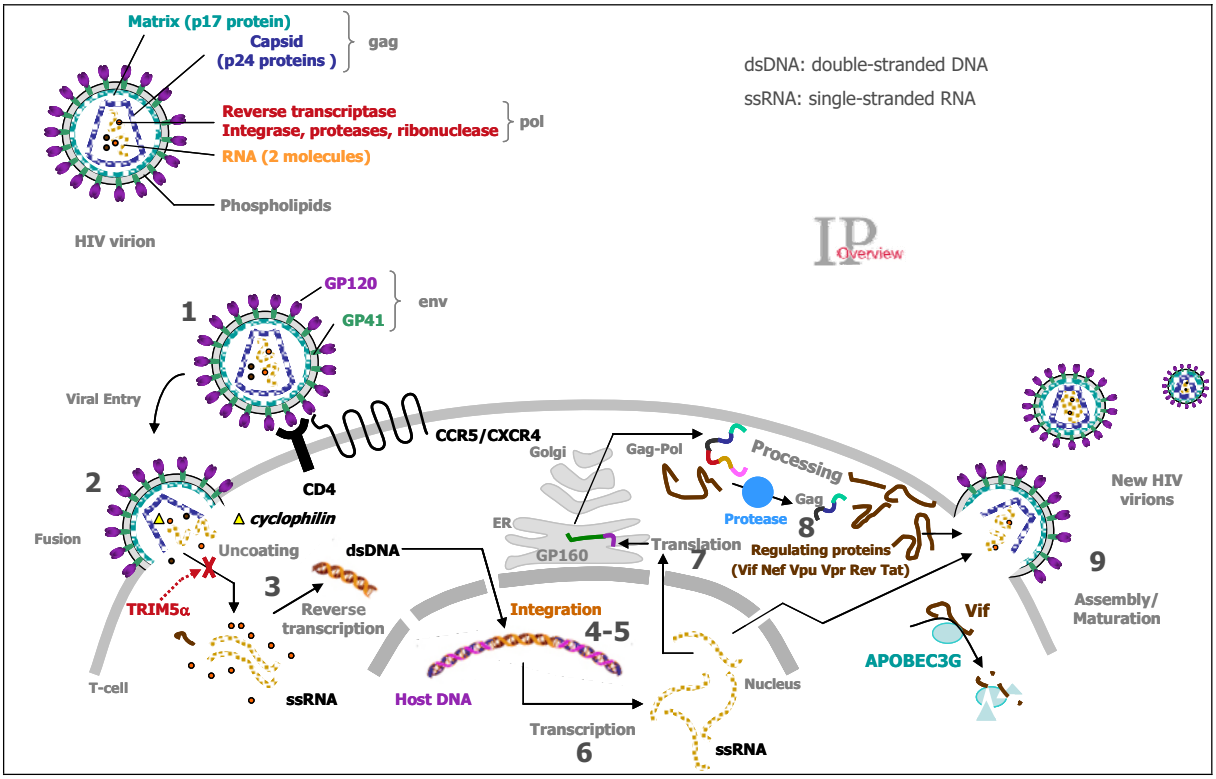


Figure 2: HIV replication cycle

HIV replication cycle	Corresponding therapeutic leads
1 Attachment of the virus to the host cell and fusion with its membrane	Inhibitors or antagonists of chemokine receptors (e.g. CCR5 and CXCR4), glycoproteins (GP41 and GP120) and CD4 proteins; cyclophilin A antagonists
2 Uncoating and penetration of viral proteins and viral RNA into the host cell	TRIM5α
3 Reverse transcription (Viral RNA is transcribed into DNA) and the destruction of viral RNA by ribonuclease	Reverse transcriptase inhibitors. Creation of transcription errors (APOBEC3G). Vif antagonists
4 Integration of viral DNA into the host cell genome	Integrase inhibitors
5 Duplication of viral DNA	Replication inhibitors (e.g. Nef)
6 DNA-RNA transcription *	Transactivator tat antagonists
7 Viral protein synthesis by the translation of messenger RNA *	Ribosome inactivating proteins, antisense oligonucleotides, RNAi
8 Formation of virions by cleavage of mother proteins by proteases	Protease inhibitors
9 Budding of the virion and infection of new cells.	Maturation inhibitors

Table 1: Therapeutic targets explored in the many steps of the viral replication cycle

** Some therapeutic research focuses on deactivating the functions of all or part of the viral genes at different stages of the replication cycle. The three main HIV genes are gag, pol and env genes which define the physical structure of the virus (gag), the reproductive mechanisms (pol) and code the envelope glycoproteins (env). The six other genes are tat, rev, vpr, nef, vif, and vpu for HIV-1 or vpx for HIV-2 which code for the regulatory proteins*

As shown in the table above, non-viral targets are being studied, for example cell proteins such as APOBEC3G, Trim5α (a protein that is naturally present in monkeys) and cyclophilin A. These proteins act as natural antagonists or agonists (cyclophilin A) to the virus.

Another approach in therapeutic research is stimulating the immune system without necessarily acting on the viral replication cycle itself. Finally, several therapies target diseases directly associated with the weakened immune system, or so called opportunistic infections.

Moreover, to identify new anti-viral molecules and monitor the efficacy of certain treatments, therapeutic research has also focused on developing appropriate evaluation and screening methods.

Finally to improve the delivery and/or the pharmacokinetics of a treatment, research has developed pharmaceutical formulations adapted to the novel active ingredients.

With a global market of 10 billion US$, many institutional and industrial players have shown a keen interest in developing HIV therapies and have already marked out their positions in this field by building strategic patent portfolios. As a result, more than 6800 patents and patent applications were filed between 1983 and 2006. The aim of this IP Overview is to present a comprehensive picture of the intellectual property in the field of HIV Therapy and to analyze the strategic positions of the research teams and companies in this sector.

1 Brief outline of the market

In 2007 the global market for HIV Therapy was nearly 10 billion $US[1]. Growth is expected to continue and should reach approximately 15 billion $US in 2012, driven by the dominant position of drugs on the market (for a revenue of 10 billion $US), by novel therapies (for a revenue of 4 billion $US) and by the entry of generics onto the market (for a revenue of 1 billion $US.)

At present, 95% of the market is shared by three classes of drugs:

- Nucleoside reverse transcriptase inhibitors (NRTIs) (50% of the market share)
- Protease inhibitors (PIs) (30% of the market share)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (15% of the market share)

The main classes of novel therapeutics are entry inhibitors which prevent the virus from entering the cell, integrase inhibitors and maturation inhibitors.

Currently 90% of the HIV therapy market is dominated by 6 leading companies, which include, in descending order of their market share: Gilead, GlaxoSmithKline, BristolMyerSquibb, Abbott, Roche and Boehringer-Ingelheim.

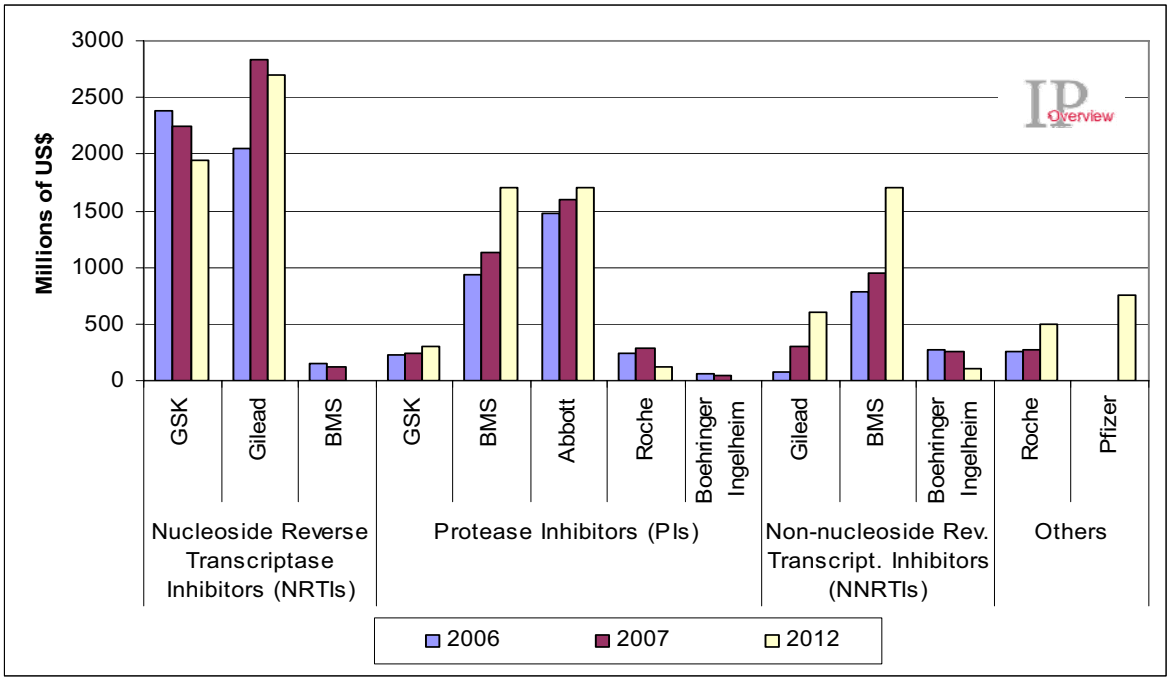


Figure 3: HIV Therapy Market Evolution Prospects and the Main Players

Approximately 60% of the market is located in the United States and 30% in Europe.

[1] *Sources: 2007 Activity Reports of the companies Abbott, BMS, Boehringer Ingelheim, Gilead, GSK, Roche, Merck&co, Pfizer and Johnson&Johnson*

GlaxoSmithKline, which has led the market for many years with 6 products, has, for the first time, been surpassed in terms of revenues by an alliance between the companies Gilead and BristolMyerSquibb[2]

2 http://money.cnn.com/2007/11/19/news/companies/hiv/index.htm with updated data for 2007

2 A brief outline of the pipeline

There are more than 90 therapeutic antiviral molecules for HIV registered in different clinical trials to date. Fifty of these drugs are in Phase I clinical trials, 35 in Phase II and 12 in Phase III. The molecules are being developed by many different companies, without any one having a clear lead.

The most frequent sub-categories of molecules in the pipe-line are Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Nucleoside reverse transcriptase inhibitors (NRTIs), CCR5 Co-receptor inhibitors/antagonists. Many preventive vaccines have reached early stages of development but tend to fail before reaching further stages.

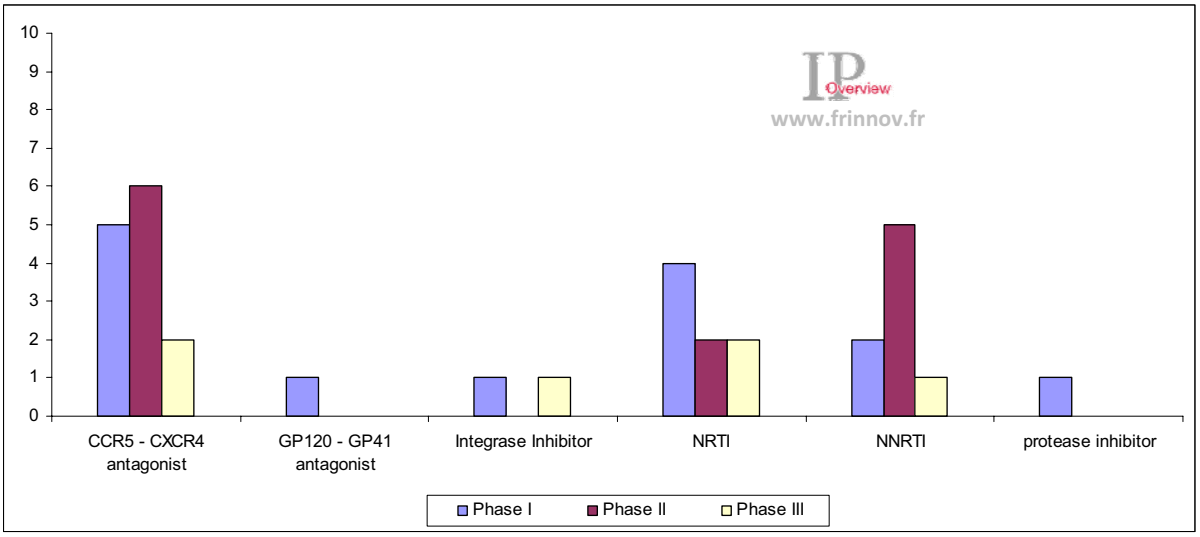


Figure 4: Molecules under development by class of antiviral (already marketed)

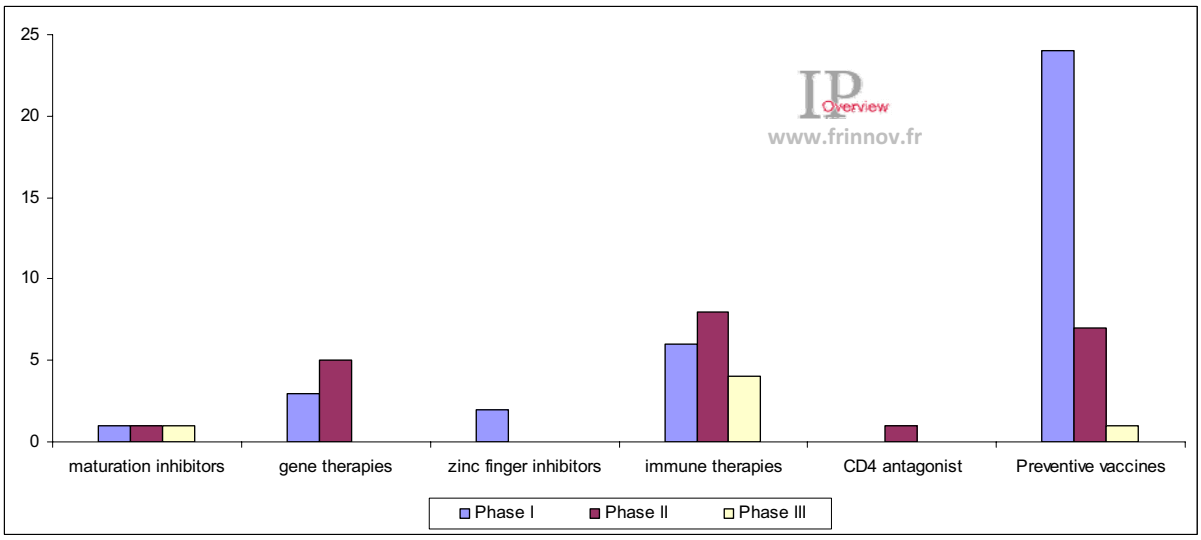


Figure 5: Molecules under development by class of antiviral (not yet marketed)

3 Protection strategies

3.1 Evolution of patent filings

To study the intellectual property environment in the field of HIV therapy, a patent search was performed using the following key-words: HIV, treatment, inhibition, agonist, antagonist, compound, vaccine and all related words. The search with these key-words had no restrictions by date. Although a patent is valid for 20 years, limiting our search over time would have eliminated older patents which may still be valid because of supplementary protection certificates and would have prevented us from developing certain points which we wanted to bring to light in this analysis. The search resulted in 6800 families of patents and patent applications published as of November 10, 2008.

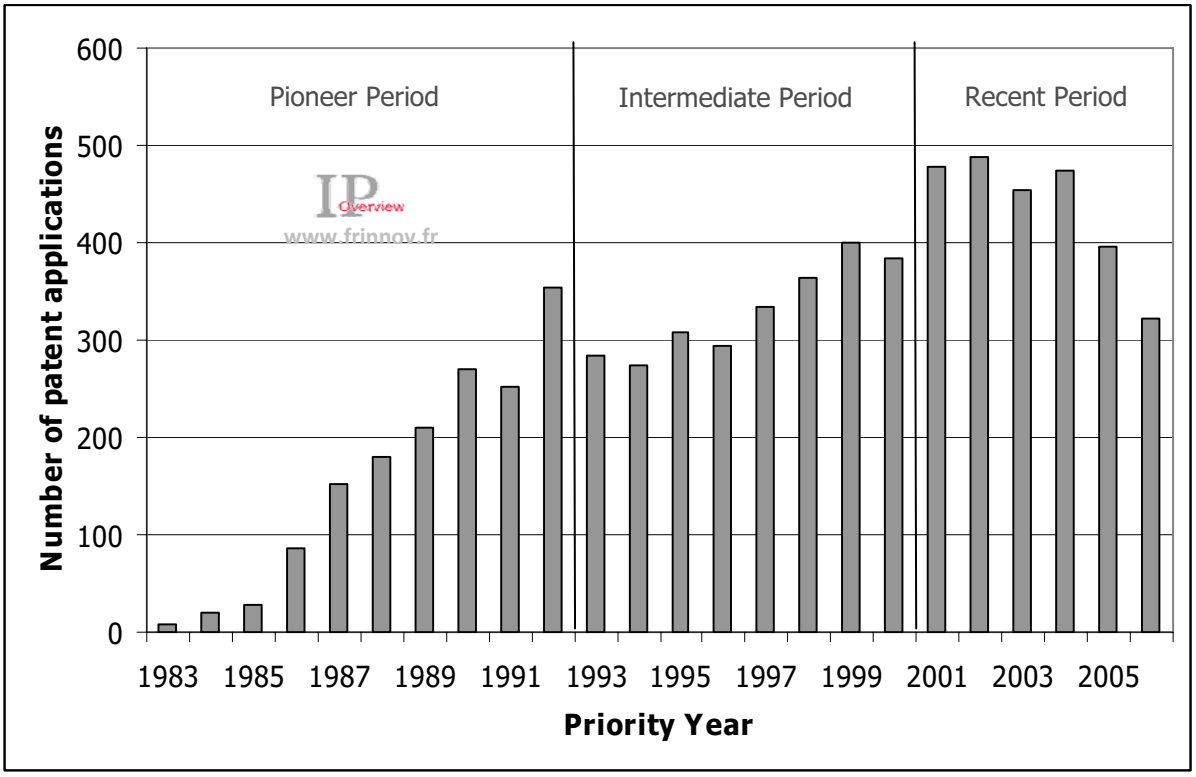


Figure 6: Evolution in patent filings

The number of patent applications filed is underestimated by approximately 20% until November 2000, when the US patent legislation changed. In fact before this date, US patent applications were only published when the patent was granted. Indeed, applications that were not granted were never published.

Patent filings began as of 1983 when the HIV virus was discovered and grew exponentially to reach approximately 300 patents per year in the 1990's. There was an intermediate period between 1993 and 2000 with a linear increase in the number of filings from 300 to 450 applications per year. A plateau was reached between 2001 and 2004 followed by a marked downturn in the filing rate in 2005

and 2006. It should be noted that when this study was performed (November 2008), a certain number of applications, in particular those filed at the end of 2006, may not yet have been available on all databases because of the time needed for patent offices and data bases to update information concerning the publication of applications. (Delay to publication 18 months after filing, plus the time to transfer and process information by database providers). Nevertheless, the downturn in the filing rate is certain.

3.2 Priority patent applications

An analysis of the place of filing of priority patents results in the following map.

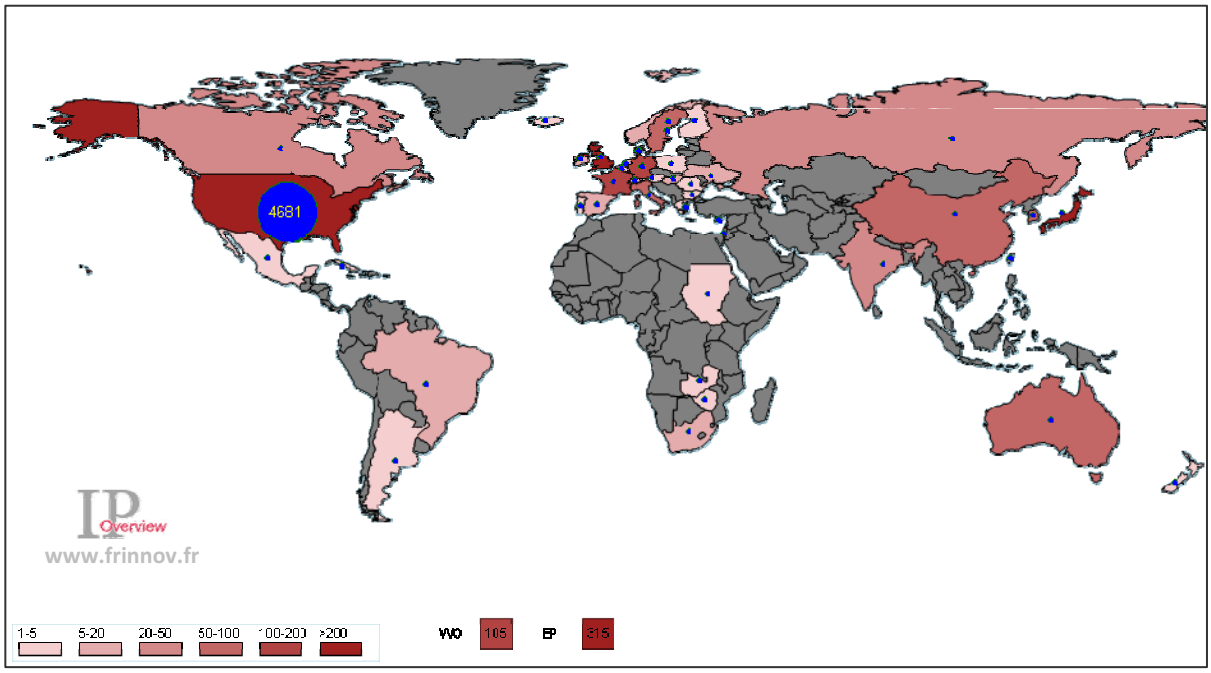


Figure 7: Geographic distribution of priority filings

The United States is indisputably the country where the most priority patents have been filed in this field (a little more than 4600 patent applications). This is due to several factors, mainly because this country is a major market. It is also due to the nationality of the main applicants and the major role that universities and international pharmaceutical companies located in the United States have played. Finally, because of the differences in legislation from 1983-1995 and the flexibility of US legislators as well as their lead in the protection of biotechnologies, certain European institutions chose to file priority US patent applications.

With approximately 1200 priority patent applications filed, Europe is in second place for the number of priority patent filings. Japan is third with 340 priority filings.

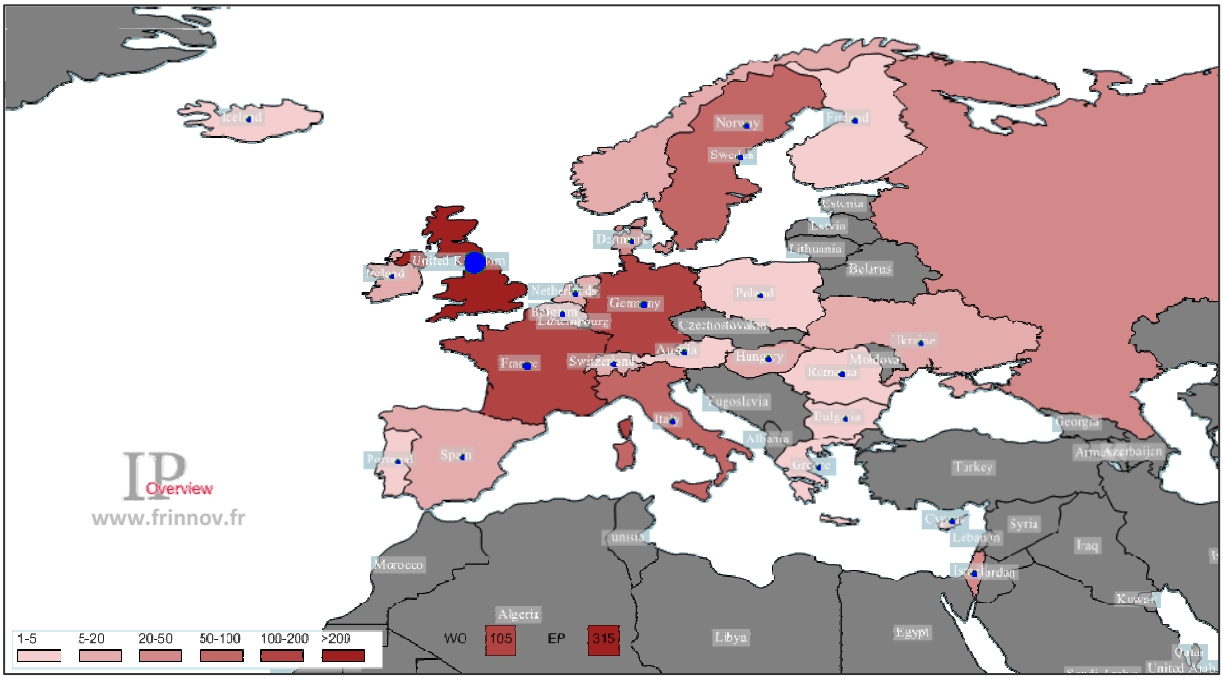


Figure 8: Geographic distribution of priority filings/Close-up: Europe

In Europe, the UK has the most filings (420). France and Germany follow with 170 and 150 applications respectively. The evolution of the geographic distribution of priority filings over time shows that the first priority patents were filed in 1983-1984 simultaneously in France, the UK and the United States. As of 1986 the United States established and has maintained its leading position with the most priority filings.

	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06
NORWAY															1		2	6	1	2				
INDIA														1			1	1	2	4	4	7	8	5
RUSSIAN FED											2	1	1	1		3	1	1	9	2	3	3	2	1
CHINA											2	1	1	1	1		5	4	8	10	11	13	8	11
KOREA										8	5	5	7	1	2	5	4	7	13	6	6	2		
CANADA							3	2	2	3	1	2		2	4	3	4	3	3	4	2	1	1	
ITALY						2	1	3	5	4		1	6	3	7	2	2	2	6	4	3	3	1	
SWITZERLD						1		1	1	1	1		1	3		1							6	3
IRELAND						2	2	2										2	2	2	1			
WORLD					1		1			2	2	4	1		6	7	6	9	12	7	14	10	12	11
ISRAEL					1					5	1	4	4		4	1		3	2	4				
EUROPE				10	1	7	2	10	11	2	6	4	5	7	4	13	9	23	35	27	28	40	32	39
DENMARK				1	1							2	2	1			3	2	1	6	2	5	4	2
AUSTRALIA				3	2			1		4		7	3	2	1	4	7	2	8	5	6	6	3	6
SWEDEN				2	8	2	4	7	2	1		1	1	1	2	5	1	1	3			2	5	3
JAPAN				1	12	15	11	17	12	19	10	24	30	15	14	24	27	18	16	20	18	16	17	5
GERMANY			1	1	4	5	10	5	12	17	5	6	9	7	4	14	10	5	10	10	4	6	3	
FRANCE		7	1	14	8	4	12	9	7	5	12	8	9	5	3	9	8	11	16	5	2	7	2	2
U.S.A.	4	12	24	49	101	125	142	182	174	249	218	189	203	212	253	238	277	259	300	345	311	334	266	214
UK	4	1		3	12	16	18	28	22	25	16	11	16	30	26	31	26	20	24	19	32	11	16	16

Table 2: Evolution of priority filings

Once these pioneer countries had begun filing, priority applications were then filed in many countries as time went on: Germany in 1985, Japan, Sweden and Australia in 1986, Italy in 1988, Canada in 1989. As of 1992, priority patents were filed in Korea then in China and India as of 1999.

The priority filing rate in the US, Japan, the UK and France and Germany remained vigorous throughout the entire period.

3.3 Extensions

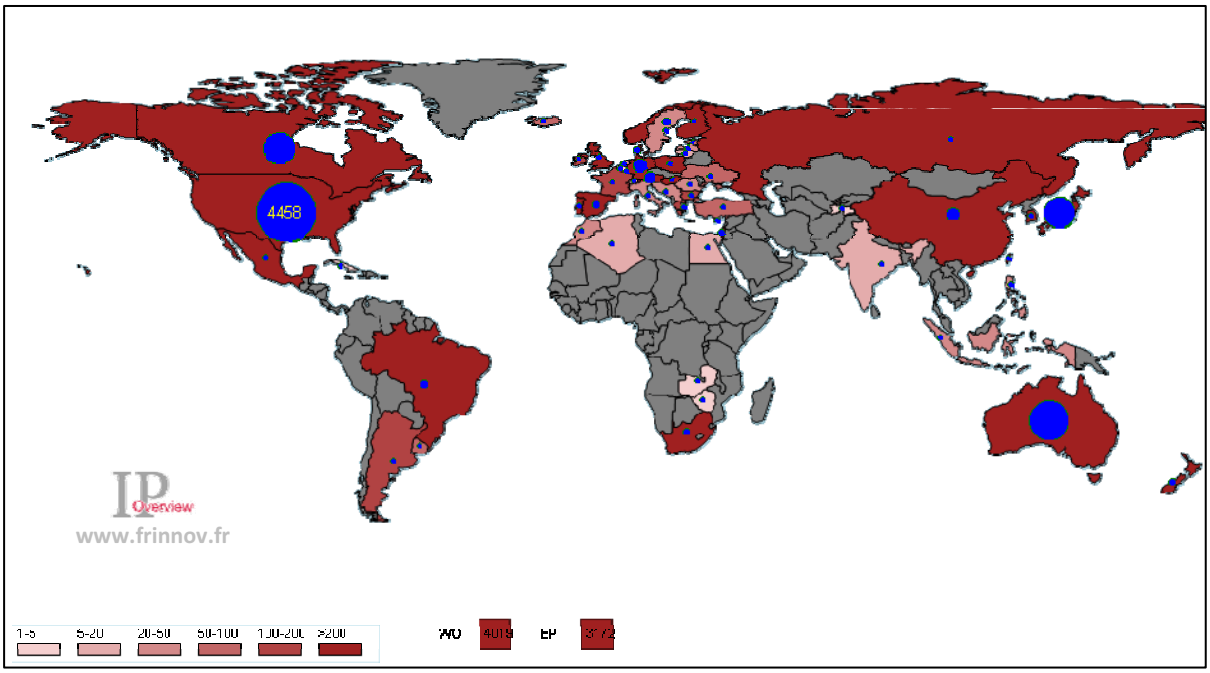


Figure 9: Geographic distribution of extensions

An analysis of the countries chosen for the extension of priority filings is an indicator of the markets and/or the production sites of the applicants. The choice of countries may also be guided by a company's competitors and potential infringers, even if there is no market in these corresponding territories.

	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06
MEXICO				1	5	1	7	14	24	28	5	34	40	4	5	13	32	45	72	92	71	26		
POLAND				2	1		3	7	4	22	15	16	25	27	31	31	27	29	45	49	9	1		
BRAZIL				2	2	2	4	12	8	24	10	25	37	43	39	51	48	50	66	83	76	80	2	
CHINA			1	3	6	6	9	10	13	31	35	33	42	47	55	59	63	68	98	106	102	120	74	11
NORWAY			4	7	22	16	19	26	18	37	20	26	27	34	33	31	34	34	37	51	42	48	18	
NEW ZEAL		2	4	12	22	17	19	20	12	37	30	31	33	35	31	42	26	34	42	51	10			
KOREA		1		6	11	9	18	15	16	23	11	8	11	26	6	12	8	9	19	50	68	71	61	4
JAPAN		4	11	28	69	66	100	119	91	113	86	106	99	92	132	134	149	140	163	189	168	197	56	4
ISRAEL		1	5	11	26	31	24	27	23	41	29	28	24	37	46	43	34	40	54	44				
HUNGARY		1	1	4	10	8	24	28	19	37	24	28	30	30	31	32	33	33	42	5		2	1	
GERMANY		3	9	20	49	44	64	58	62	96	60	74	72	59	60	73	81	48	55	40	24	16	3	
EUROPE		6	11	27	80	75	106	129	108	139	108	124	115	118	159	187	205	186	242	262	255	257	238	35
DENMARK		1	5	16	42	32	49	40	30	51	34	35	40	24	26	25	32	18	20	10	10	2		
CANADA		2	8	12	32	31	88	112	84	115	89	105	90	110	145	143	157	144	174	211	184	207	163	9
AUSTRIA		2	9	15	42	36	58	56	48	77	52	65	64	49	56	65	77	42	53	32	19	12		
AUSTRALIA		4	8	24	60	61	68	105	95	130	123	140	131	137	185	192	243	222	174	358	141	147	128	32
SPAIN		1	4	10	17	22	47	41	32	63	43	47	53	37	35	40	50	28	36	22	12	5	1	1
SH AFRICA		1	1	7	21	29	30	27	28	39	30	22	25	22	27	35	36	34	50	48	6			
WORLD		4	8	15	43	45	72	95	101	139	136	158	142	145	209	222	274	240	315	366	332	357	319	282
U.S.A.	8	16	19	68	82	108	110	151	134	248	184	179	229	210	228	259	278	314	371	382	318	304	161	97

Table 3: Evolution of extensions

Table 3 shows the evolution of extensions by country over time. As of 1984, patents were extended to countries covering the 5 continents. China was named very early (1986) in the extension of priority filings as were Brazil, Poland, South Africa, Mexico and Korea.

Paradoxically, there are fewer US patents than there are US priority filings. This is due to two factors:

- first, for older patents (before 2000) there are numerous US priority filings that were extended to other countries but never published because they were never granted in the US,
- after 2000, US provisional patents may have been filed then directly filed as PCT applications so the US extension has not yet been published.

3.4 Analysis of industrial patents over time

Throughout the entire period the proportion of industrial patents has remained relatively stable, with a ratio of industrial patents to institutional patents of approximately 75/25 respectively. Most of the patents classified as "Others" are the many US patents filed naming the inventors as applicants. The high number of institutional patents is a reflection of the continued importance of basic research in HIV therapies.

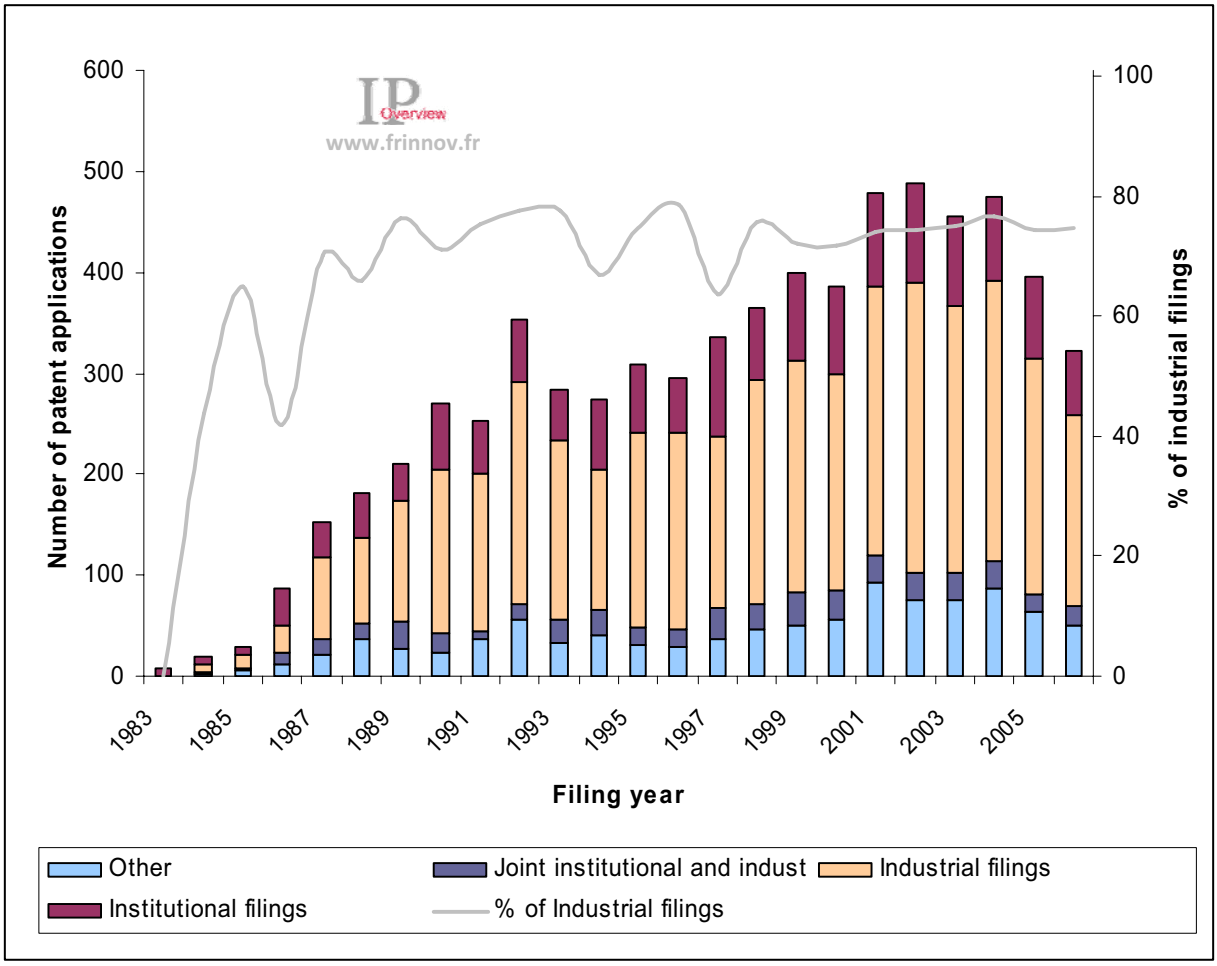


Figure 10: Evolution of the breakdown of industrial patents

3.5 Study of the granting of US patents

The evolution of the granting of patents (time and ratio) provides an overview of how a patent environment may be blocked in a given sector. Because of the filing practices of the players in this field, this analysis focused on the granting of US patents. However, data is also provided for Europe.

Traditionally, the grant rate in an emerging sector is initially very high then tends to drop as successive filings are made, since novelty and inventive step become increasingly difficult to prove because of the increasingly sizeable prior art. However, it is important to take into account the time between the filing of a patent application and when it is granted, which can vary depending on the topic.

To date, nearly 4500 US patent applications have been filed (priority + extensions) and around 2700 have been granted.

The figure below illustrates the average grant time observed for granted US patents.

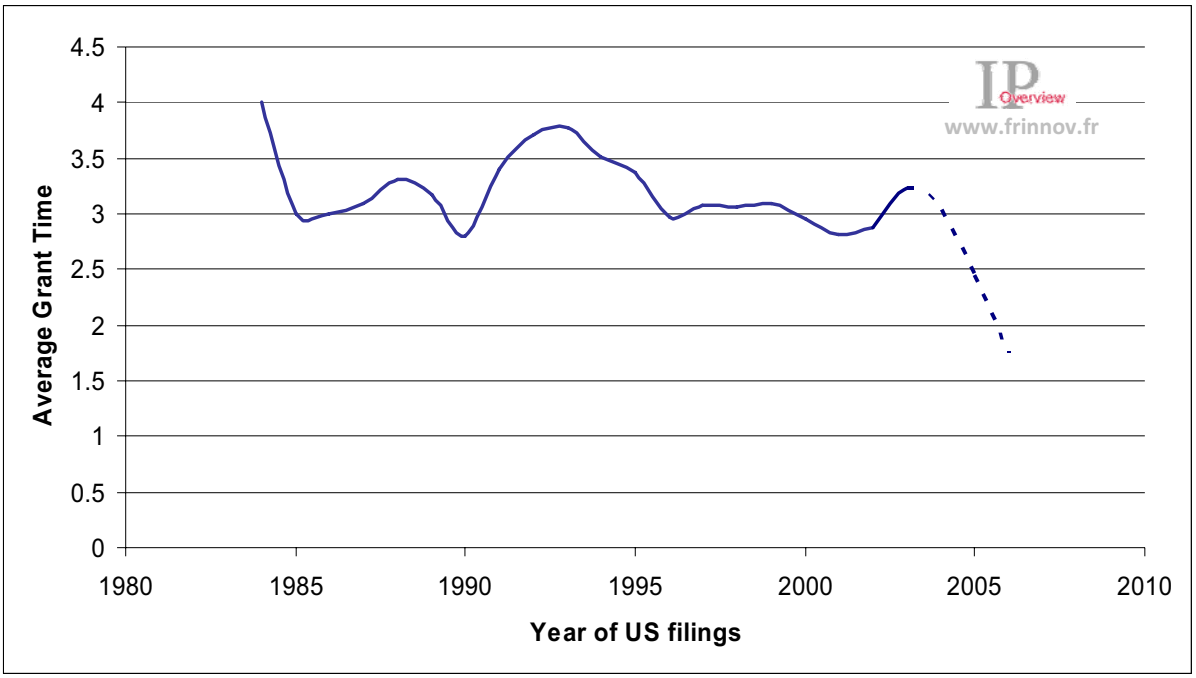


Figure 11: Evolution of average grant time for US patents

Since 1986 the average grant time of patents has been fairly stable and is approximately 3 years. Therefore, the analysis of granting percentage, shown in the figure below, is only significant until 2003. In fact, the average grant time for granted patents in subsequent years cannot yet be analysed because sufficient time has not elapsed. This calculation can be used to determine the time window for meaningful analysis of the grant rate and its evolution.

Furthermore, the grant rate observed in the figure is only significant for US patent applications filed after November 2000. In fact, before this date, US patent applications were only published on the day the patent was granted. In fact, applications that were not granted were never published.

Because of this legislation, it should also be noted that the data on the number of US filings is underestimated by approximately 20%.

This analysis shows the evolution of the grant percentage between 2001 and 2003.

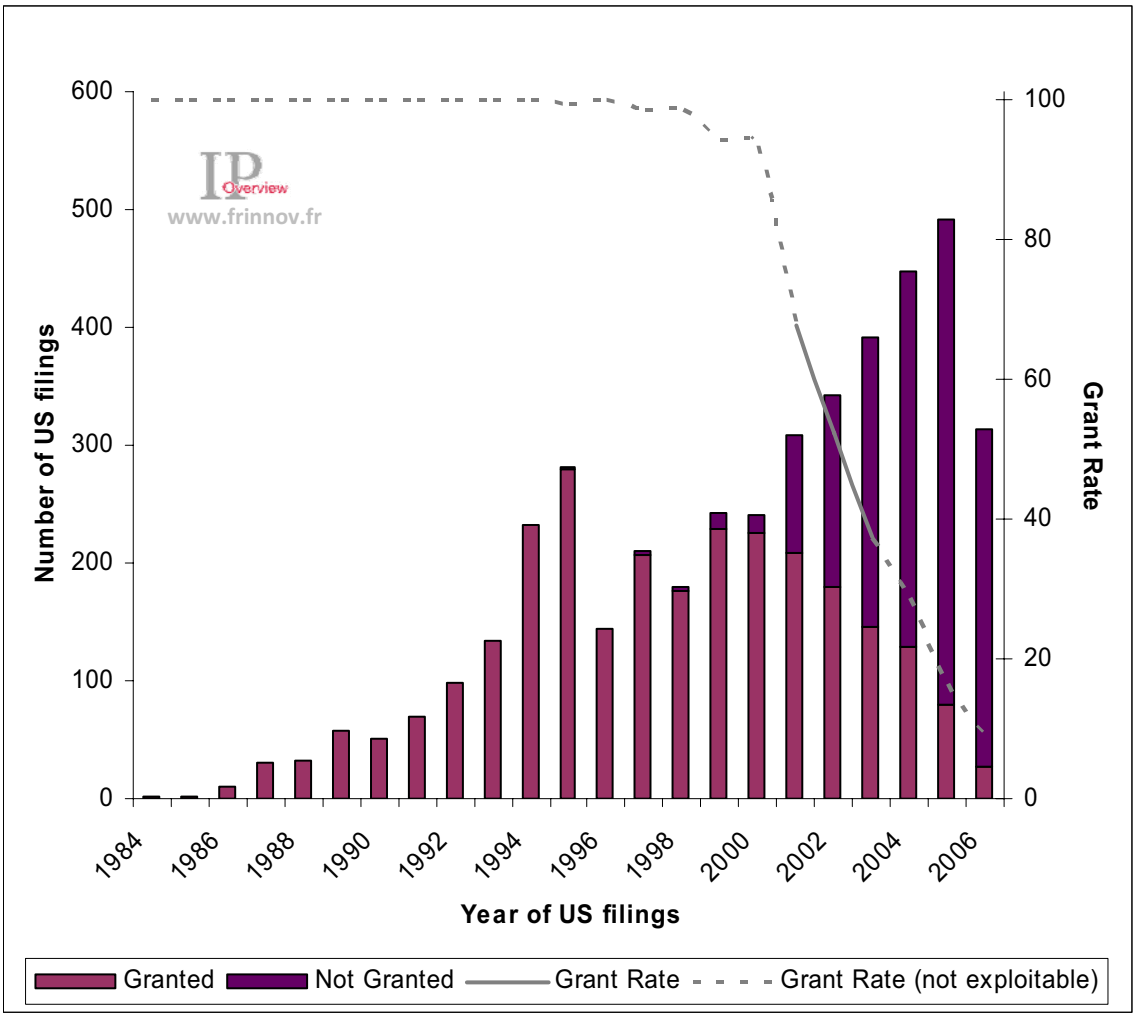


Figure 12: Evolution of the granting of US patents

This graph shows that a high proportion of US patent applications filed in 2001 were granted (70% grant rate). There is a rapid downturn in this percentage in 2002 (55%) and 2003 (35%). It should be noted that compared to similar sectors, for which the average grant time is also around 3 years, the grant rates observed for these patent applications are normal. The 2003 percentage is comparatively low, which could be the sign of tougher examination in the United States and should be correlated with a slightly longer examination time.

NB: It is important to bear in mind that this rate could change over the coming years as and when patents that may have taken more than 3 or 4 years to be granted are actually granted.

The same type of analysis was performed for the granting of European patents.

3.6 Study of the granting of European patents

This figure shows the evolution of the average grant time of granted European patents over time

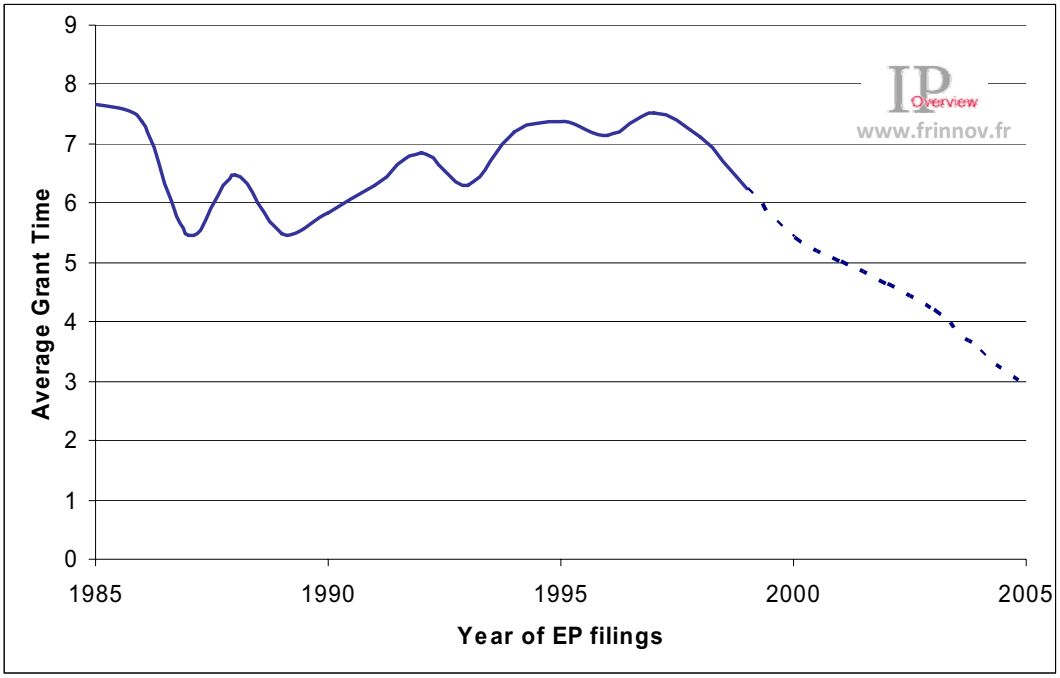


Figure 13: Evolution of the average grant time of EP patents

In Europe, the grant time, which is between 6 and 7 years, has also remained fairly stable.

Therefore the analysis of grant percentage in the figure below is only significant up to 1999.

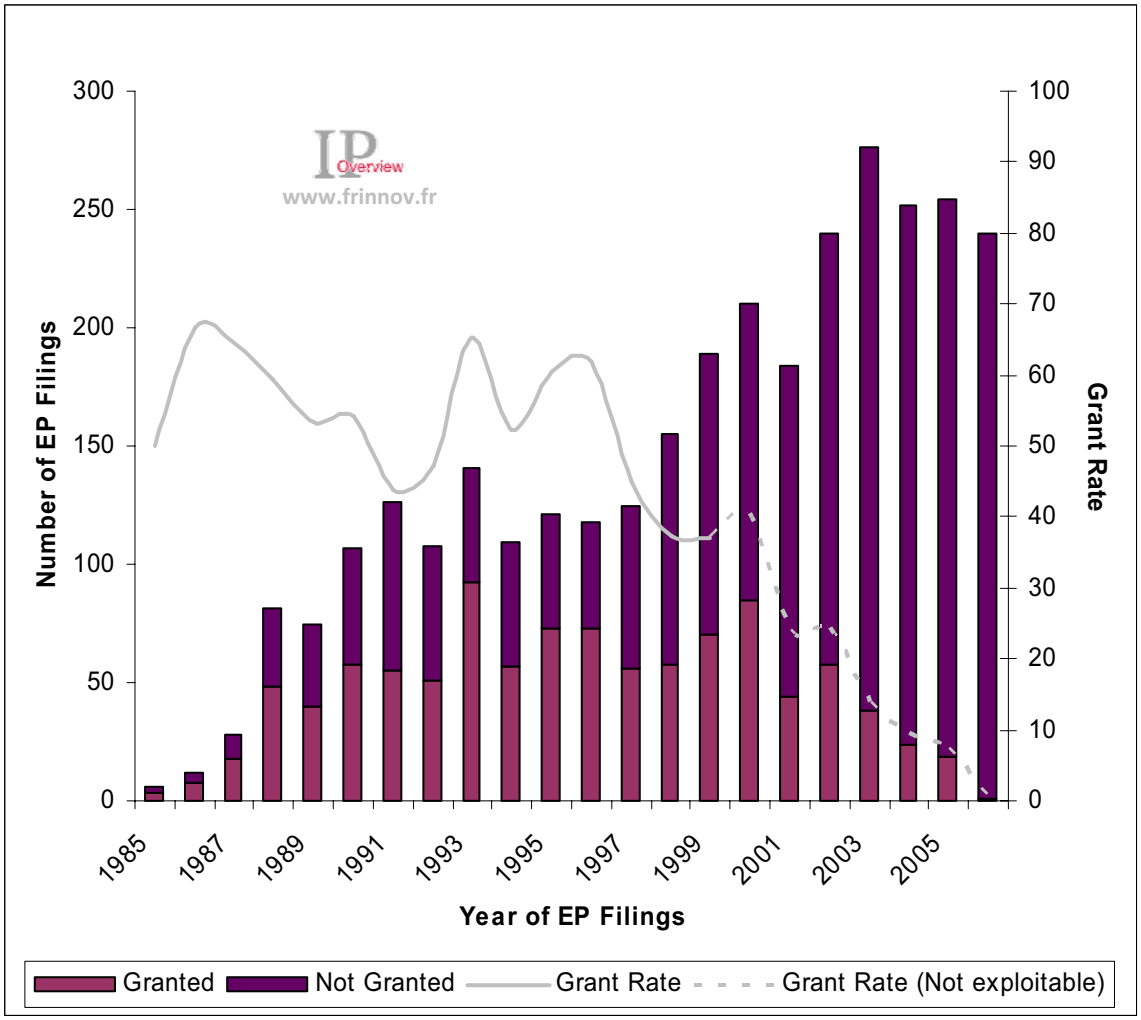


Figure 14: Evolution of the granting of EP patents

The percentage of European patents granted is around 50%. Nevertheless, it should be noted that the 55-60% grant rate in the first years of the study decreased slightly to 40-45% after 2000.

3.7 Evolution of the number of applicants

Figure 15 shows the evolution of the number of applicants per year (dark grey curve). Since a player in the field may not have filed one year but may have filed in preceding years, these data do not represent the total number of active players in the field of HIV Therapy.

The light grey curve shows the number of new applicants per year.

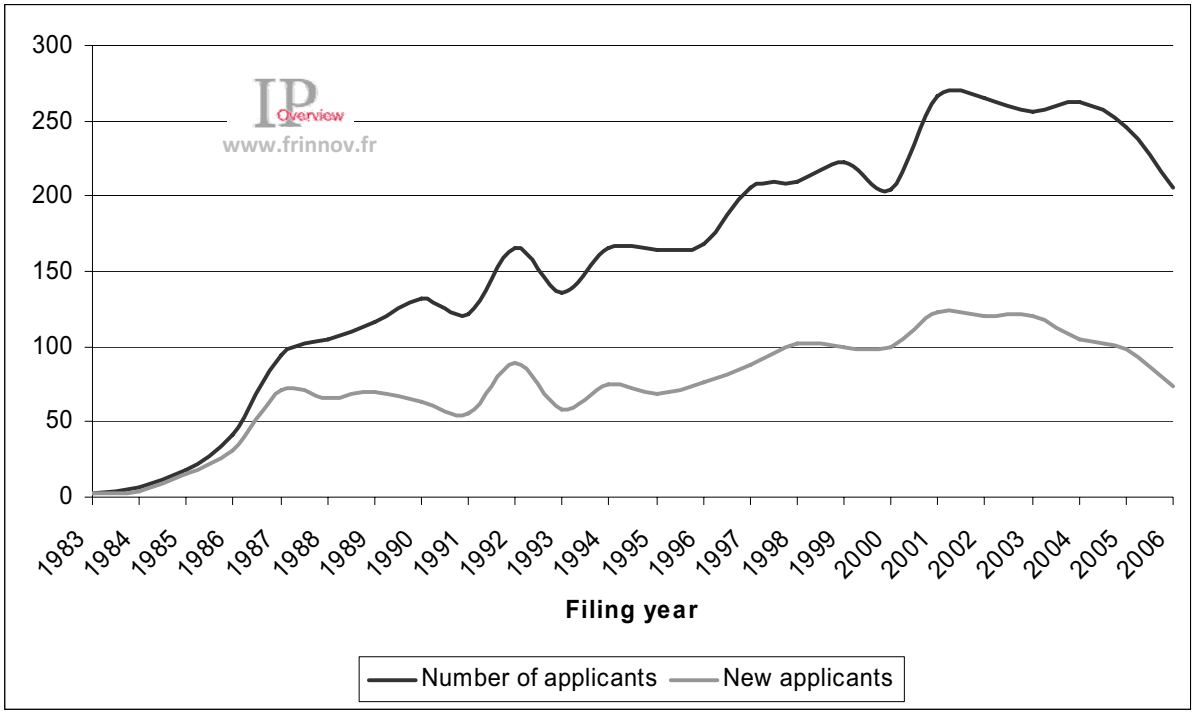


Figure 15: Evolution of the number of applicants

The number of applicants and new applicants has evolved in three phases:

- The first phase, between 1983 and 1987, was a 5 year period of strong growth with approximately one hundred pioneer applicants positioning themselves in the field;
- During the second phase, between 1987-2001 growth was linear with the number of applicants progressing from 100 applicants per year to 200 by then end of this period.
- During the third phase from 2001-2006, growth flattened out followed by a downturn in the number of applicants per year after 2005. This decrease will certainly continue in the coming years. Globally, there was a reaction to a significant reduction in R&D spending during the latter period resulting in a decrease in the number of new applicants (from 120 new applicants in 2000 to 70 in 2006)

4 Topology of patents in the sector

To analyse all HIV Therapy patents, the portfolio was broken down into several categories. It should be kept in mind that some patents could not be classified into any of the categories, while on the other hand one patent may be classified in several categories.

The portfolio was broken down into the following categories:

- Therapeutic targets (Reverse Transcriptase, Protease, …)
- Applications (inhibitor, vaccine, …)
- Classes of componds (chemical, peptide, …)
- IPC codes

4.1 Breakdown of patents into therapeutic targets

To develop HIV Therapies, proteins playing a major role in the life cycle of the virus have been targeted. These are mainly viral proteins but there are also host cell proteins (CD4 and chemokine receptors). Thus patents protecting HIV Therapies were classified according to these potential therapeutic targets.

The potential target proteins to prevent viral entry into the host cell are:

- **CD4 receptors**
- **CCR5 and CXCR4 and other chemokine receptors**
- **Glycoproteins (GP41, GP120) and their coding gene (env)**

To prevent the viral RNA liberated by the virus in the host cell from becoming transcribed into DNA, or this DNA from being integrated into the DNA of the host cell, the targets are respectively:

- **Reverse Transcriptase and its coding gene (pol)**
- **Integrase**

The step that offers another focus for therapeutic targets is the step from DNA transcription to the formation of virions. The corresponding targets are:

- **Regulatory proteins and their coding genes (tat, rev, nef, vif, vpr, vpu, vpx)**
- **Protease**

Once the virions have been formed, or to prevent the formation of proteins necessary to synthesize these virions, the following factors may be targeted:

- **Structural proteins and their coding gene (gag)**

This analysis only included patents describing a treatment whose aim was to interfere with the above mentioned targets and/or use them (entirely or partially) as an immunogen. However, the latter parameter was not applied to the categories "reverse transcriptase", "integrase" or "protease".

The following map shows the proportion of patents for each therapeutic target.

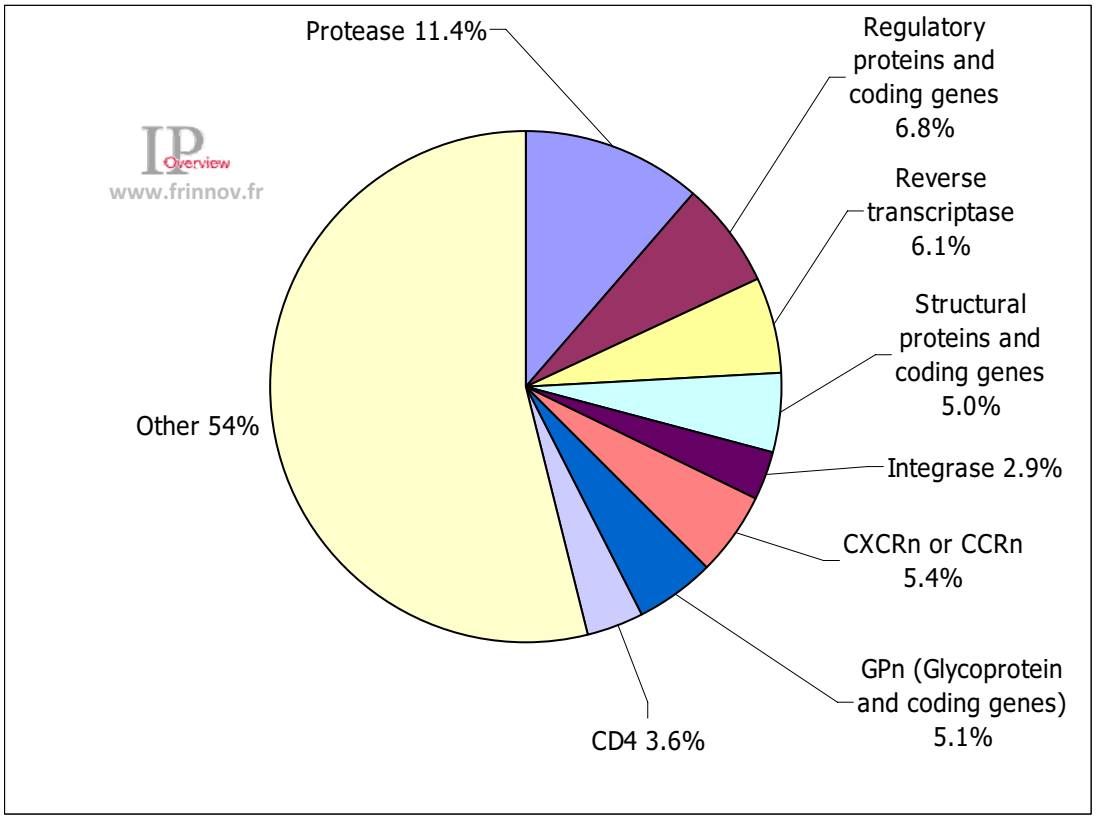


Figure 16: Breakdown of the portfolio by therapeutic target

	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07
Protease					6	15	18	44	34	118	63	65	98	60	45	44	58	42	60	52	33	49	35	26	
HIV regulatory proteins and coding genes		5		13	8	6	23	20	16	21	21	24	27	21	31	30	33	39	55	44	40	41	26	22	
Reverse transcriptase			1	2	5	7	6	16	20	15	18	21	22	25	32	52	32	44	36	41	23	52	24	26	
CXCRn or CCRn (Chemokine Receptor)								1					5	29	29	31	58	38	57	57	37	48	34	30	
Structural proteins and coding genes		6	6	17	10	14	18	15	11	22	10	17	10	19	16	11	18	39	65	37	25	26	14	14	
GPn (Glycoprotein and coding genes	2	3	3	16	16	21	17	36	12	11	19	8	14	10	17	24	19	22	23	35	21	32	27	19	
Integrase								2		1	2	8	4	8	5	18	13	21	15	26	22	47	35	21	
CD4	1				4	8	6	19	9	4	16	5	7	17	14	11	4	9	10	12	13	14	6	3	

Table 4: Evolution of the breakdown by therapeutic target

Black circles indicate FDA approval of one or two (double circle) drugs

In 1985, reverse transcriptase was already a potential therapeutic target. Indeed, the first anti-HIV drugs to be approved were reverse transcriptase inhibitors (the first was azidovudine or AZT). Although many patents have been filed for this target since 1987, the number of protease patents has always outnumbered reverse transcriptase patents reaching 100 applications per year in 1992 alone and then stabilizing after 1996. While numerous anti-HIV drugs targeting protease have been approved since 1995, it is interesting to note that up to now, a greater proportion of anti-reverse transcriptase drugs have been approved compared to the number of patents filed to protect this target.

Treatments targeting structural and regulatory proteins were protected as of 1984 and the number of patents has progressed in a similar manner, with a peak around 2001.

Glycoproteins rapidly became a therapeutic target and two peak periods of interest are observed, the first around 1990 and the second between 1998 and 2005. In 2003, a first inhibitor preventing viral entry into the host cell targeted the envelope glycoproteins. This was enfuvirtide, discovered by researchers at Duke University who founded the company Trimeris and collaborated with Roche as of 1999 to develop this drug.

Finally, although potential treatments targeting CD4 cells have been patented since 1987, results have been less successful, with only one potential drug in the pipeline to date.

More recently two other therapeutic targets have been investigated.

The first was integrase which was protected by patents describing anti-HIV therapies as early as 1990 with a peak in interest in 2004; the first integrase inhibitor was commercialised in 2007 (discovered by "IRBM P. Angeletti" a research subsidiary of Merck&co as of 2000 – and developed by the company Merck&co).

Beginning in 1995, chemokine receptors became a second target. Many patents covering this target have been filed since the year 2000, and a CCR5 inhibitor was commercialized in 2007 (Maraviroc, developed by Pfizer).

Among the non-classified patents in this category are those that describe other, less extensively studied, therapeutic targets. (e.g. cyclophilin, TRIM5α, APOBEC3G), or weakened or inactivated virus for vaccines, as well as patents without a specific target. It is difficult to identify a general theme in these remaining patents, which is why we have chosen not to include them in the analysis.

4.2 Breakdown of patents by application

The patent portfolio can also be broken down into applications. This illustrates what types of treatments are under study: specific inhibitors of one (or several) therapeutic target(s), combination therapies, stimulation/suppression of the immune system of the infected host (without administering a weakened version of HIV to the host or HIV derived particles, thus immunomodulation) or vaccines. It is interesting to observe what proportion of inventions concern the identification and evaluation of

novel treatments (Biomarkers/Screening methods) and what proportion of patents protect pharmaceutical formulations (galenic preparations) of therapeutic molecules.
It should be noted that many patents protect applications for both the diagnosis and the treatment of HIV. However the aim of our extraction was to identify HIV therapeutics. Thus a diagnostics category does not correspond to this aim and the result would have been very incomplete.

Based on these elements, the following applications were chosen:

- **Inhibitors**
- **Combination therapies**
- **Vaccines**
- **Immunomodulation**
- **Biomarkers and Screening methods**
- **Pharmaceutical formulations (Galenic preparations)**

For the category "pharmaceutical formulations", it should be remembered that many patents can describe a treatment while also claiming a pharmaceutical formula. We chose not to include these patents in this category and to only include patents that have a pharmaceutical formula as one of their main claims.

The following map shows the proportion of patents in each category:

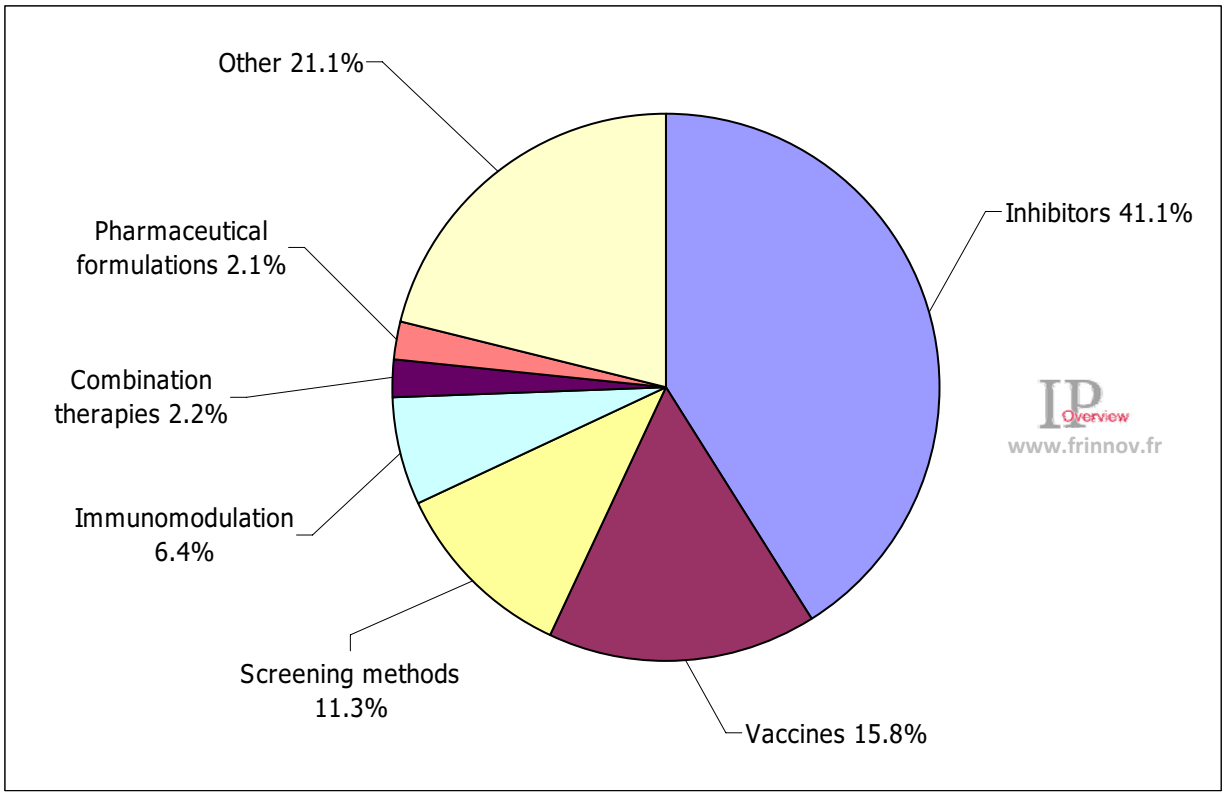


Figure 17: Breakdown of the portfolio by application

	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06
Inhibitors		3	9	13	51	71	87	137	106	204	171	157	180	169	177	208	208	188	234	248	211	252	203	150
Vaccines	5	16	12	38	40	53	49	69	73	57	64	38	50	48	65	55	61	92	89	87	69	68	60	61
Screening methods	2	6	8	20	13	11	22	24	19	23	26	39	28	40	57	55	63	91	102	88	64	57	48	43
Immunomodulation			1	8	9	5	8	14	12	19	19	19	10	21	31	28	45	42	49	58	50	45	21	21
Combination therapies					1	2	6	7	8	4	13	9	10	12	13	5	6	9	11	9	16	21	10	14
Pharmaceutical formulations				2	3	1	4	2	5	6	7	5	11	4	5	15	17	5	9	15	18	17	15	7

Table 5: Evolution of the breakdown by application

Since 1987, most of the therapeutic HIV discoveries have been made in the class of inhibitors. The number of patents filed in this class increased continually until 1992 when it reached 200 patents per year and has continued at practically the same rate since. In the five years after the virus was discovered, numerous vaccines were protected. Since then, the number of patents filed protecting vaccines has remained relatively constant. The quantitative leap in the number of patents filed after the 2000 in the categories "Vaccines" and "Biomarkers/Screening Methods" is mainly due to a change in US patent legislation (Publication of patent applications rather than granted patents). It is interesting to note that although there are many patents claiming vaccine formulations, no HIV vaccine has been approved by regulatory drug administrations.

Interest in biomarkers/screening methods, which are the third largest group of patents, grew steadily for four years after the virus was discovered then remained fairly constant until 1994 when a large number of patents were filed with this application. This trend can be correlated to the growing expertise in high throughput screening techniques such as proteomics and genomics (DNA chips).

Since 1985, there has been less, but still substantial interest in developing treatments to stimulate or suppress the host immune system.

4.3 Cross-analysis of the categories "applications" and "therapeutic targets"

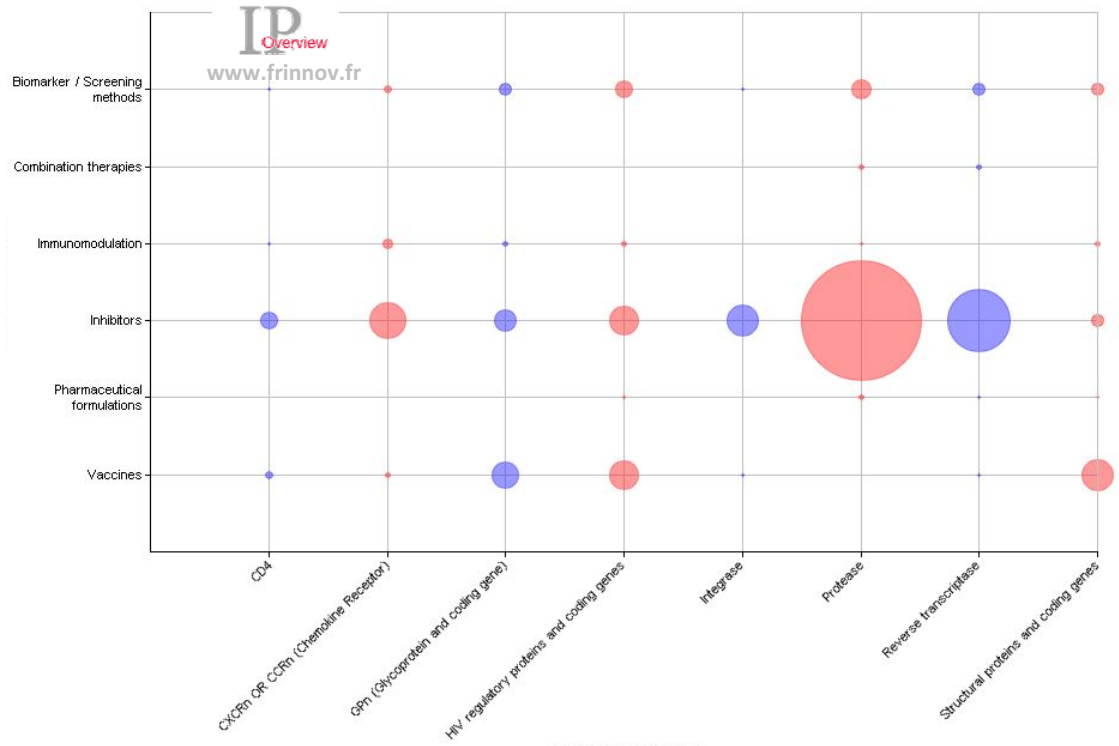


Figure 18: Cross-analysis of the categories applications and therapeutic targets

Cross-analysis of the categories applications and therapeutic targets gives a general idea of the most important targets and their applications. This graph shows that viral protein inhibitors (or their coding genes) have been an important focus of development, with most inhibitors developed against protease and reverse transcriptase. HIV receptor antagonists against the immune system (mainly lymphocyte T receptors) have also been a subject of research, especially chemokine receptors.
Some of these inhibitors have been protected by patents describing combination therapies. The main patented inhibitor combinations are anti-proteases and anti-reverse transcriptases. Moreover, five of the six combination inhibitors commercialised today are anti-reverse transcriptase combinations, with only one combination of two anti-proteases.

As expected, most of the pharmaceutical formulations are for therapeutic inhibitors, that is, transcriptase and reverse transcriptase inhibitors. Nevertheless, it is interesting to note that there are certain pharmaceutical formulations for inventions concerning interference RNA (RNAi) or gene delivery. In this case the therapeutic targets are the genes coding for HIV regulatory proteins. Except for patents protecting chemokine and CD4 receptors, there is no reason for patents describing immunomodulation to be associated with the therapeutic targets presented here. The rare patents associated with proteins or viral genes that claim immunomodulation are patents that describe both

the inhibitors of these proteins and claim that the activity of their compound is improved when it is associated with an immunomodulator.

Vaccine formulations specific for one class of compound are usually composed of viral envelope glycoproteins (GP41 and GP120) as well as the envelope proteins of the viral matrix and capsid or derived peptides (p24, p6 and p17 coded by the gag gene). Several vaccine formulations also target regulatory proteins. One reason for this is that several patents describe both structural and regulatory HIV proteins. Vaccines involving chemokine and CD4 receptors have been developed with fragments of these receptors to prevent HIV from binding to the host cell (thus preventing it from entering the lymphocyte) by binding an antibody to the site instead. Nevertheless, the interest in this type of technology remains limited.

Although there is research on the biomarkers and new inhibitors for all of these therapeutic targets via the development of screening methods, there is less general interest in integrase and CD4 receptors and cells than in others.

4.4 Breakdown of patents by class of compounds

Several classes of therapeutic compounds are being developed to fight HIV. Thus, we broke down the patent portfolio into classes of compounds.

We identified four main classes of compounds resulting in the following categories:

- **Chemical compounds**
- **Peptide compounds (peptides or proteins)**
- **Therapeutic antibodies**
- **Nucleosides/(Poly)nucleotides & analogs**

It should be noted that many patents describe anti-HIV antibodies for diagnostic rather than therapeutic purposes. Therefore these patents were not included in this analysis. Moreover, although antibodies are peptide compounds, they were not included in the latter class because of their specific function.

The following map shows the proportion of patents in each category.

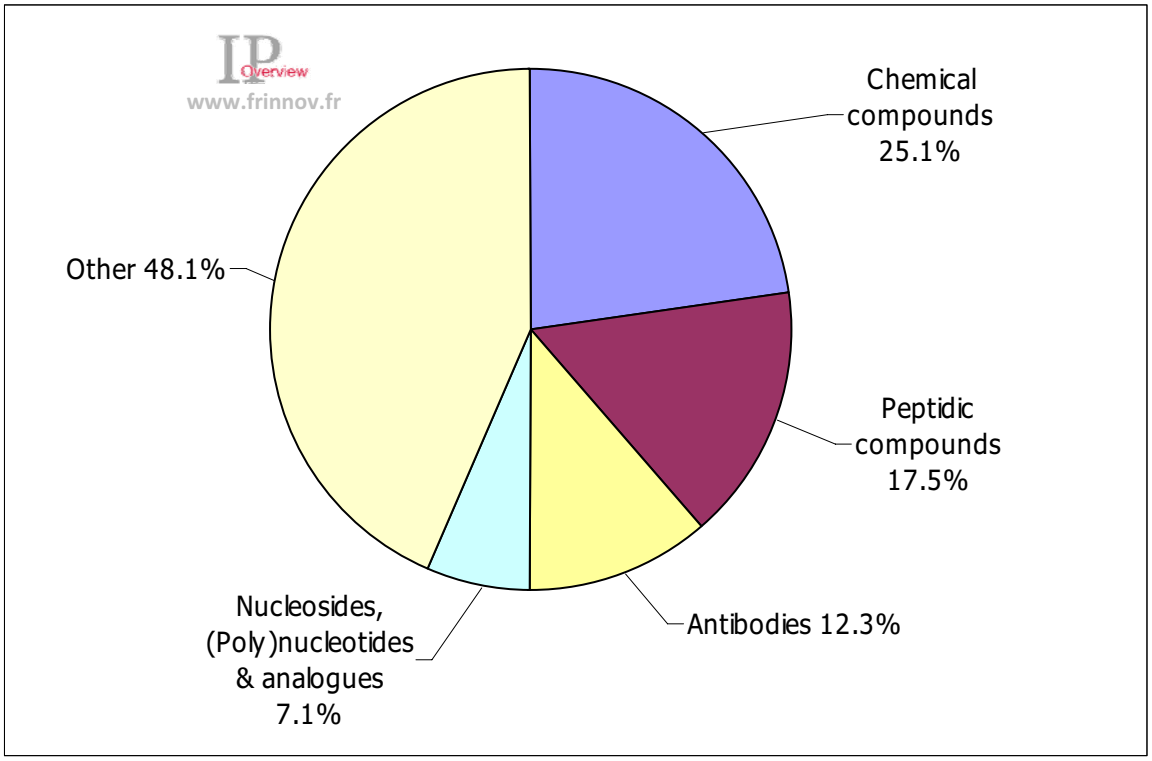


Figure 19: Breakdown of patents by class of compound

	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07
Chemical compounds			1	8	19	19	41	32	59	85	48	71	78	63	56	86	105	95	122	131	135	150	111	72	
Peptidic compounds	6	13	13	39	40	27	36	56	38	46	40	25	34	51	63	42	79	80	102	73	67	55	44	37	
Antibodies	1	3	1	17	38	26	26	31	33	33	30	22	35	42	41	30	32	45	75	58	35	49	41	30	
Nucleosides, (Poly)Nucleotides & analogues			4	7	21	16	16	36	19	14	9	14	15	12	21	28	25	31	40	35	26	25	21	13	

Table 6: Evolution in the breakdown by class of compound

Black circles indicate FDA approval of a drug

The first patents filed described therapeutic peptide compounds. The number of patents filed grew steadily until 1987 then the rate stabilized until 1995 before another period of growth lasting until 2000. Since 2002, the number of patents describing peptide compounds as potential therapeutics has decreased but is still relatively high. Today, peptide compounds are the second most frequently patented class of compounds. It should be noted that there are very few therapeutic peptides on the market. Certain therapeutic molecules contain peptide bonds (ie certain protease inhibitors) but these compounds have been classed as chemical compounds. Only one existing drug is actually a peptide. This is a fusion inhibitor (enfurvitide developed by the University of Duke in collaboration with Roche and approved in 2003). Therapeutic antibodies targeting the key viral proteins are the second oldest class of therapeutic agents. The number of patents protecting therapeutic antibodies has evolved in the same manner as peptide compounds but there were fewer (~30% less) patents. It should be

noted that there are no therapeutic antibodies being marketed today and only 6 ongoing clinical trials on this topic.

Chemical compounds came into the picture a little later (in 1986), but are the most important class of potential therapeutics today, and were the subject of most of the patents filed in 1992. The most active period of filing occurred after 2000 with as many as 150 patents filed in 2004.

Finally, the number of patents filed for nucelosides, (poly) nucleotides and their analogs which were first discovered in 1985, is somewhat lower than that protecting the other classes, even though seven of these reverse transcriptase inhibitors have been commercialised. There was a renewal of interest in this class of drugs after 2000.

4.5 Cross-analysis of the categories "class of compound" and "therapeutic target"

Cross-analysis of the patents by class of compound and therapeutic target gives a general idea of the most important targets in relation to the classes of compounds.

This graph shows that most therapeutic antibodies developed to date target viral entry into the host cell because most are directed against surface viral glycoproteins, but also regulatory proteins and key enzymes of the viral cycle (protease and reverse transcriptase). Sometimes certain patents describe these antibodies not for therapeutic purposes, but to show the efficacy of another drug by dosing the quantity of these proteins in the patient's blood.

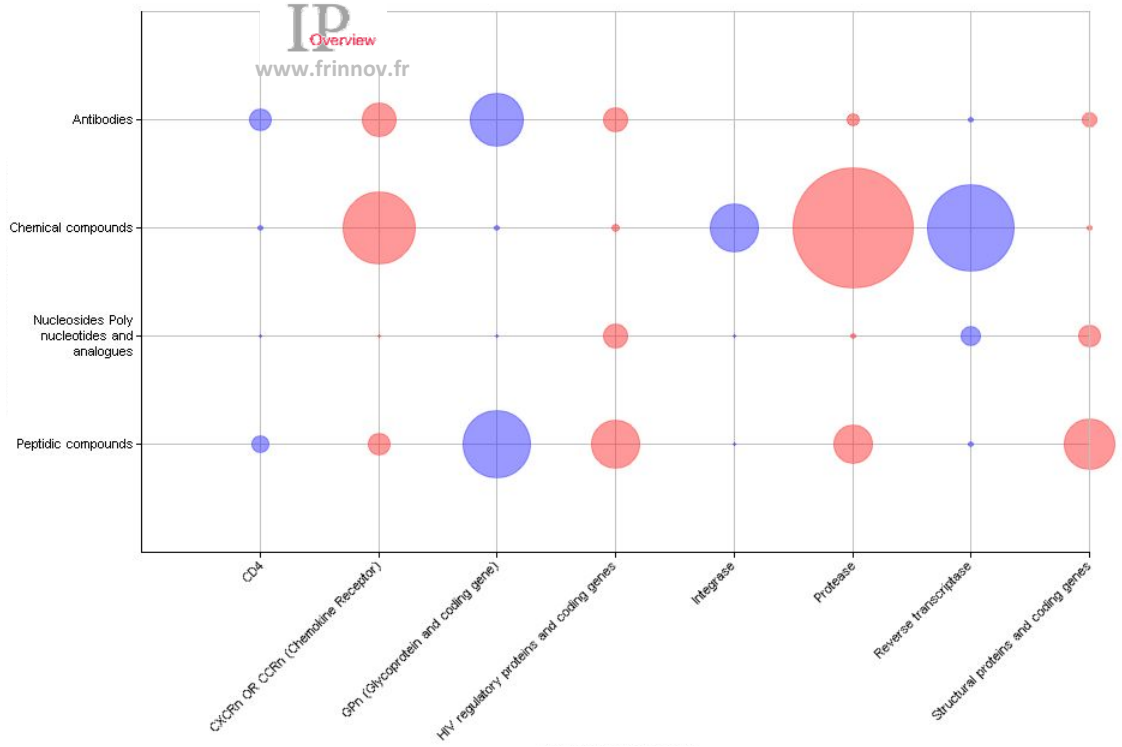


Figure 20: Cross-analysis of the categories class of compound and therapeutic target

Although there are chemical compounds described as inhibitors (or activators) for all the therapeutic targets, most of the chemical compounds target protease, reverse transcriptase, chemokine or integrase receptors. The targets for nucleosides/(poly)nucleotides & their analogs are mainly the regulatory and structural proteins and their genes. Most of the RNAi's are found in this category. In addition, a certain number of reverse transcriptase inhibitors are nucleoside or nucleotide analogs.

Finally, peptide compounds also target all the therapeutic targets, although somewhat less integrase and reverse transcriptase inhibitors. Peptide compounds targeting glycoproteins and the structural genes are mostly immunogenic peptides used as vaccines. They play the role of antagonists (eg CD4 and chemokine receptors) or inhibitors (protease) in other targets, and in the latter case, are mostly oligonucleotide analogs.

4.6 Cross-analysis of the categories "class of compound" and "application"

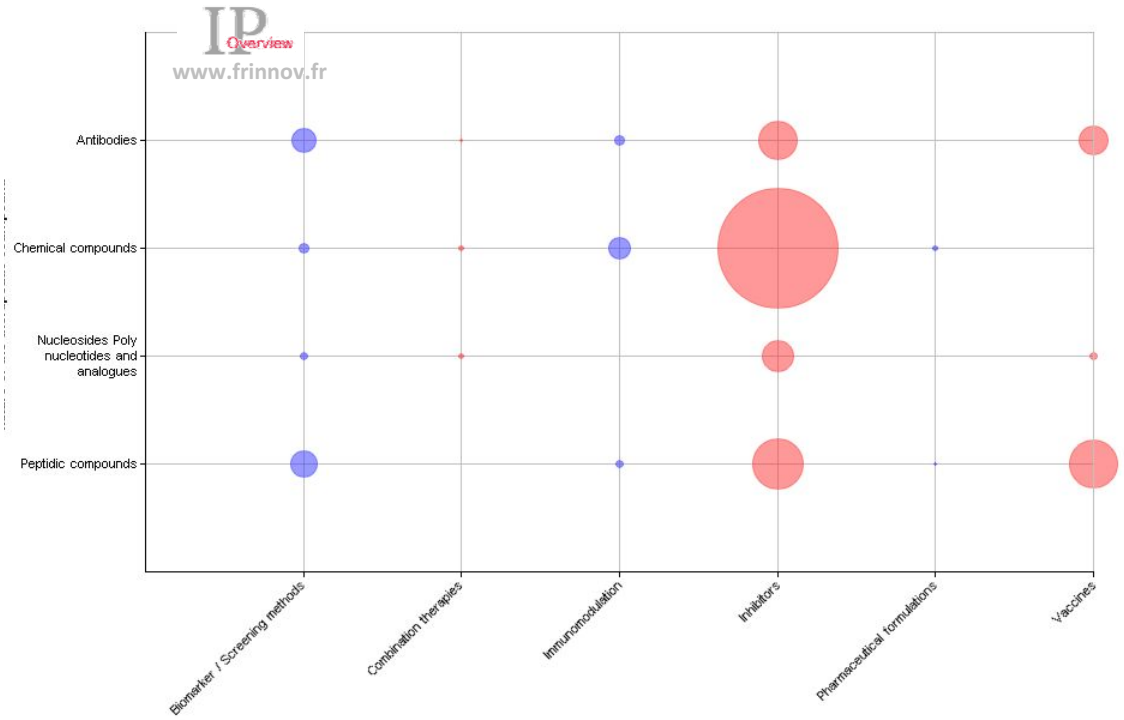


Figure 21: Cross-analysis of the categories class of compound and application

Cross-analysis of the categories class of compound and application gives a general idea of the most important applications in relation to the classes of compounds.

This graph shows that most inhibitors are chemical compounds. Although all classes of compounds are used as inhibitors, most are chemical compounds. A significant number of screening methods have been developed to evaluate the most effective antibodies and peptide compounds. As a result, the number of patents filed in these two classes will probably increase in the upcoming years.

Combination therapies associate chemical compounds and/or nucleosides/(poly)nucleotides & analogs, and correspond to compounds that are already on the market, thus mainly nucleoside (or nucleotide) analogs combined with chemical compounds.

Pharmaceutical formulations are the main claim in very few patents even though all therapeutic compounds have pharmaceutical formulations.

Immunomodulation is usually obtained with chemical compounds, but certain antibodies and peptide compounds have also been developed for this purpose.

HIV vaccines are mostly immunogenic peptide compounds, but several patents protecting HIV DNA vaccines have been filed.

4.7 Breakdown of the main IPC codes of patents

The most widely represented IPC codes in HIV therapy patents were extracted and their distribution is shown in the following figure.

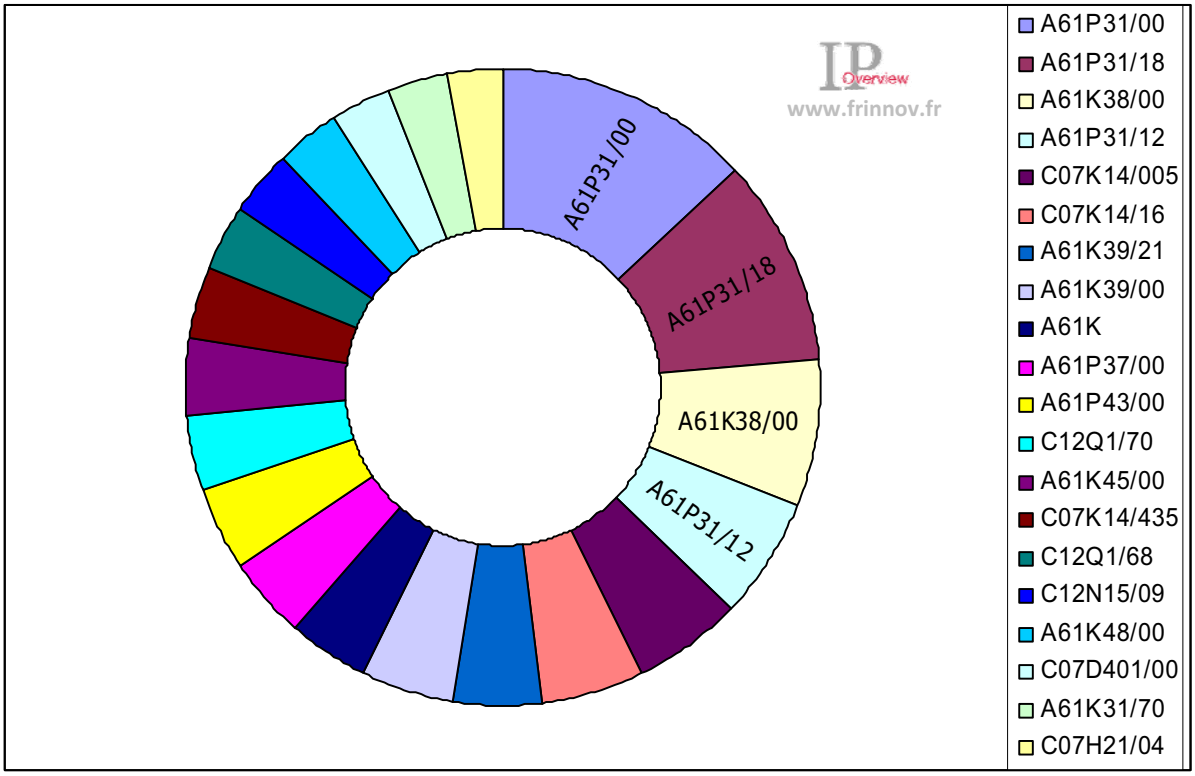


Figure 22: Distribution of the 20 main IPC codes

IPC	Description of the IPC codes
A61P31/00	Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics
A61P31/18	Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics, Antivirals, for RNA viruses, for HIV
A61K38/00	Medicinal preparations containing peptides
A61P31/12	Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics, Antivirals
C07K14/005	Peptides having more than 20 amino acids, from viruses

IPC	Description of the IPC codes
C07K14/16	Peptides having more than 20 amino acids, from viruses, RNA viruses, Retroviridae, e.g. bovine leukaemia virus, feline leukaemia virus, human T-cell leukaemia-lymphoma virus, Lentiviridae, e.g. human immunodeficiency virus (HIV), visna-maedi virus, equine infectious anaemia virus, HIV-1
A61K39/21	Medicinal preparations containing antigens or antibodies, Viral antigens, Retroviridae, e.g. equine infectious anemia virus
A61K39/00	Medicinal preparations containing antigens or antibodies
A61K	Preparations for medical, dental, or toilet purposes
A61P37/00	Drugs for immunological or allergic disorders
A61P43/00	Drugs for specific purposes, not provided for in groups
C12Q1/70	Measuring or testing processes involving enzymes or micro-organisms, involving virus or bacteriophage
A61K45/00	Medicinal preparations containing active ingredients not provided for in groups A61K 31/00 to A61K 41/00
C07K14/435	Peptides having more than 20 amino acids, from animals
C12Q1/68	Measuring or testing processes involving enzymes or micro-organisms, involving nucleic acids
C12N15/09	Mutation or genetic engineering, Recombinant DNA-technology
A61K48/00	Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases
C07D401/00	Heterocyclic compounds containing two or more hetero rings, having nitrogen atoms as the only ring hetero atoms, at least one ring being a six-membered ring with only one nitrogen atom
A61K31/70	Medicinal preparations containing organic active ingredients, Carbohydrates
C07H21/04	Compounds containing two or more mononucleotide units having separate phosphate or polyphosphate groups linked by saccharide radicals of nucleoside groups, e.g. nucleic acids, with deoxyribosyl as saccharide radical

Table 7: Description of the 20 main IPC codes

Although these main IPC codes have been fairly stable over time and are representative of this sector they do not provide an overview of the main and emerging topics, applications.

	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06
A61P31/00		4	5	16	45	50	70	100	83	113	85	104	90	93	119	144	183	163	214	211	205	235	138	106
A61P31/18		4	2	9	21	30	36	49	45	57	44	65	71	76	108	127	175	148	202	198	182	219	126	86
A61K38/00		7	5	32	53	53	59	102	68	108	82	69	77	84	105	71	89	79	100	86	57	51	19	17
A61P31/12		2	4	13	43	48	64	97	76	101	71	89	63	34	41	44	61	39	59	65	66	69	30	25
C07K14/005	2	11	13	47	48	54	58	80	36	56	59	34	40	44	60	40	56	78	92	79	52	43	21	19
C07K14/16	2	11	13	44	44	52	55	76	32	48	56	33	38	41	51	36	51	73	91	75	44	36	14	15
A61K39/21		7	7	32	35	40	47	46	27	44	47	22	32	38	42	37	45	70	71	68	48	39	27	18
A61K39/00		4	11	39	39	47	50	57	39	53	39	24	28	34	56	40	52	58	57	45	36	34	21	17
A61K		2	7	8	29	25	39	41	30	49	36	25	36	40	40	50	54	52	100	118	75	1		
A61P37/00		1	2	1	6	13	20	27	18	34	22	41	32	35	70	52	49	51	80	70	66	72	29	16
A61P43/00			1	1	3	6	11	17	17	18	10	22	28	26	39	50	63	58	73	96	101	115	32	17
C12Q1/70	3	8	8	28	23	16	17	26	10	45	24	26	23	39	47	42	48	73	88	80	46	39	28	16
A61K45/00			1	1	7	4	10	7	22	20	17	19	25	39	52	56	69	66	79	90	65	60	21	13
C07K14/435		2	3	15	25	22	28	33	33	29	23	21	25	43	65	53	53	52	57	38	35	28	17	15
C12Q1/68	4	6	2	11	13	3	14	20	8	31	19	26	25	29	55	42	40	70	68	68	47	33	23	15

Table 8: Evolution of the main IPC codes

5 Applicants

5.1 Analysis for the entire period (1983-2006)

5.1.1 Main applicants (1983-2006)

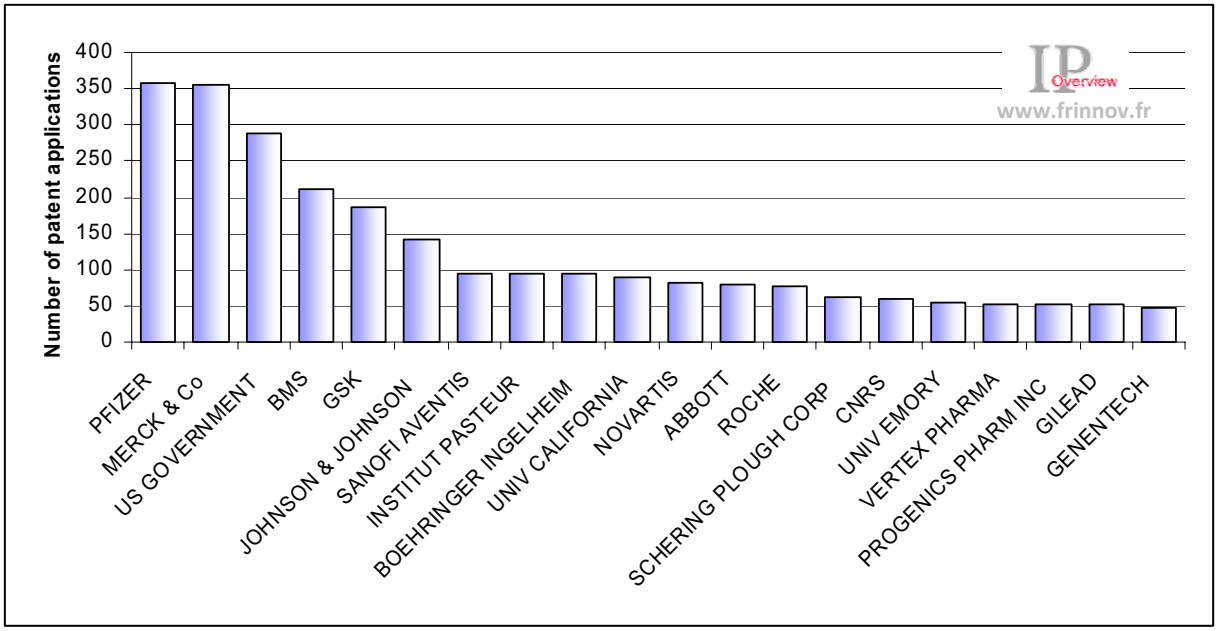


Figure 23: Main applicants for the entire period (1983-2006)

The largest patent portfolios are shown in the above figure. Sixteen major pharmaceutical groups and four public research institutions share this prize. The top two spots are filled by the companies Pfizer and Merck&co which have a clear lead over the others, with more than 350 patent families in the field. Their position is surprising since these two companies are not the most dominant market players (3 anti-HIVs on the market for Pfizer and 4 for Merck&co with the most promising only approved recently).

It should be noted that Pfizer's portfolio also includes the portfolios of all the companies that it has acquired (in particular Pharmacia and Warner Lambert, which also means Monsanto, Agouron and Upjohn).

In a similar manner, the portfolios of the other large companies have been grouped together. In a more in depth analysis of each period, we separated those acquired portfolios to get a better overall picture of the IP environment and provide a better view of how it has evolved.

In descending order by market share, Gilead, which is the leader in the market, is only in 19th place in terms of number of patents, GlaxoSmithKline is 5th, BristolMyersSquibb is 4th, Abbott is 12th, Roche 13th and Boehringer-Ingelheim in 9th position.

US government laboratories are in first place for the number of patents held by an academic research institution with nearly 300 patent families, while Institut Pasteur, the ever present French research institute in the field of HIV, is in 7th place.

It should be remembered that the present analysis evaluates only HIV therapies and not diagnostics, which both these institutions have developed extensively.

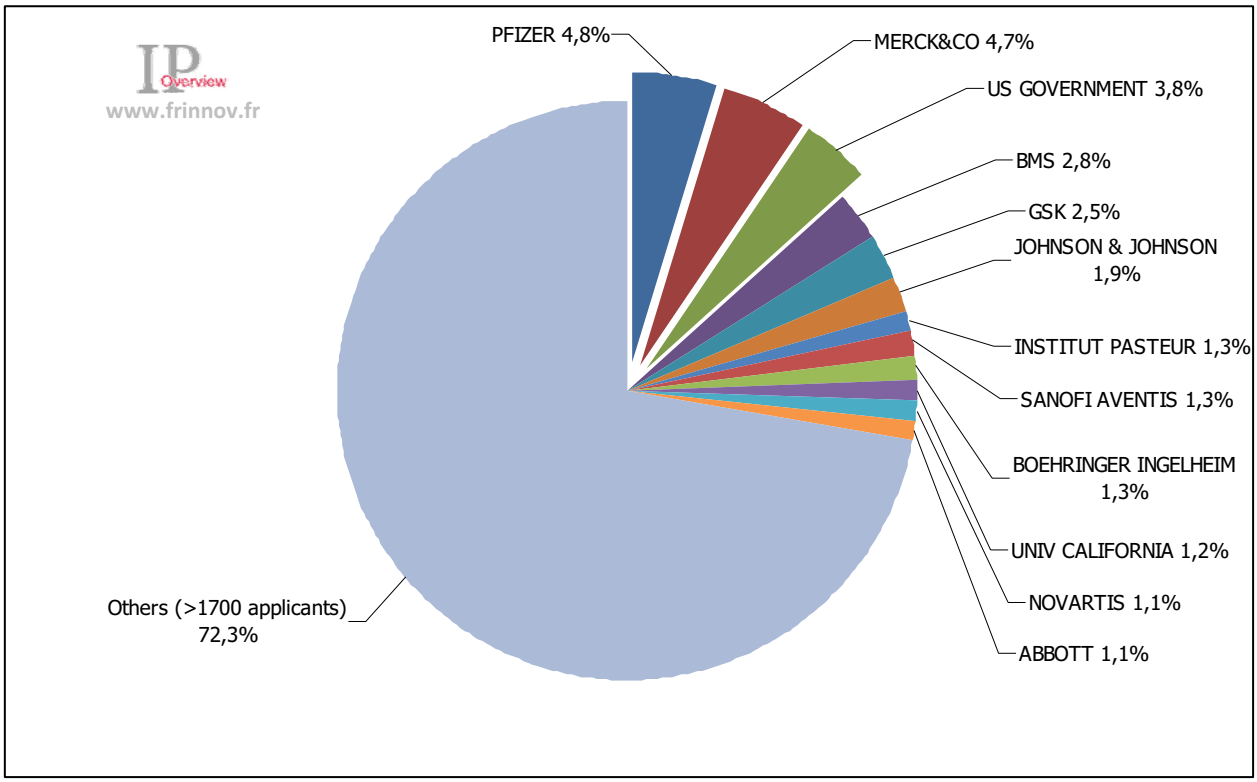


Figure 24: Breakdown of the main patent portfolios

The largest patent portfolios only represent a small percentage of all the patents in this field. Pfizer and Merck&co's portfolios each only make up 5% of the total number of patents in this field, and the players in 6th and 7th position only own 1.5% of the total portfolio. This is mainly due to the many market players in this field (more than 1700)

5.1.2 Collaborations (1983-2006)

The figure below shows the clusters of collaborations among applicants for the entire period). Only collaborations which resulted in 3 joint filings have been included.

Two major clusters of collaborations can be seen: one is concentrated around US government laboratories and another around the Institut Pasteur, the CNRS and INSERM. Another important collaboration between institutional partners was established between the Universities of Emory and Georgia, resulting in 18 joint patents.

The most successful industrial collaboration in terms of patent filings (20) was between Agouron Pharmaceuticals (which is now part of the group Pfizer) and Japan Tobacco. In fact, the drug Nelfinavir (Viracept) was launched as a result of this collaboration.

This analysis could not identify informal collaborations which did not result in the official filing of joint patents.This is true for example between Institut Pasteur and US government laboratories, in particular because of the participation of Luc Montagnier, the companies Bayer AG and Takeda, Panacos with the University of North Carolina, Institut Curie with Johnson & Johnson and UCB and Darwin Discover ltd with Dow Chemical.

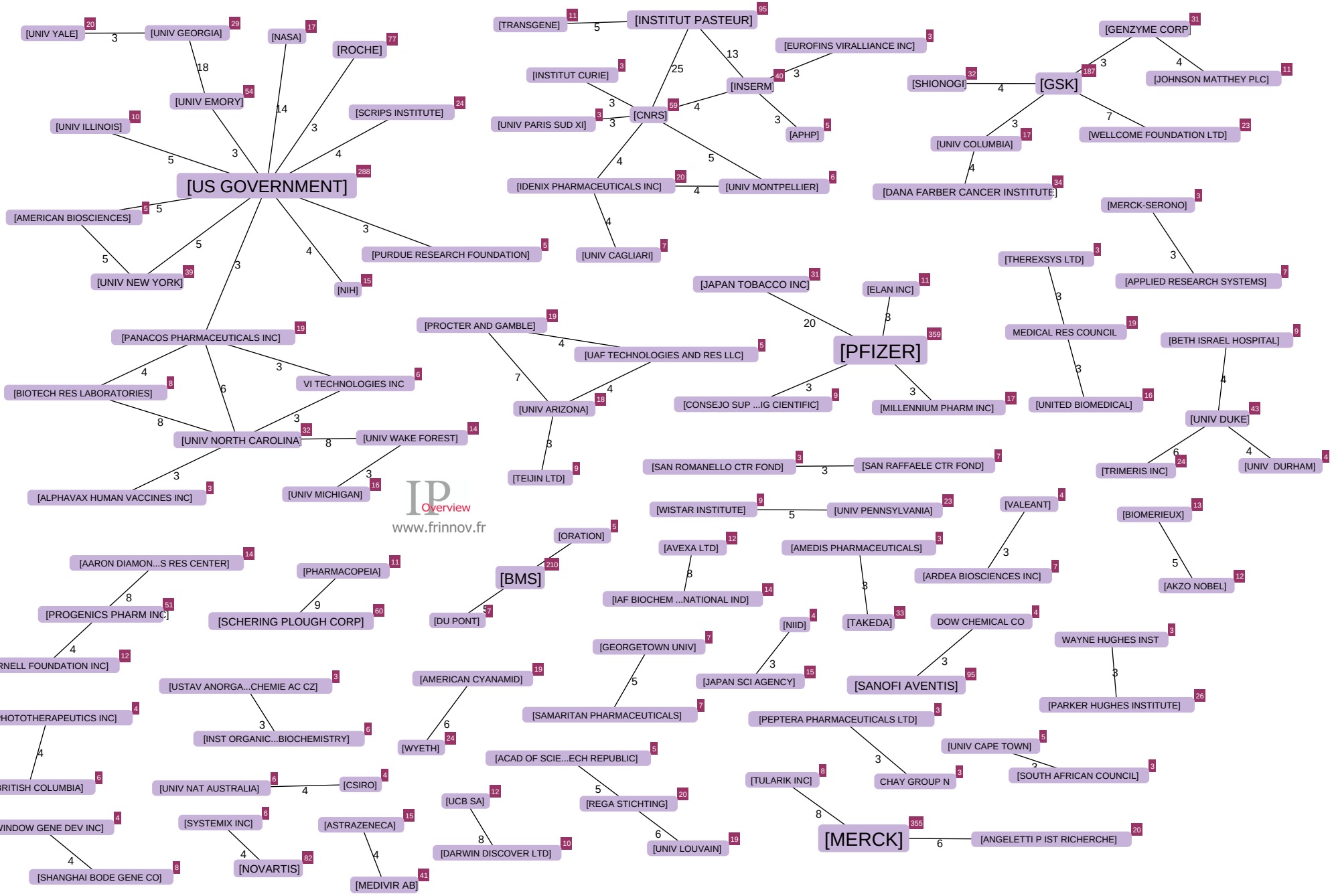


Figure 25 : Major collaborations by number of joint filings for the entire period (1983-2006)

5.1.3 Topics protected (1983-2006)

The next three figures present an analysis of the applicants according to three categories: therapeutic target, application and class of compound. The players are clearly separated into institutional and industrial applicants and among the industrial applicants themselves.

Institutional applicants tend to protect inventions targeting regulatory and structural proteins as well as viral entry glycoproteins. The main therapeutic compounds developed are peptide compounds and therapeutic antibodies. Most applications target inhibition of the HIV cycle (mostly US universities and US government labs), screening methods and vaccines.

Industrial players tend to protect chemical compounds inhibiting protease, reverse transcriptase and more recently integrase and chemokine receptors. Several industrial players, who have filed fewer than 40 patents, have concentrated their intellectual property on one target, one application or one class of compound.

- Abbott, Ambrilia Biopharma, LG Group and Vertex Pharmaceuticals have protected chemical compounds inhibiting protease.
- Genzyme (via the acquisition of Anormed in 2006), Schering Plough Corp and Takeda have concentrated their portfolio on chemical compound which are chemokine receptor antagonists,
- Monogram Biosciences has protected nucleosides/(Poly)nucleotides & analogs as well as screening methods targeting reverse transcriptase, protease and chemokine receptors.
- Progenics Pharmaceuticals has protected antibodies and peptide compounds inhibiting viral entry (CD4, Glycoproteins and Chemokine Receptors).
- Shinogi has protected chemical compounds inhibiting integrase.

The larger companies with more extensive portfolios have diversified their research into several areas.

- Gilead has concentrated on chemical compounds inhibiting protease, integrase and reverse transcriptase.
- Pfizer and BMS have portfolios with chemical compounds inhibiting protease, integrase and reverse transcriptase and chemokine receptors. Pfizer has an impressive portfolio of protease inhibitors.
- Roche has developed screening methods and chemical compounds inhibiting reverse transcriptase, protease and chemokine receptors.
- Johnson & Johnson (via its subsidiary Tibotec) has developed screening methods and chemical compound inhibiting protease and reverse transcriptase.

Finally, two companies GSK and Merck&co have extensive portfolios covering all targets and applications. Merck&co has also focused on vaccines. In their coverage of all targets, these two portfolios are similar to that of the US government laboratories.

Remark: the colors of the circles (blue or red) are only to make the columns more legible.

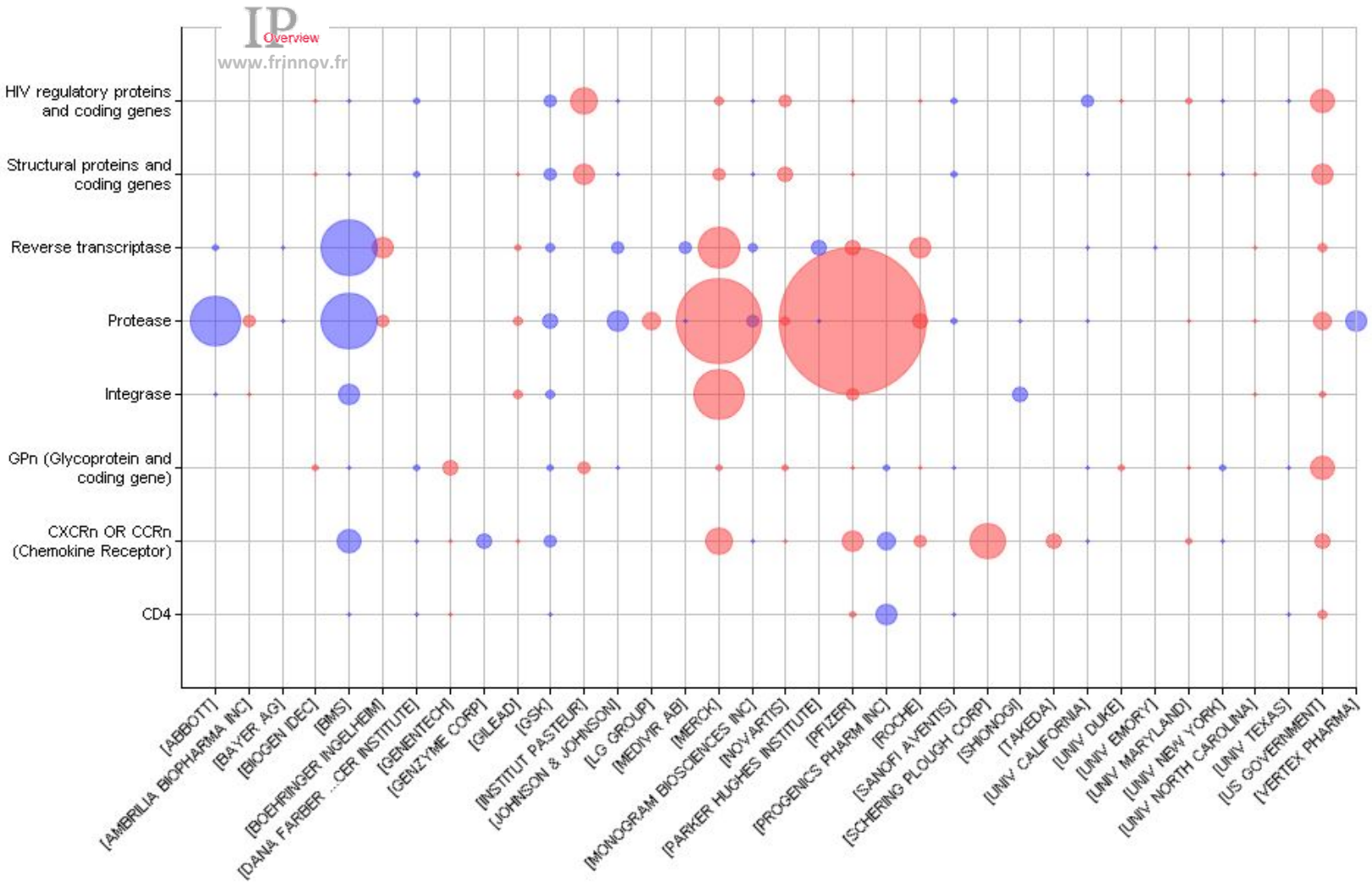


Figure 26: Therapeutic targets of the major players for the entire period (1983-2006)

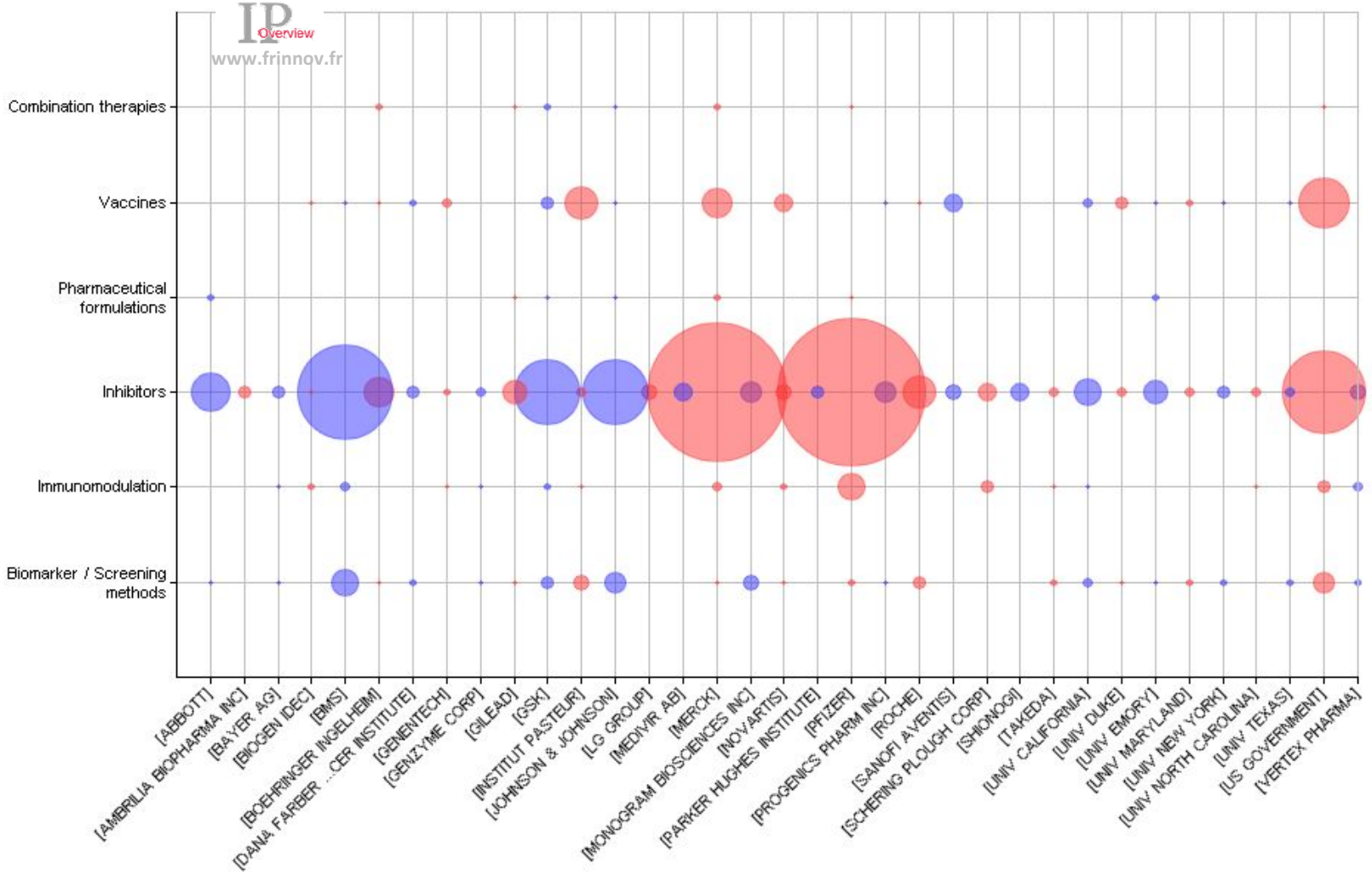


Figure 27: Applications of the major players for the entire period (1983-2006)

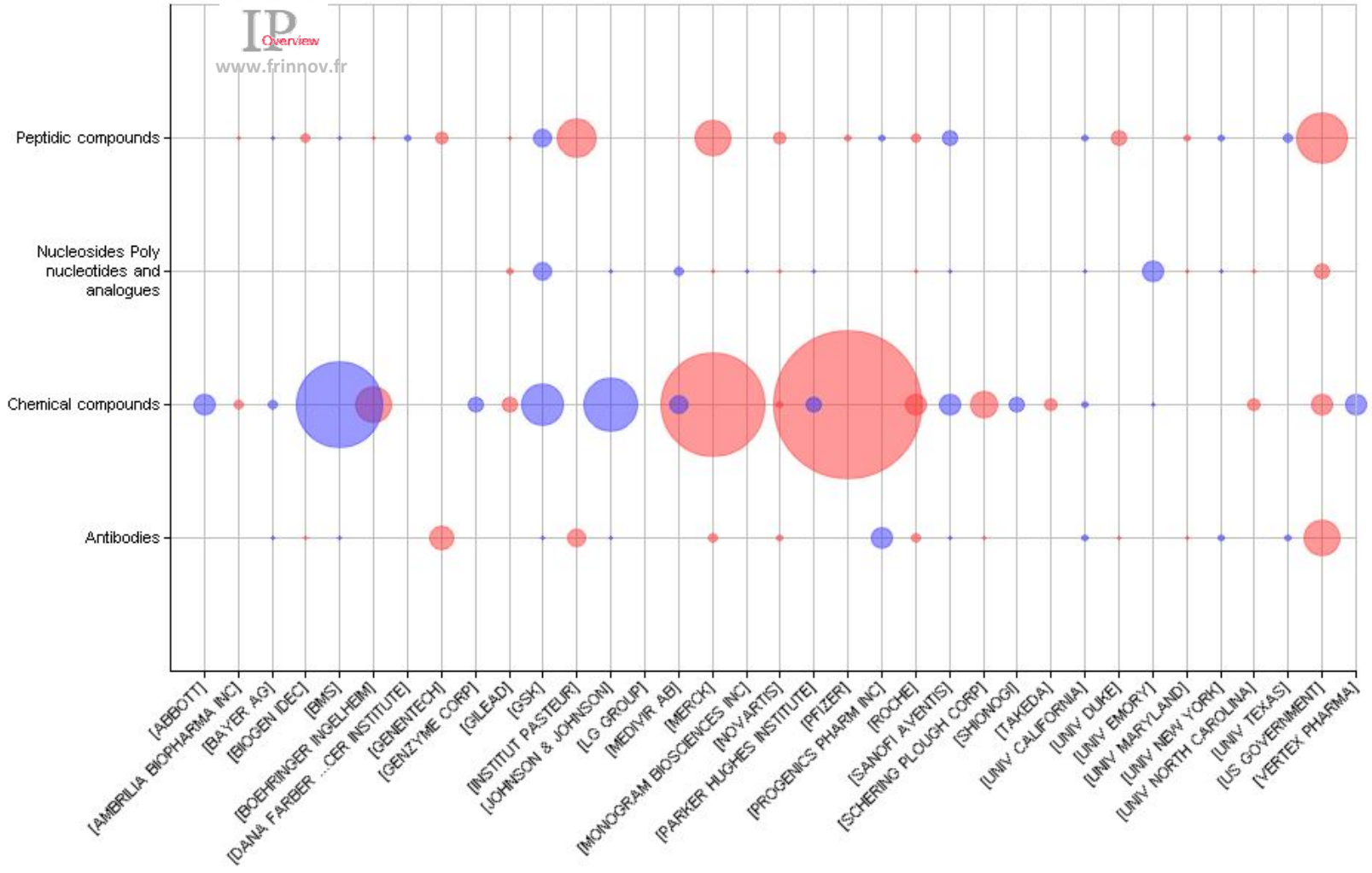


Figure 28: Classes of compounds of the major players for the entire period (1983-2006)

5.2 Analysis for the pioneer period (1983-1992)

5.2.1 Pioneer applicants (1983-1992)

From 1983 to 1992, 1562 patent applications were filed naming more than 2300 inventors.

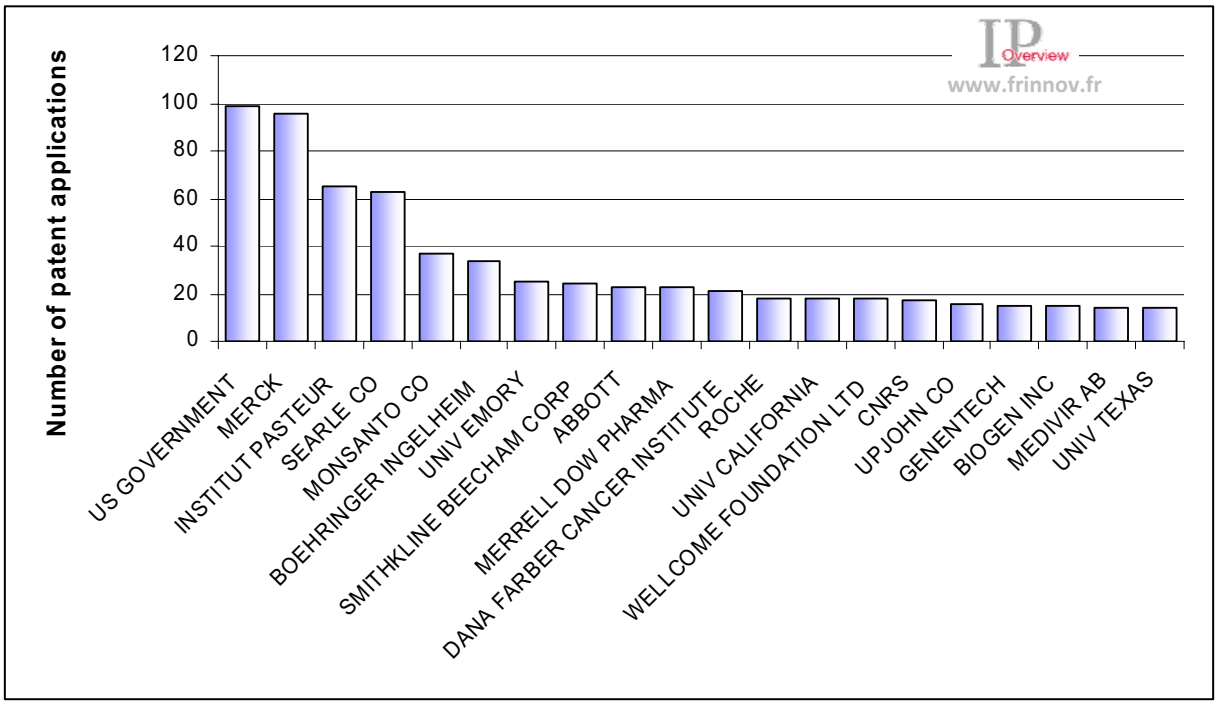


Figure 29: Major applicants from 1983-1992

This figure shows the 20 top applicants from 1983 to 1992. Merck&co is the leader of the pharmaceutical groups with nearly 100 filings followed by Searle. The US government laboratories and Institut Pasteur filed 99 and 65 applications respectively. Besides these 4 top applicants all the other players filed fewer than 40 patents during this period.

	83	84	85	86	87	88	89	90	91	92
US GOVERNMENT	3	2	6	14	10	13	3	17	13	18
MERCK & Co						8	11	27	37	13
INSTITUT PASTEUR	5	7	1	23	10	6	6	5	2	
SEARLE CO							1	14		48
MONSANTO CO					2	2		7		26
BOEHRINGER INGELHEIM					1		20	4	5	4
UNIV EMORY				3	2	1	2	13	3	1
SMITHKLINE BEECHAM CORP						2	5	8	6	3
ABBOTT					2	3	9	2	1	6
MERRELL DOW PHARMA					1	8	4	4	4	2
DANA FARBER CANCER INSTITUTE		2		5	1		3	6	1	3
UNIV CALIFORNIA				2	6	1		2	4	3
WELLCOME FOUNDATION LTD				2	3	2	3	1	4	3
ROCHE			2	5	2		5	3		1
CNRS	2	8			3	3		1		
UPJOHN CO					2	1	4	2	2	5
BIOGEN INC				2	2	2	3	3	3	
GENENTECH				1	7			5	1	1
UNIV TEXAS					3		3	1	5	2
MEDIVIR AB				2	5	1		1	4	1

Table 9: Evolution of filings by major applicants from 1983-1992

The evolution over time of filings by the top applicants corresponds to their entry into and desire to position themselves in the field. The first applicants to position themselves were the CNRS, Institut Pasteur and the US government laboratories. Only the latter has continued to file vigorously while Institut Pasteur and the CNRS, after an initial period of vigorous filing, seemed to turn away from this topic. Thus the first applicants in the field are not necessarily those with the largest portfolios today.
The industrial applicants and major applicants only began working on this topic four years after the virus was discovered and the first pioneer patents were filed (between 1987 and 1988).
Merck&co took a leading position as early as 1990. Searle (subsidiary of Monsanto since 1985), Monsanto and Boehringer-Ingelheim filed their first patent applications in 1987 and filed massively after 1990.

5.2.2 Collaborations from 1983-1992

The figure below shows the clusters of collaborations among applicants for the period from 1983 to 1992. Only collaborations which resulted in 2 joint filings have been included.

In the early years, there were very few collaborations. The most notable were:

- CNRS and Institut Pasteur with 15 joint filings
- Searle and Monsanto: 20 joint filings (Searle has been a subsidiary of Monsanto since 1985)
- The University of Georgia and the University of Emory: 7 joint filings

This analysis could not identify informal collaborations which did not result in the official filing of joint patents. This is true for example of collaborations between Institut Pasteur, CNRS and INSERM on one hand and the US government laboratories on the other, Institut Pasteur with the company Transgene (because of Simon Wain-Hobson's work at the Institut Pasteur and then Transgene), GSK (when it was SmithKline Beecham) with the University of Columbia (with Wayne Hendrickson's and Peter Kwong's work at Columbia University and Raymond Sweet at SmithKline Beecham) and Astra AB with Medivir AB.

The companies Ciba Geigy AG and Sandoz SA, which were merged in 1996 to form Novartis were already collaborating at that time. The creation of Novartis, however, is not to be taken into account, because it is a result of the transfer of intellectual property filed before 1996 to this new legal entity.

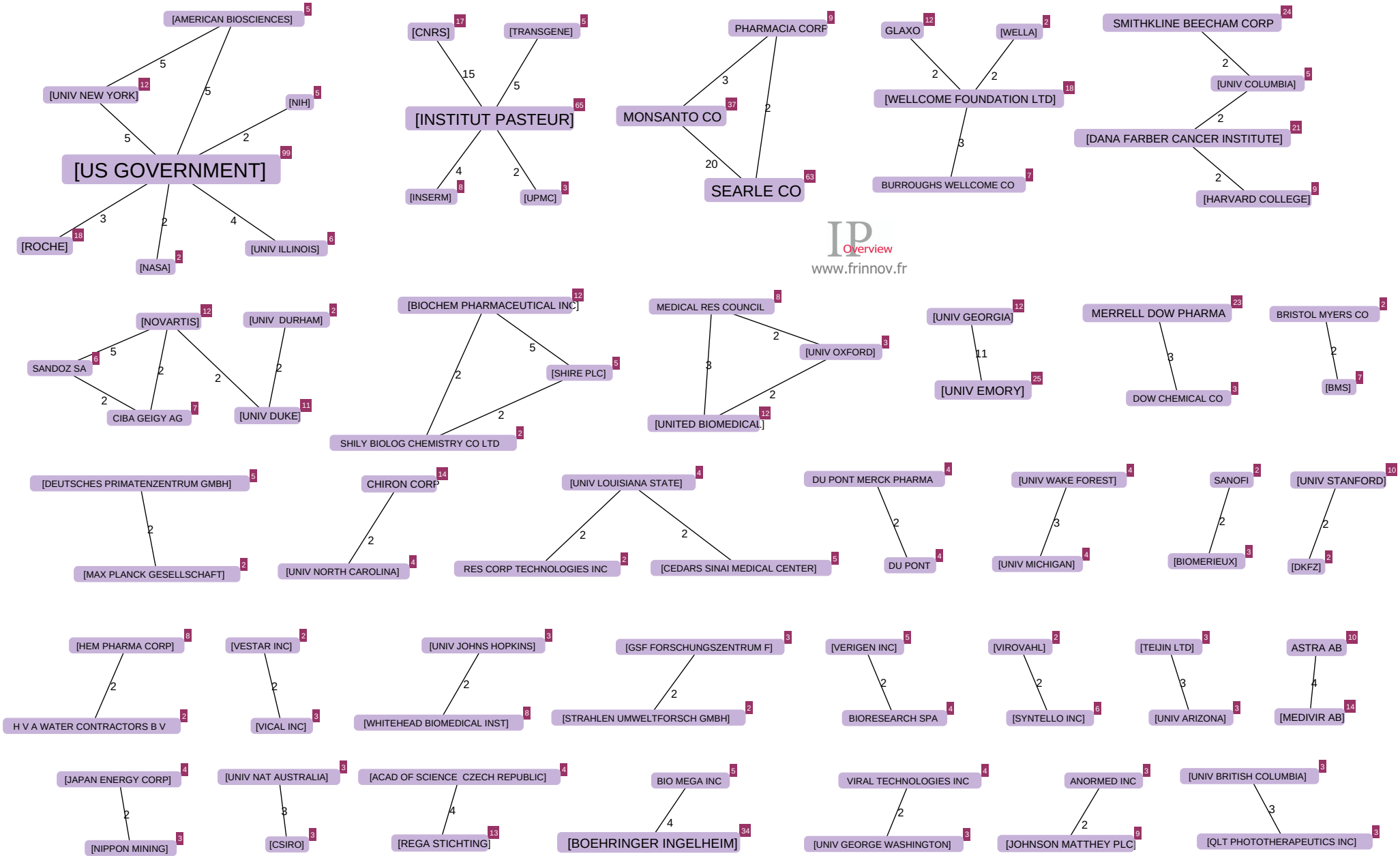


Figure 30 : The major collaborations by number of joint filings from 1983 to 1992

5.2.3 Topics protected (1983-1992)

Three targets strongly dominate this period: protease, envelope proteins and reverse transcriptase. All four classes of compounds are the subject of research, but especially peptide compounds. This is because the first patent applications describe the virus and its variants. Peptide compounds derived from the viral structure were claimed as potential immunogens at that time, and thus potential vaccines.

In the same way, Merck&co concentrated its research on the discovery of chemical and peptide compounds inhibiting reverse transcriptase and protease. Merck&co also worked on developing a vaccine and was the only major applicant to focus on integrase inhibitors at that time.

Searle, Monsanto (and thus Pharmacia since a certain number of these companies' patents were transferred when the companies were acquired) and Merrel Dow Pharmaceuticals only concentrated their research on one target: chemical compounds inhibiting protease. This is also true, but less so, for Abbott and Boehringer-Ingelheim which each also worked on another target (structural proteins and genes and reverse transcriptase respectively).

Genentech, like the University of New York, only worked on glycoproteins and developed antibodies targetting these proteins as well as possible vaccines.

The CNRS, Institut Pasteur, Dana Farber Cancer Institute, Duke University, United Biomedical, Chiron and Novartis worked on 3 main targets (GPn, structural and regulatory proteins) and one main application (vaccine) via the injection of immunogenic peptides.

It must be remembered that the presence of Novartis at this time is due to the merger with Chiron resulting in the transfer of ownership of certain Chiron patents to Novartis.

Isis only worked on nucleosides/(poly)nucleotides & analogs inhibiting viral entry.

Smithkline Beecham concentrated its research on several targets, mainly protease and GP/CD4 to develop a vaccine and mainly chemical and peptide inhibitors.

US government laboratories investigated all targets (except integrase), all compounds and applications but especially vaccines and inhibitors.

It should also be noted that because none of the applicants was working on chemokine receptor antagonists at this time, this category was not included in the analysis for this period.

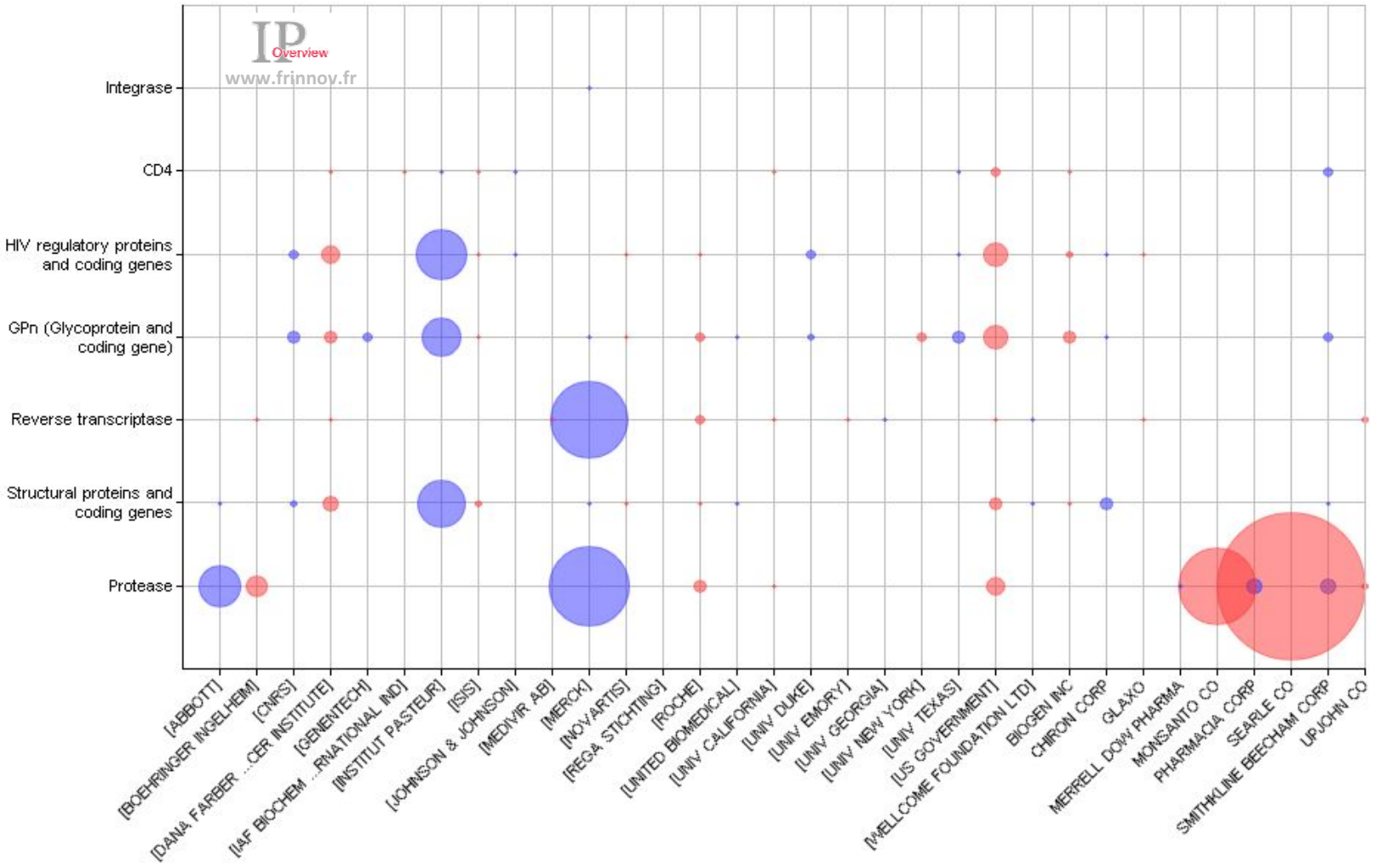


Figure 31: Therapeutic targets of the major players from 1983-1992

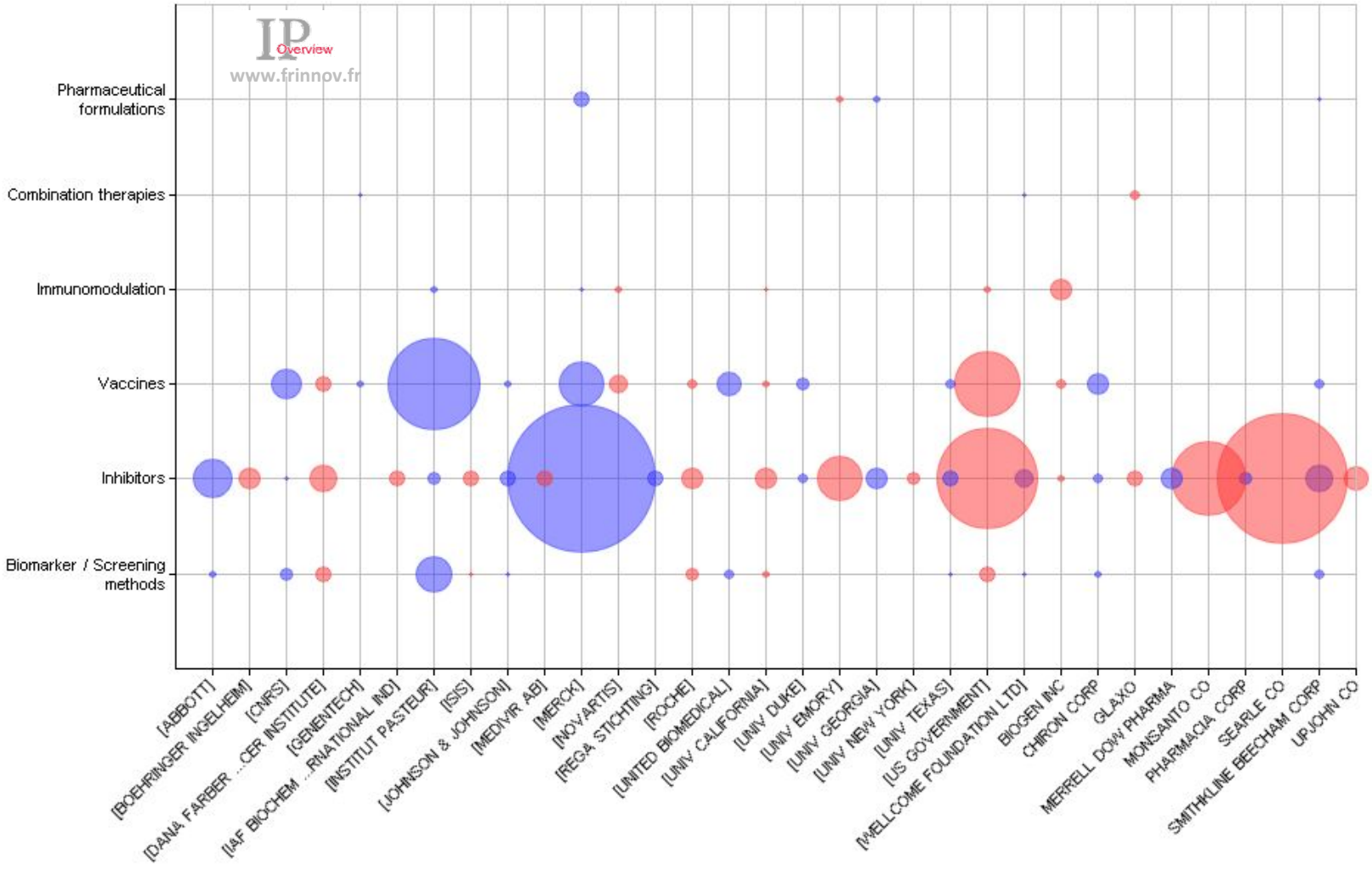


Figure 32: Applications of the major players from 1983-1992

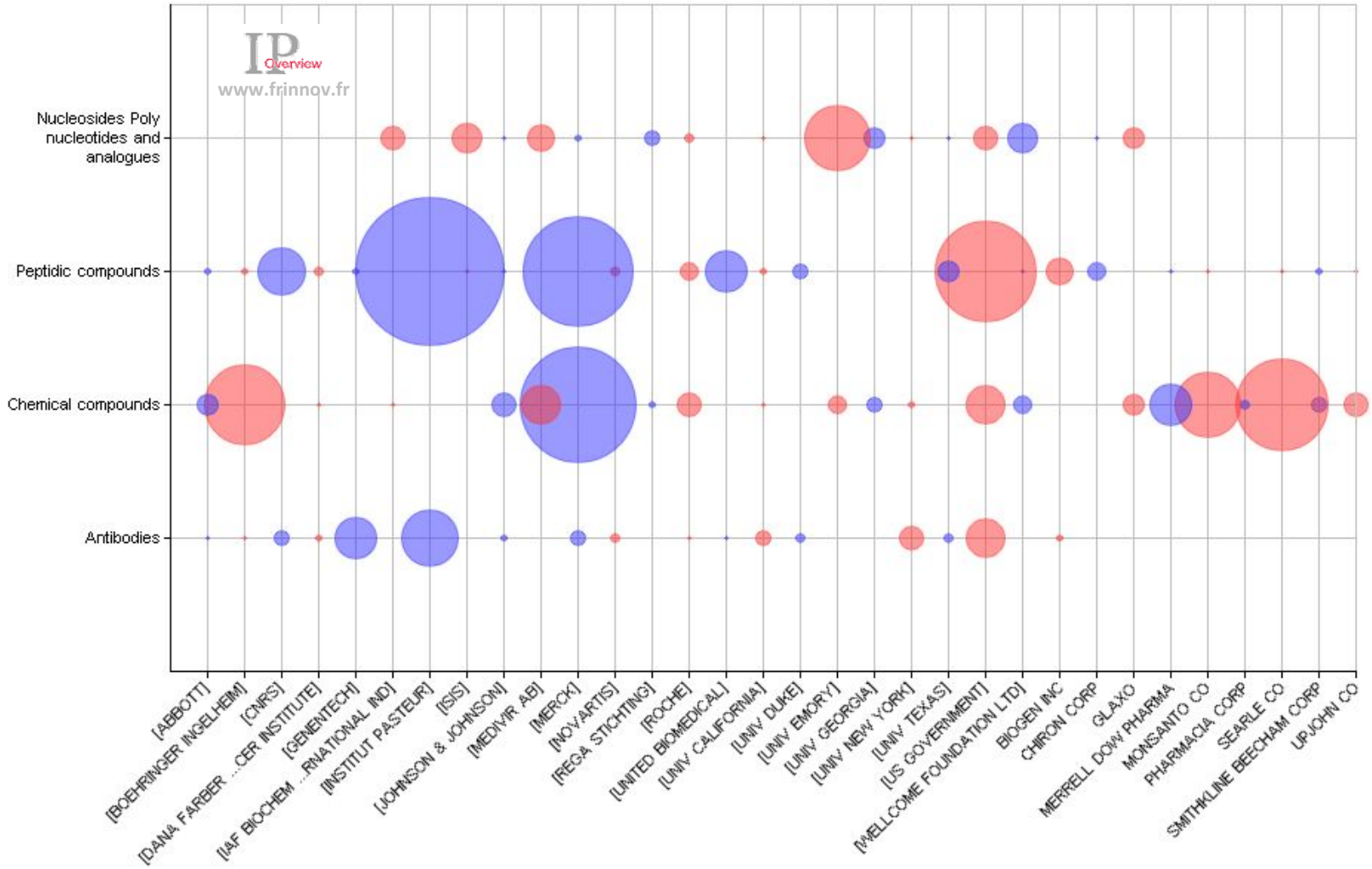


Figure 33: Classes of compounds of the major players from 1983-1992

5.3 Analysis for the intermediary period (1993-2000)

5.3.1 Main applicants (1993-2000)

There were 2645 filings naming 4600 inventors during this period. The number of filings increased significantly. During the pioneer period (1983-1992), there were an average of 150 patents filed per year, reaching 330 filings per year between 1993 and 2000.

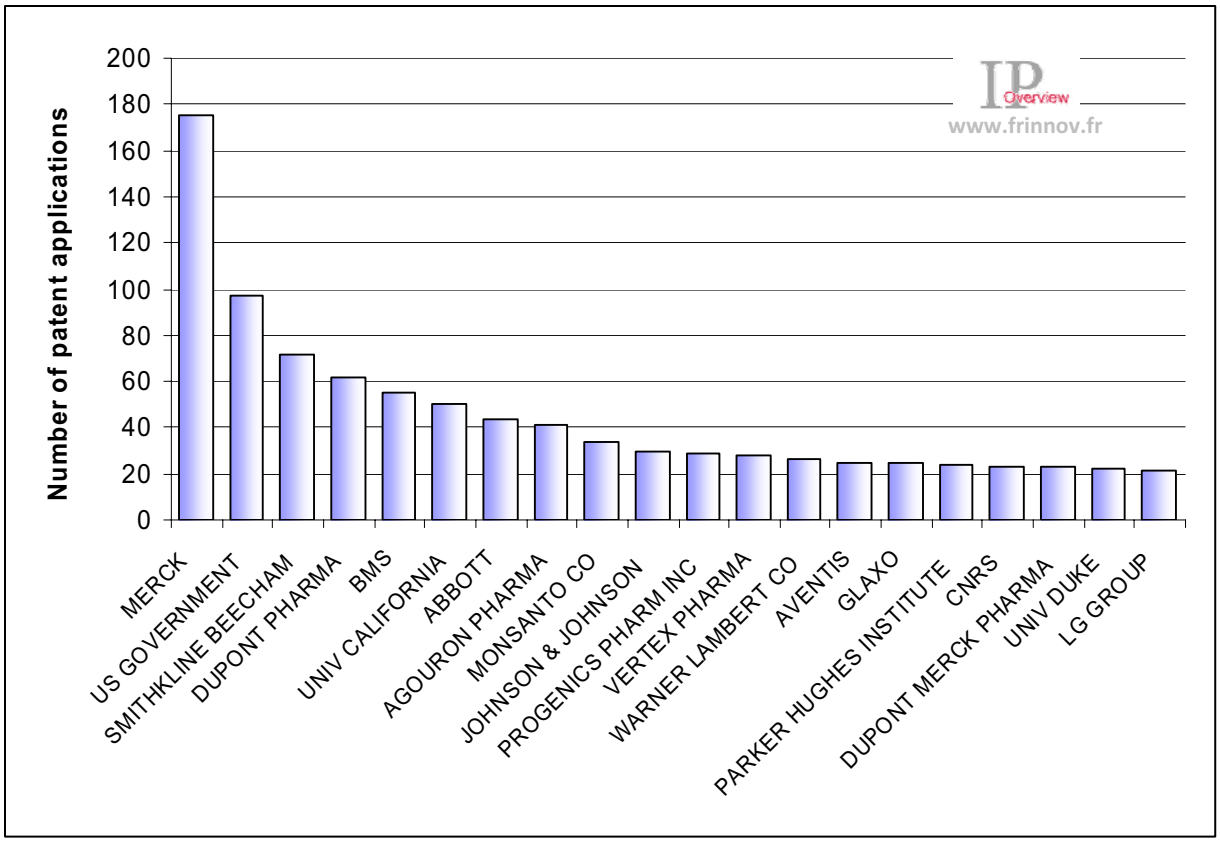


Figure 34: Major applicants from 1993 - 2000

From 1993 to 2000, Merck&co and the US government laboratories are the two top applicants. Merck&co is clearly in the lead with more than 175 filings while the US government labs only filed 98 applications during the same period.

Smithkline-Beecham, which was in the 8th position during the pioneer period (1983-1992), is now in 3rd place. The University of California, in 12th position during the pioneer period, moves up to 6th place. Abbott maintains its position and moves from 9th to 7thplace.

Many new applicants appear on the list: Dupont pharmaceuticals (which bought DuPont-Merck licenses in 1998) and BMS (which bought DuPont Pharmaceuticals in 2001) can be found in 4th and 5th place respectively. Agouron, Johnson & Johnson, Progenics Pharmaceuticals, Vertex Pharmaceuticals

and Warner Lambert also suddenly appear on the scene. Institut Pasteur is no longer one of the top applicants. Aventis, created in 1999 with the merger between Hoechst AG (which merged with Merrel Dow in 1995 and Roussel Uclaf in 1997) and Rhône Poulenc Rorer SA becomes a player (45 patents if all the filings of these companies are added together).

Monsanto which has acquired Searle moves from 5th to 9th place. Institut Pasteur with 20 patents, Dana Farber Cancer Institute with 7 and Roche with 13 patents can no longer be found on the list.

Upjohn (acquired by Pharmacia in 1995), Biogen (3 patents), Genentech (13 patents), University of Texas (11 patents) and Medivir (13 patents) have also disappeared.

	93	94	95	96	97	98	99	00
MERCK & Co	23	20	15	30	20	21	28	18
US GOVERNMENT	13	9	10	11	15	11	18	10
SMITHKLINE BEECHAM CORP	7	2	2	4	9	16	24	8
DUPONT PHARMA	2	1	3	13	9	21	8	5
BMS	2	3	2	6	8	9	8	17
UNIV CALIFORNIA	10	8	6	3	11	4	4	4
ABBOTT	11	2	8	5	3	2	8	5
AGOURON PHARMA	8	3	7	15	2	4	1	1
MONSANTO CO	2		26	1		5		
JOHNSON & JOHNSON	3	2	1	3		12	3	6
PROGENICS PHARM INC	3	1	2	9	1	6	2	5
VERTEX PHARMA		1	6	2	6	4	6	3
WARNER LAMBERT CO	7	7	3	2	1	2	4	
GLAXO		1		5	3	6	8	2
AVENTIS	1	1		3		8	3	9
PARKER HUGHES INSTITUTE						10	5	9
DU PONT MERCK PHARMA	3	4	3	9	4			
CNRS	1	2	3	1	1	6	4	5
UNIV DUKE	8	5	3				1	5
PFIZER			1	3	3	5		9

Table 10: Evolution of filings by applicant from 1993-2000

An analysis of filings over time is an indicator of which of the most active players continued to file vigorously throughout the entire period, for example, the company Merck&co with 20 applications per year or the US government laboratories with nearly 10 filings per year.

The Parker Hughes Institute also plays a top role during this period after 1997.

5.3.2 Collaborations (1993-2000)

The figure below shows the clusters of collaborations among applicants for the period from 1993 to 2000. Only collaborations which resulted in 2 joint filings have been included.

The collaborations that resulted in the most joint filings were between Agouron and Japan Tobacco (20 joint filings), the joint venture between Dupont Merck and DuPont Pharmaceuticals (15 joint filings), and Merck&co with Tularik (8 joint filings), Duke University with Trimeris (6 joint filings), University of North Carolina with Biotech Research Laboratories (7 joint filings), with the University of Wake Forest (6 joint filings), with Panacos (5 joint filings) and with Alphavax (3 joint filings).

This analysis could not identify informal collaborations which did not result in any joint filings, which occurred, for example between the CNRS, Institut Curie and the company Johnson & Johnson and the University of North Carolina with Wyeth.

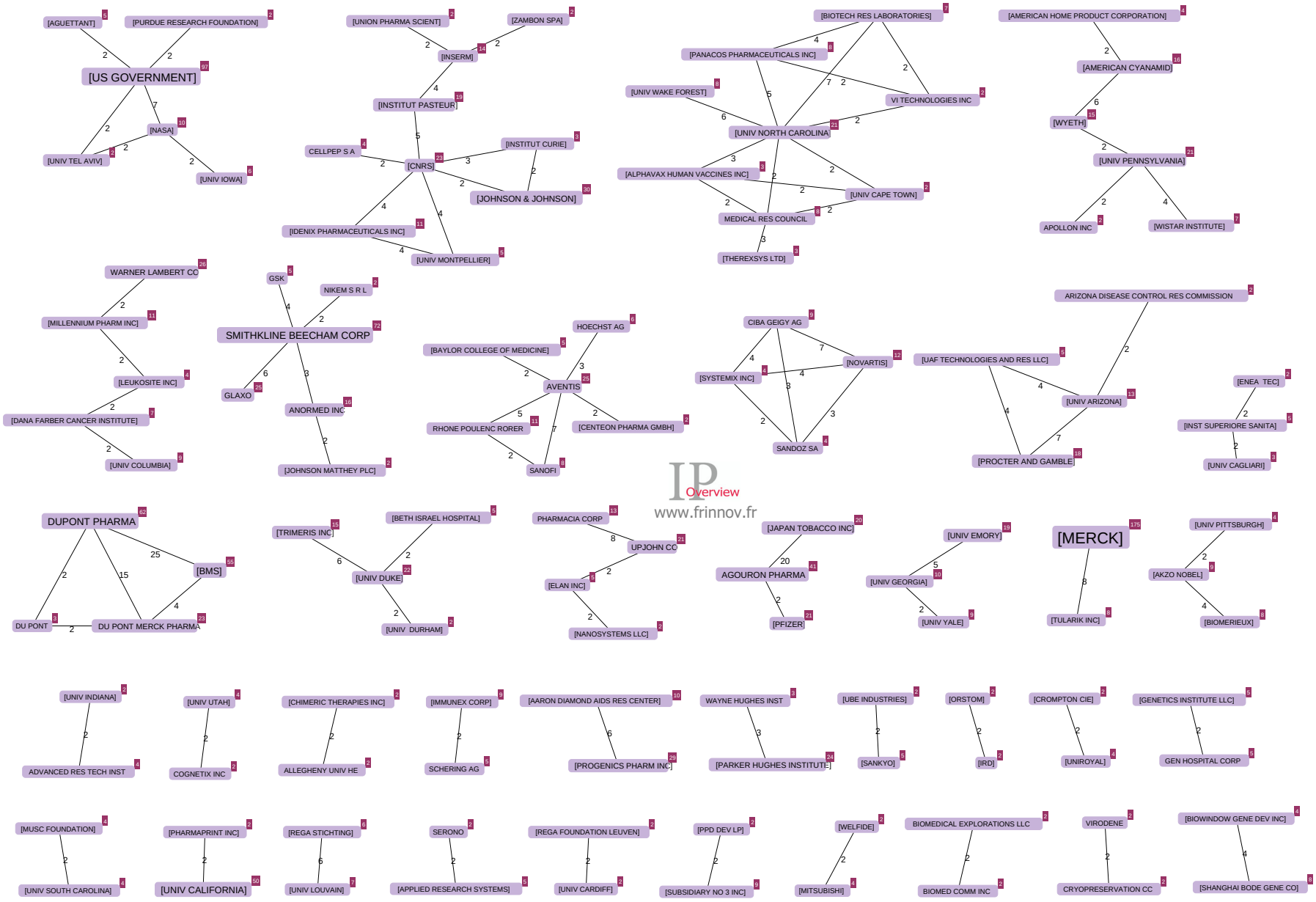


Figure 35: The major collaborations and the number of joint filings from 1993-2000

5.3.3 Topics protected (1993-2000)

The main differences from the previous period (1983-1992) were:

1. the interest in chemokine receptors corresponding to Pfizer, Progenics, Takeda and Anormed becoming top applicants mainly for the application of antagonists but also for immunomodulation.
2. the increasing interest in integrase inhibitors (especially Merck&co, Shionogi, UAB Research Foundation, University of North Carolina and US government laboratories).
3. research gradually turned away from peptide compounds and thus vaccines. Only academic researchers continued to work on this subject as well as the industrials Aventis and Merck&co (and less intensively BMS, Boehringer-Ingelheim and Smithkline Beecham).

Merck&co strongly diversified its research, focusing especially on the discovery of chemical compounds inhibiting protease and integrase and interfering with chemokine receptor. Merck&co was the only major applicant to continue working on a vaccine. It is also interesting to note that Merck&co, after being a pioneer in integrase inhibitors, remains clearly in the lead as applicant in this sector from 1993-2000. Merck&co is also a pioneer in the protection of combination therapies.

Dupont Pharmaceuticals, BMS, Abbott, Dupont Merck, Glaxo, Parker Hughes Institute and Boehringer-Ingelheim all mainly developed reverse transcriptase and protease inhibitors. Abbott concentrated its research on protease and Parker Hughes Institute and Boehringer-Ingelheim on reverse transcriptase. These inhibitors are mostly chemical compounds but two applicants, Parker Hughes Institute and Glaxo also developed compounds in the class of.

Monsanto, Upjohn and LG group concentrated on chemical compounds inhibiting protease. The companies Vertex Pharmaceuticals, Warner Lambert, Agouron, Japan Tobacco and Procter&Gamble also began working on this target.

The company Progenics focused on a strategy of inhibiting viral entry by strongly dominating CD4 research.
The University of Emory concentrated on but, as our graph shows, without an associated target. In fact these were Fluoronucleosides which have no specific target.

Smithkline and Aventis were working on antibodies, chemical and peptide compounds inhibiting viral entry as well as regulatory and structural proteins. Smithkline also patented nucleosides/(poly)nucleotides & analog compounds.

Finally, Johnson & Johnson concentrated on chemical compound inhibiting reverse transcriptase.

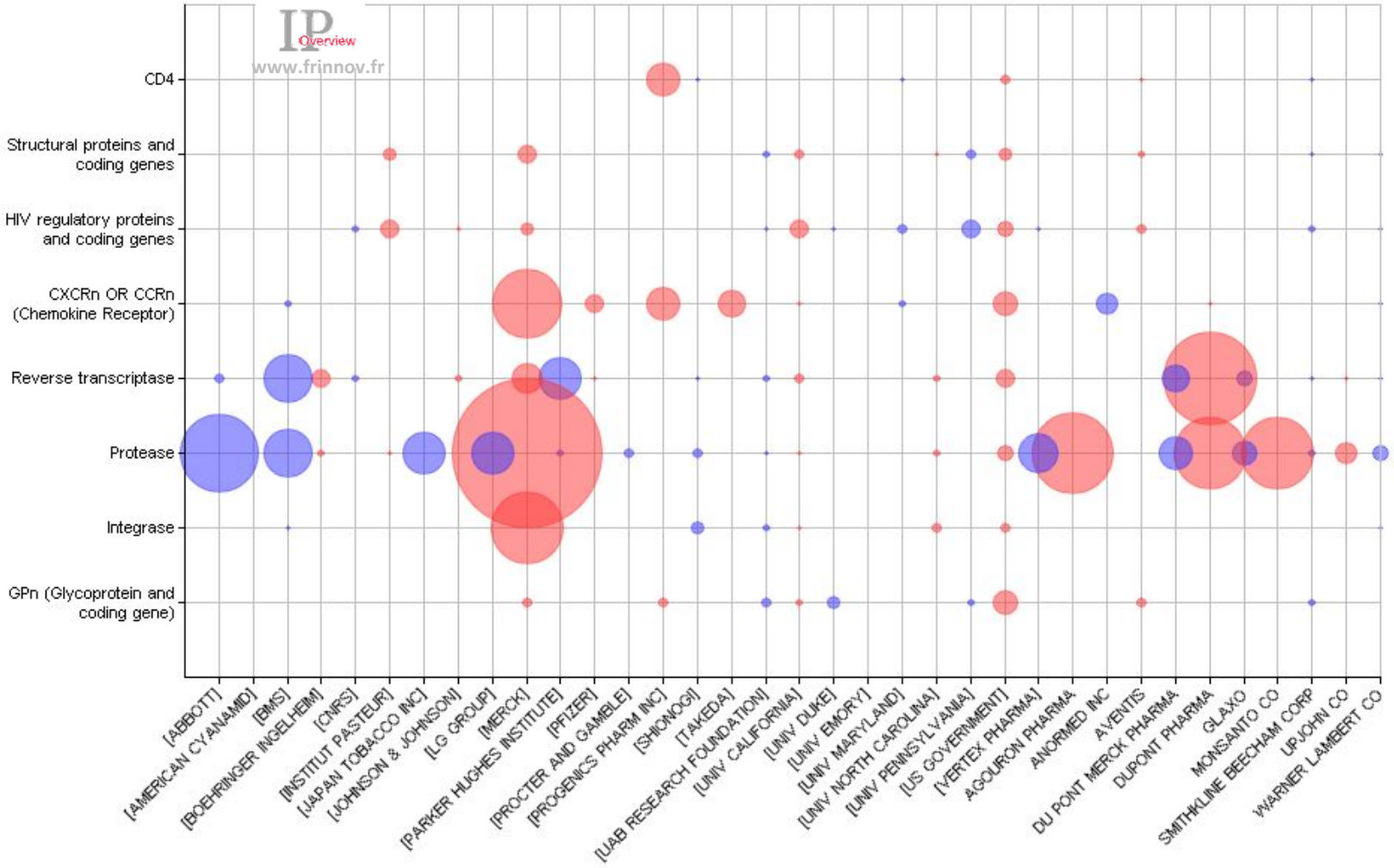


Figure 36: Therapeutic targets of the major players from 1993-2000

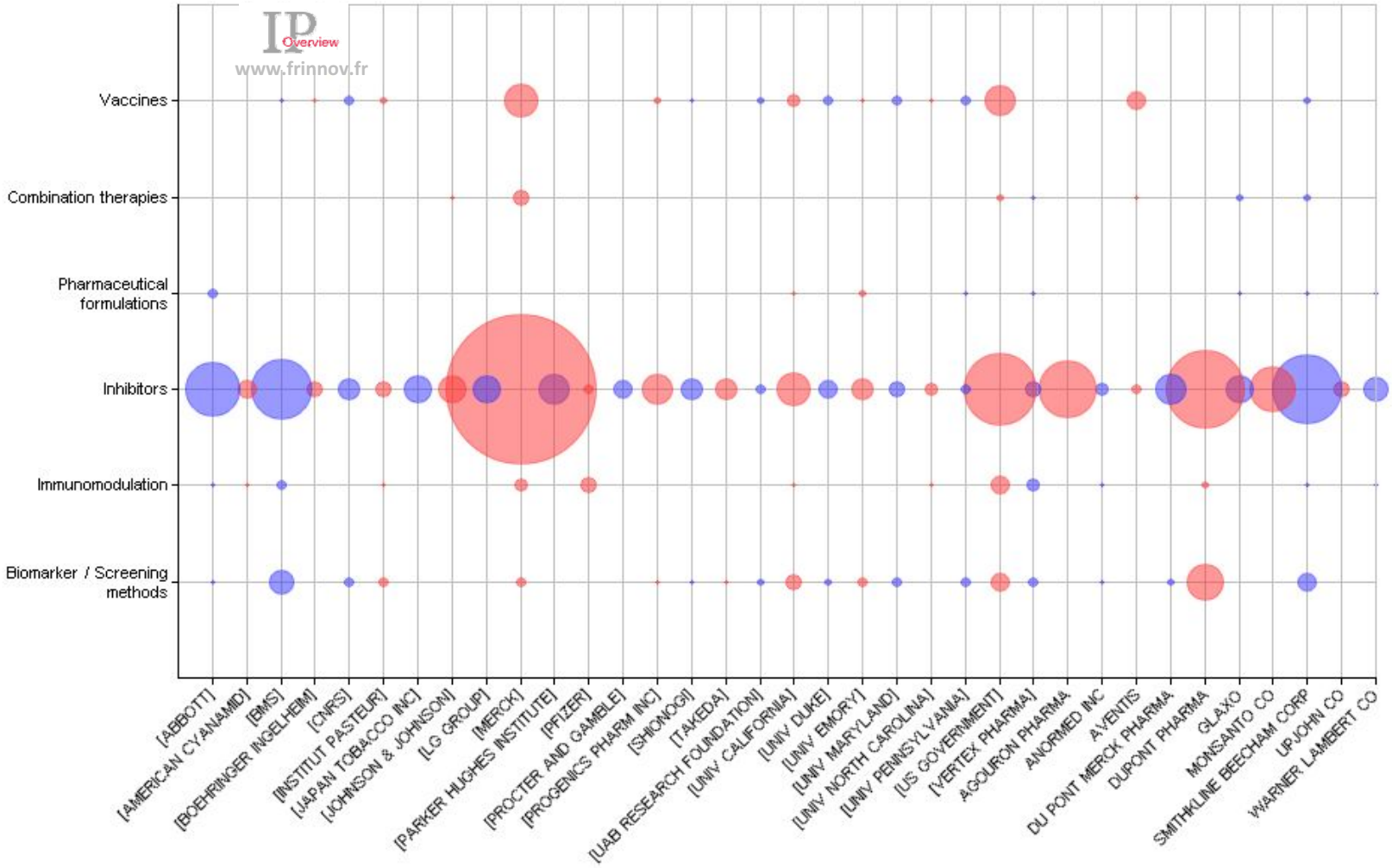


Figure 37: Applications of the major players from 1993-2000

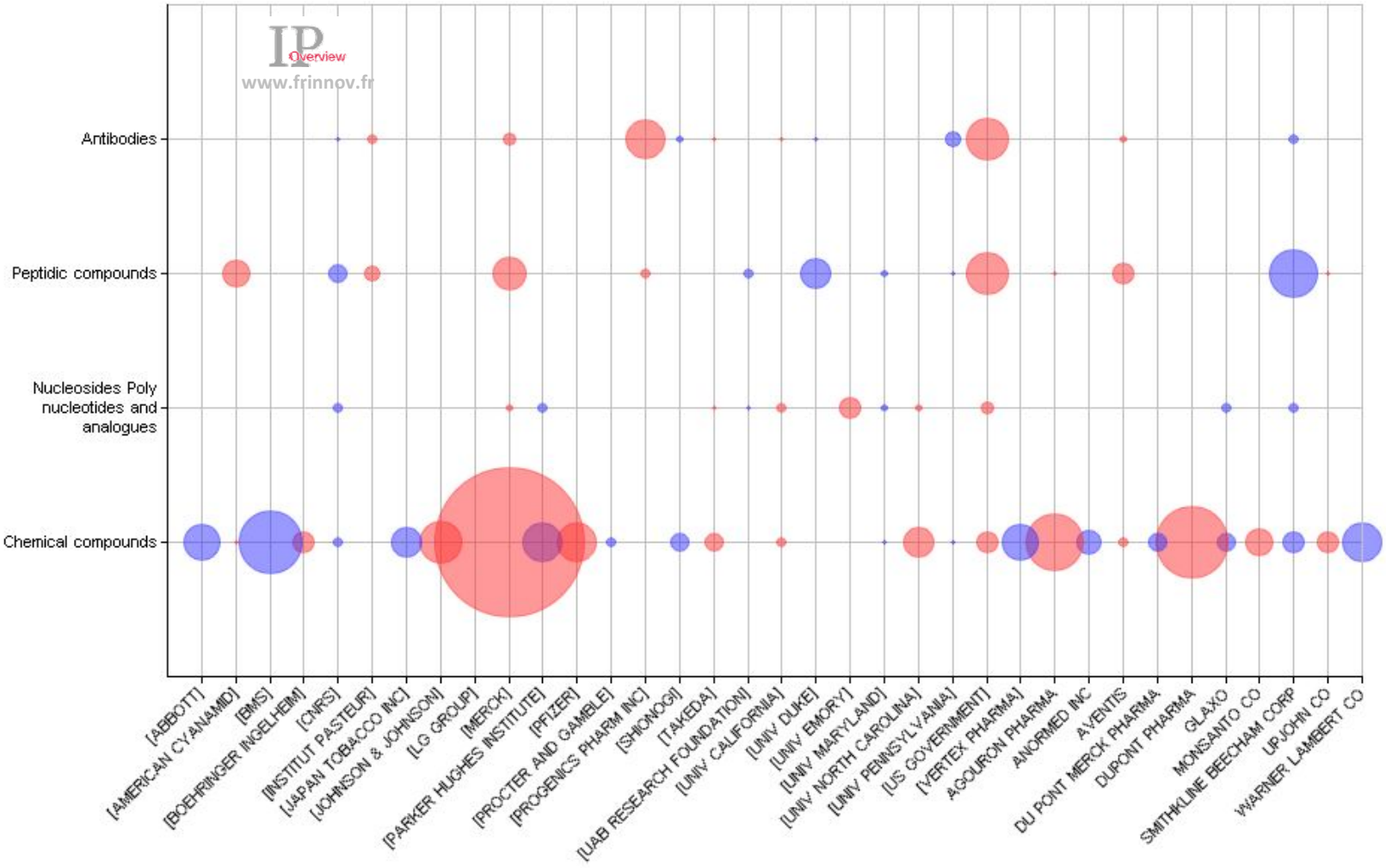


Figure 38: Classes of compounds of the major players from 1993-2000

5.4 Analysis for the most recent period (2001 - 2006)

5.4.1 Major applicants (2001-2006)

2616 patents were filed during this period naming more than 5900 inventors. The number of filings is similar to that of the intermediary period (2616 versus 2645) although the latter was shorter (6 years versus 8). As a result even if there is a tendency for a downturn in the number of applications, the filing rate remains vigorous. The significant increase in the number of inventors should be noted for a similar number of filings (6000 versus 4800), which is a sign of stronger collaborations and sharing of expertise to favour innovation.

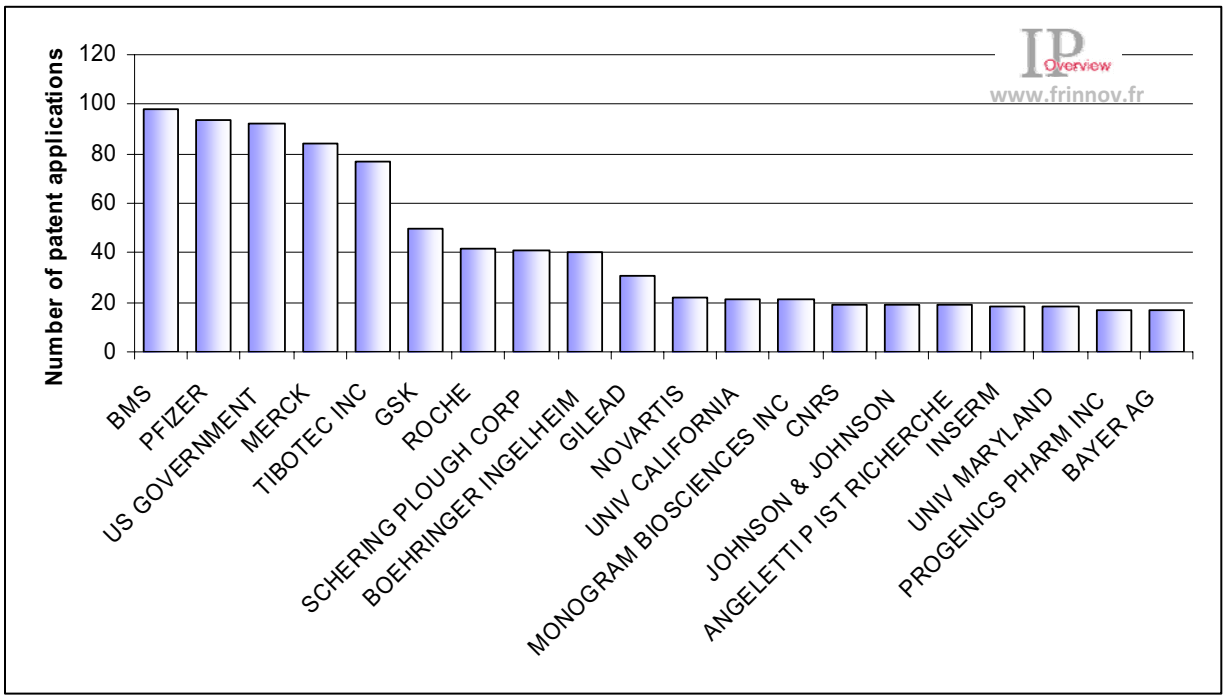


Figure 39: Major applicants from 2001 - 2006

Many of the players were already found in the top 20 during the intermediary period, usually large pharmaceutical groups. BMS, which now includes DuPont Pharmaceuticals and DuPont Merck moves from 5th to 1st place, Pfizer which now includes Warner Lambert and Agouron moves up to 2nd place. Merck&co remains in a leading position with more than 80 filings. GSK which now includes SmithKline Beecham and Glaxo (3rd and 15th place respectively from 1993-2000) moves up to 6th position but with a marked slowdown in the filing rate. This same tendency is seen for Progenics Pharmaceuticals which nevertheless remains a top applicant.

Tibotec appears for the first time in a top position in 5th place, as well as Schering Plough Corp in 8th, Gilead in 10th and Novartis in the 13th place. Roche is found in 7th place and Boehringer-Ingelheim in 9th both returning to the list after having disappeared during the intermediary period.

Monogram Biosciences, and Bayer AG are now Top 20 applicants, but with fewer filings than others.

Abbott and Vertex Pharmaceuticals which had been well positioned during the intermediary period have disappeared from the list.

The new entity Sanofi-Aventis (created in 2004 when Sanofi-Synthelabo acquired Aventis which was one of the Top 20 from 1993-2000) has now disappeared.

US government laboratories are the only academic research institute to continue to invest massively in this topic, and less spectacularly the University of California and the CNRS. INSERM is now on the list, moving up from 40th to 17th place, showing its growing interest in this topic.

	01	02	03	04	05	06
BMS	14	21	14	24	15	10
PFIZER	13	19	30	22	6	4
US GOVERNMENT	19	11	24	23	7	8
MERCK & Co	14	19	12	19	12	8
TIBOTEC INC	13	12	12	12	12	16
GSK	9	13	2	8	14	4
ROCHE	11	5	7	8	4	7
SCHERING PLOUGH CORP	17	8	3	3	7	3
BOEHRINGER INGELHEIM	5	15		12	1	7
GILEAD	2	5	7	5	4	8
NOVARTIS	3	3	3	3	4	6
MONOGRAM BIOSCIENCES INC	8	5		2	5	1
UNIV CALIFORNIA	3	4	4	4	3	3
JOHNSON & JOHNSON	5	2	4	1	3	4
ANGELETTI P IST RICHERCHE	4	3		9	3	
CNRS	6	1	3	4	3	2
UNIV MARYLAND	1	5	4	2	5	1
INSERM	4	3	3	2	2	4
PROGENICS PHARM INC	7	2	2	3	1	2
BAYER AG	1	4	10	2		

Table 11: Evolution of filings by applicant from 2001- 2006

An analysis of the evolution of filings from 2001 to 2006 clearly shows two types of applicants: those that turn away from this field in 2005 and those that remain seriously invested in this topic.

Despite its acquisition of Pharmacia Corp. in 2002 (which had merged with Upjohn in 1995 then Monsanto in 2000, two very important players in this field), Pfizer, like US government laboratories and Bayer, completely discontinues research in this field after 2005. This is also true for Merck&co, but to a lesser extent.

BMS, Tibotec, Roche, Gilead, Novartis and Johnson & Johnson remain strongly invested in this topic in the last years of the study, with Tibotec, Gilead (in particular after the purchase of Triangle Pharmaceuticals) and Novartis (with the purchase of Chiron) even strengthening their positions in 2006.

It should also be noted that Tibotec was acquired by Johnson & Johnson in 2002.

The University of California, CNRS and INSERM all have a continued, but modest interest in the subject throughout this period

5.4.2 Collaborations (2001-2006)

The figure below shows the clusters of collaborations among applicants for the period from 2001 to 2006. Only collaborations which resulted in 2 joint filings have been included.
Overall, and compared to the previous periods, relatively few joint filings occurred from these collaborations. The most important include the collaborations between Schering Plough Corp. and Pharmacopeia (9 joint filings), Merck&co and « IRBM P. Angeletti » (Italian research subsidiary of Merck&co) after 2000 (6 joint filings), Georgetown University with Samaritan Pharmaceuticals (5 joint filings), and Institut Pasteur with the CNRS and INSERM (5 joint filings each).

This analysis could not identify informal collaborations that did not result in any official joint filings. These occurred for example between Takeda and the company Syrrx (which was acquired by Takeda in 2005) and with the company Paradigm Therapeutics (bought by Takeda in 2007), Genzyme and Anormed (bought by Genzyme in 2006), Astex and Astrazeneca, Progenics and the Cornell Foundation, Ambrilia with Pharmacor and Procyon (both bought by Ambrilia in 2006), Ardea and Valeant (thanks to a transfer of research teams from Valeant to Ardea) and finally Roche and Maxygen.

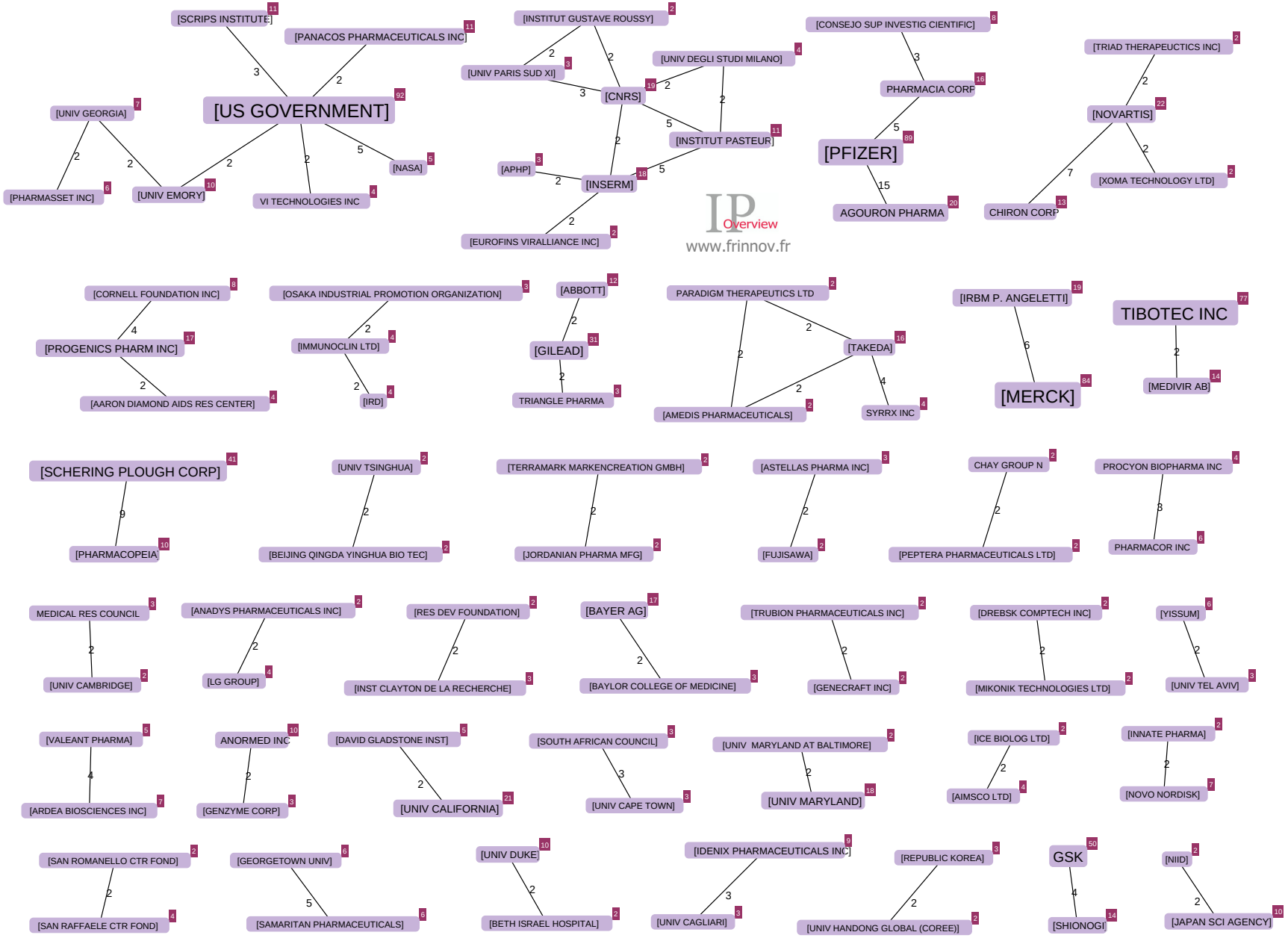


Figure 40: The major collaborations and joint filings (2001-2006)

5.4.3 Protected topics (2001-2006)

During this period, the major applicants began focusing their research on integrase inhibitors and chemokine receptors antagonists, and less markedly glycoproteins.

This is particularly true of BMS, which strengthened its reverse transcriptase and protease portfolio by by buying Dupont Pharmaceuticals in 1998.

Unexpectedly, Merck&co, which was the top applicant for chemokine receptors from 1993 to 2000, abandoned this therapeutic target between 2001 and 2006.

GSK, created from the merger of Smithkline Beecham (whose portfolio covers nearly all targets) and Glaxo (focusing on reverse transcriptase and protease) is the only player which still covers all targets with chemical or nucleosides/(poly)nucleotides & analog compounds.

Abbott and Pfizer also diversify their therapeutic targets while concentrating on chemical compounds.

Monogram Bioscience and Tibotec have the same strategy. They develop tests for the efficacy of inhibitors for most of the potential therapeutic targets. Tibotec further strengthens its position by concentrating on developing chemical or nucleosides/(poly)nucleotides & analog compounds inhibiting protease and reverse transcriptase.

Schering-Plough becomes the leader in the field of chemokine receptors and immunomodulation. Institut Pasteur and the company Chiron are the only players to continue working on potential vaccines.

Finally, Bayer explores different avenues of research without concentrating on one specific topic.

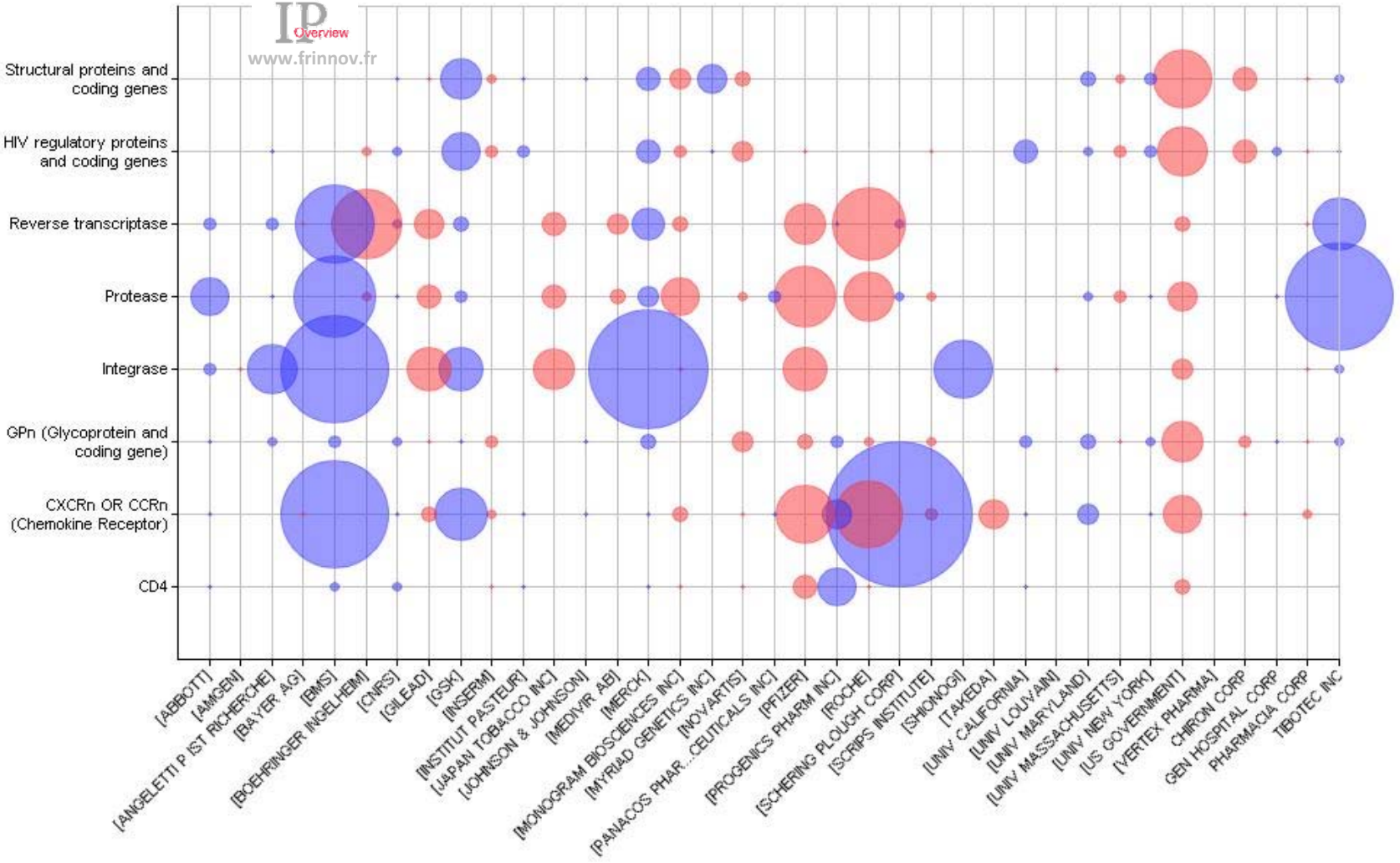


Figure 41: Therapeutic targets from 2001-2006

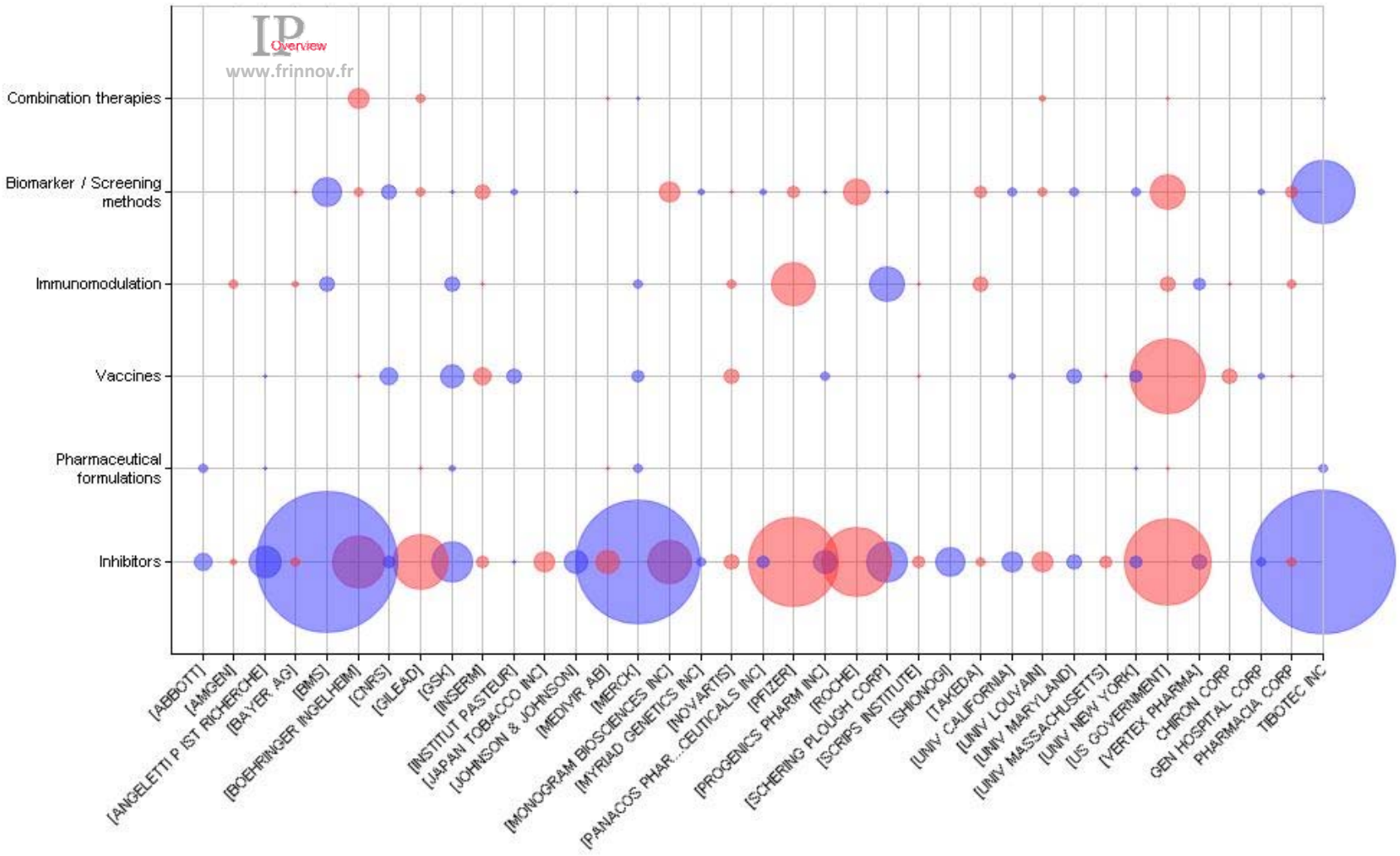


Figure 42: Applications of the major players from 2001-2006

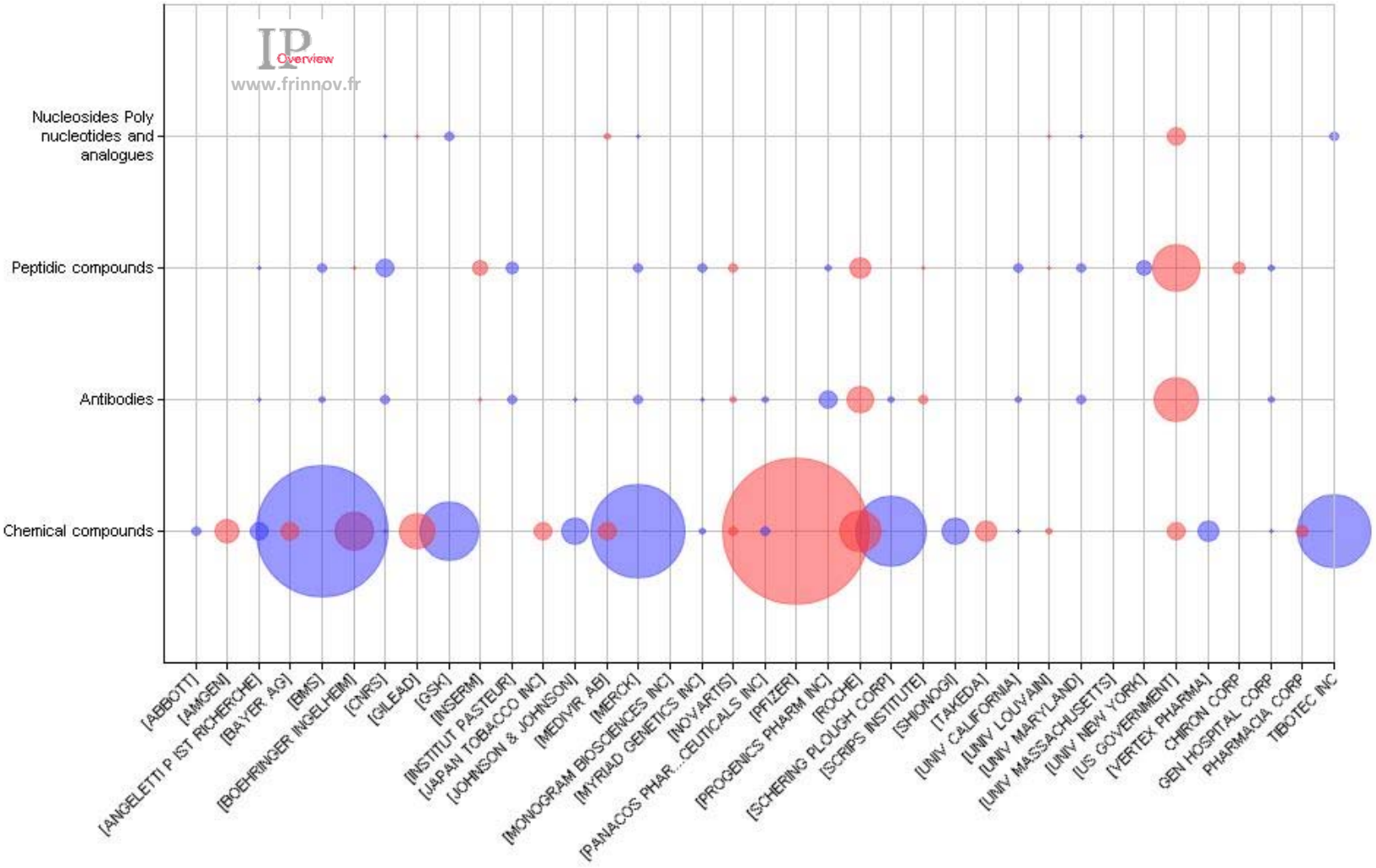


Figure 43: Classes of compounds of the major players from 2001-2006

6 Inventors in the field

The aim of this section is to identify the most important inventors in the portfolios protecting HIV treatments and determine which technologies they have developed. This evaluation is based on several criteria:

- the gross volume of patents and filings in this field,
- the "expertise factor" that is the number of patents naming an inventor, multiplied by the number of different co-inventors in those patents,
- the emerging inventors in the field, that is the inventors with the most growth in the number of patents filed citing them in this field in 2004, 2005 and 2006. This helps identify potential emerging inventors.

6.1 Inventors for the entire period (1983-2006)

6.1.1 The main inventors

The table below lists the inventors that are cited most often in patents and applications

Inventors	Nb patents	Applicants	Nb patents
Getman Daniel	106	PFIZER	102
		JOHNSON & JOHNSON	4
Decrescenzo Gary	86	PFIZER	86
Vazquez Michael	84	PFIZER	84
Talley John	76	PFIZER	75
		MICROBIA	1
Freskos John Nicholas	75	PFIZER	75
		ELAN INC	1
Mueller Richard	66	PFIZER	66
Montagnier Luc	58	INSTITUT PASTEUR	53
		CNRS	9
		TRANSGENE	5
		US GOVERNMENT	3
		INSERM	2

Inventors	Nb patents	Applicants	Nb patents
Schinazi Raymond	53	UNIV EMORY	38
		UNIV GEORGIA	18
		UNIV CALIFORNIA	3
		OKLAHOMA MED RES FOUD	3
		UAB RESERCH FOUNDATION	3
		UNIV ALABAMA	2
		JOHNSON MATTHEY PLC	2
		NOVARTIS	1
		UNIV BIRMINGHAM	1
		PHARMASSET INC	1
		ASTRAZENECA	1
		BAKER CUMMINS PHARMA	1
		CNRS	1
		IDENIX PHARMACEUTICALS INC	1
		UNIV NEW YORK	1
		UNIV YALE	1
Maddon Paul	44	PROGENICS PHARM INC	40
		AARON DIAMOND AIDS RES CENTER	7
		CORNELL FOUNDATION INC	3
		PDL BIOPHARMA INC	3
		GSK	1
		UNIV COLUMBIA	1
Sonigo Pierre	42	INSTITUT PASTEUR	37
		CNRS	14
		INSERM	2
		US GOVERNMENT	2
Alizon Marc	41	INSTITUT PASTEUR	37
		CNRS	13
		US GOVERNMENT	2
		JERINI AG	1
		TRANSGENE	1
Vacca Joseph	39	MERCK & Co	39
		TULARIK INC	2
		IRBM P. ANGELETTI	1
Wai John	38	MERCK & Co	38
		TULARIK INC	5
Janssen Paul Adriaan	37	JOHNSON & JOHNSON	32
		NPIL PHARMACEUTICALS UK LTD	1
		AVECIA PHARMACEUTICALS LTD	1
Heeres Jan	35	JOHNSON & JOHNSON	29
		NPIL PHARMACEUTICALS UK LTD	1
		AVECIA PHARMACEUTICALS LTD	1
		IDENIX PHARMACEUTICALS INC	
Kempf Dale	35	ABBOTT	33
		MERCK & Co	1
Olson William	35	PROGENICS PHARM INC	31
		AARON DIAMOND AIDS RES CENTER	5
		CORNELL FOUNDATION INC	4
		PDL BIOPHARMA INC	3
		MERCK & Co	1

Table 12: The main inventors for the entire period (1983-2006)

6.1.2 The experts

A cross analysis can be made of the number of patents naming inventors and the number of different co-inventors in those patents. This information, called the expertise factor, helps identify the most prolific inventors who developed their inventions by collaborating with different scientists. In other words the expertise factor provides information on how much an inventor « collaborates », sharing his/her expertise with others.

The following graph shows the inventors with the strongest expertise factors for the entire period.

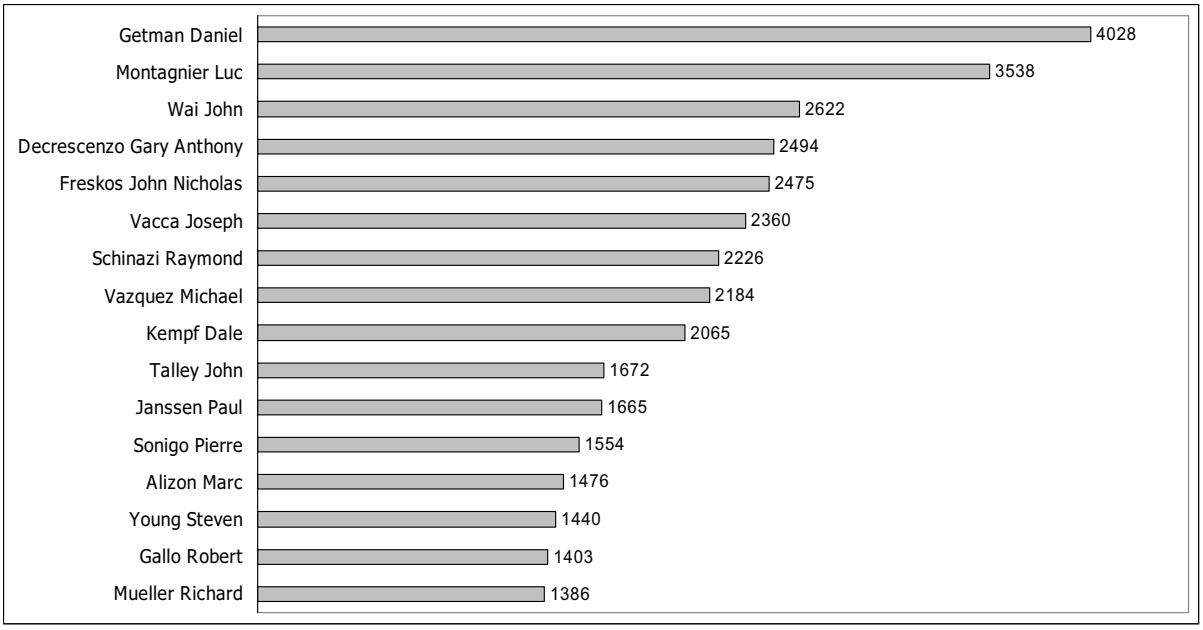


Figure 44: Expertise factor for the entire period

This analysis shows that three of the main inventors collaborate more than others thus improving their expertise rating compared to their rate of filing: Luc Montagnier, John Wai and Joseph Vacca.

6.1.3 Mobility of inventors

The figure below provides a general overview of how different inventors moved from one company to another or from a research institute to a company and vice versa. In particular, this type of map is an indicator of companies being started with institutionally owned patents and showing that researchers then joined these companies. For instance, this map provides a good idea of Dr Dani Bolognesi's and Dr. Tom Matthews' career from Duke University to the co-founding of Trimeris. Dr Graham Allaway moved from Progenics Pharmaceuticals to Panacos Pharmaceuticals in a similar manner.

This graph also gives an idea of potential collaborations that may not have resulted in joint filings, for example the collaborations between Georgetown University and Samaritan Pharmaceuticals and Merck&co and Tularik.

More unexpectedly this figure also shows that the University of Arizona received a donation of several HIV-patents previously owned by Procter & Gamble.

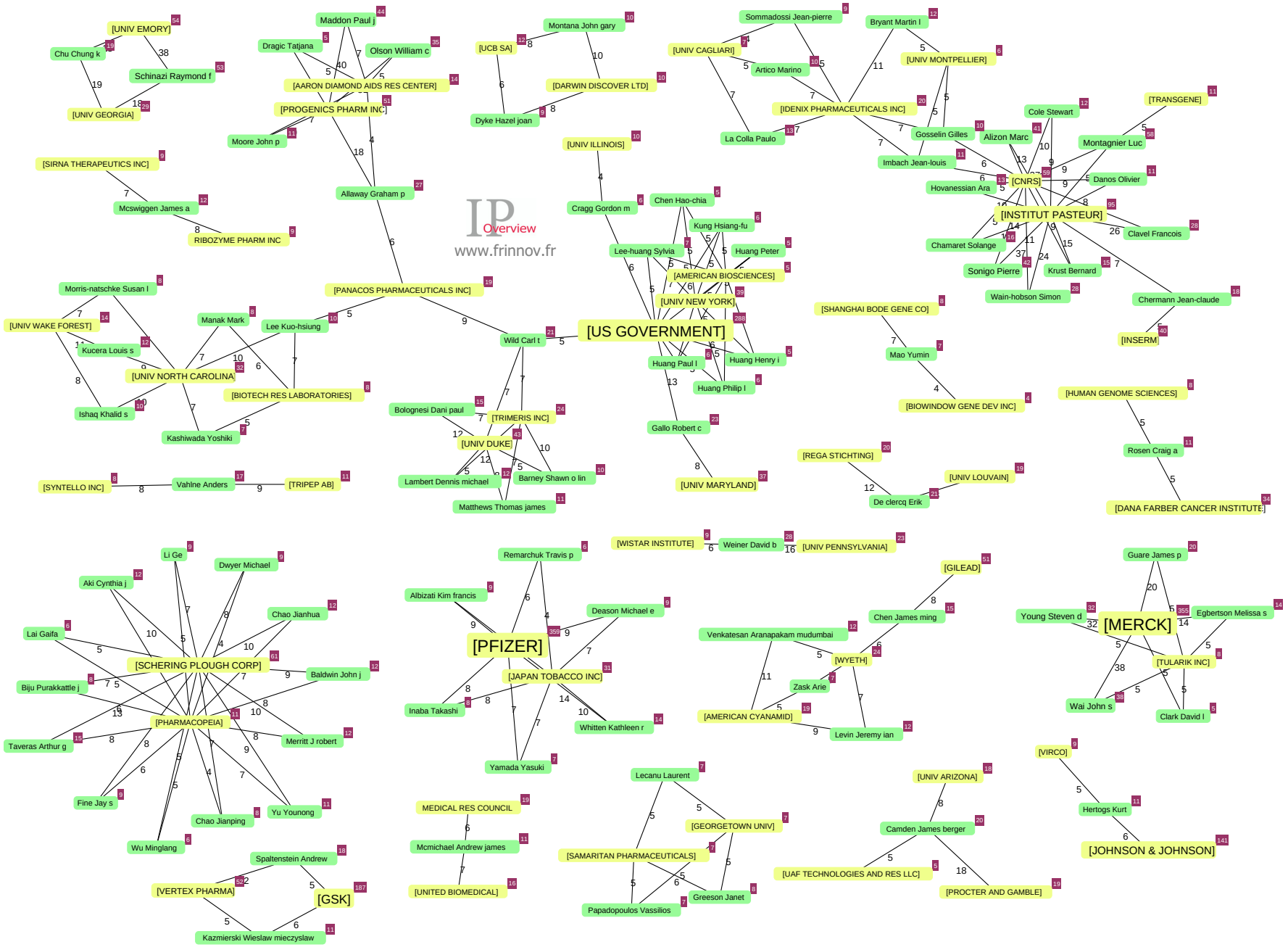


Figure 45: Mobility of inventors

1.1.1 Research teams for the entire period (1983-2006)

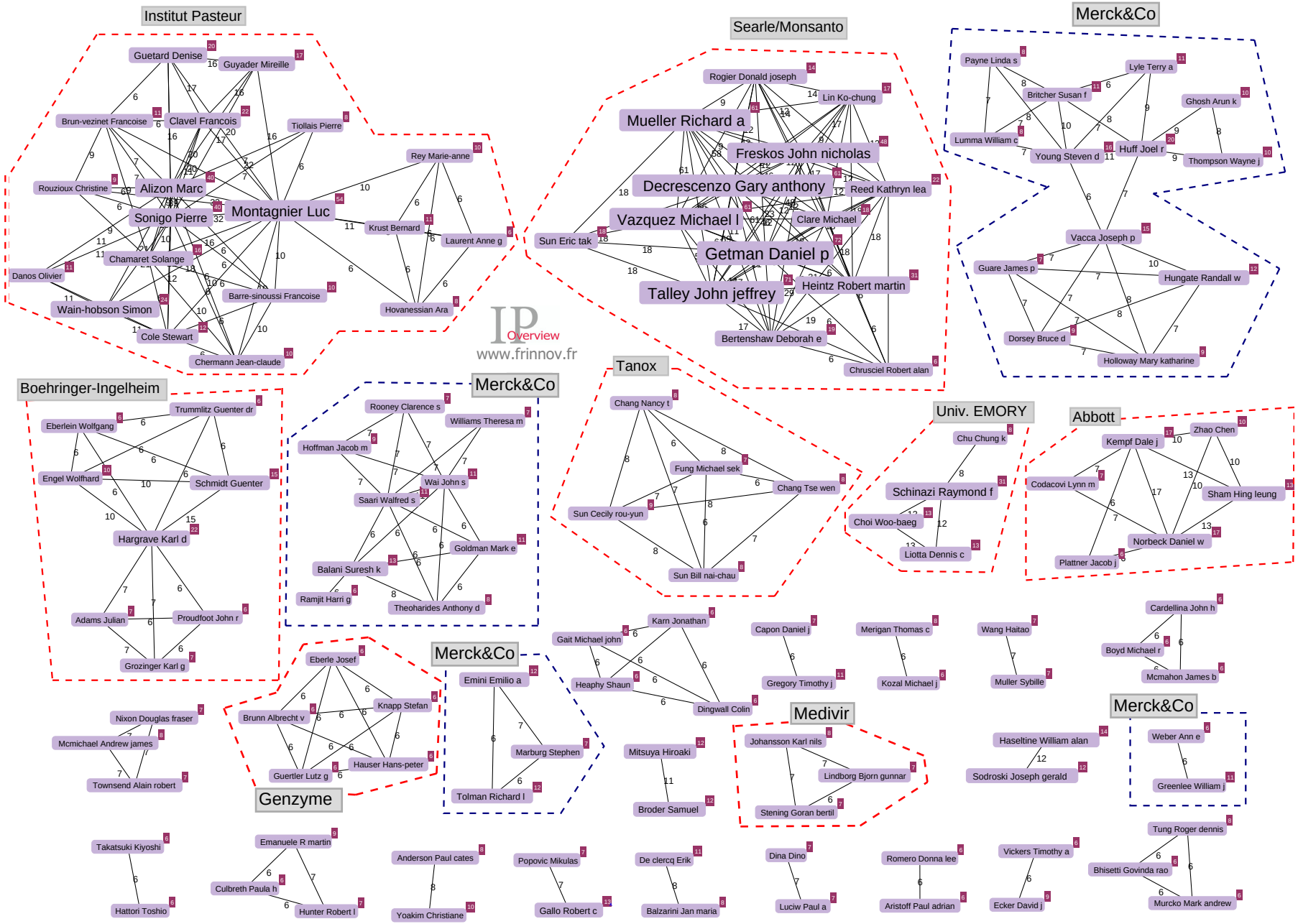


Figure 46: Research teams for the entire period (1983-2006)

It should be noted that only inventors having at least 12 joint filings with another inventor are shown in this map.

6.1.5 Topics

The following figures provide a breakdown of the filings of the main inventors and/or experts into 4 categories

- Industrial/institutional filings

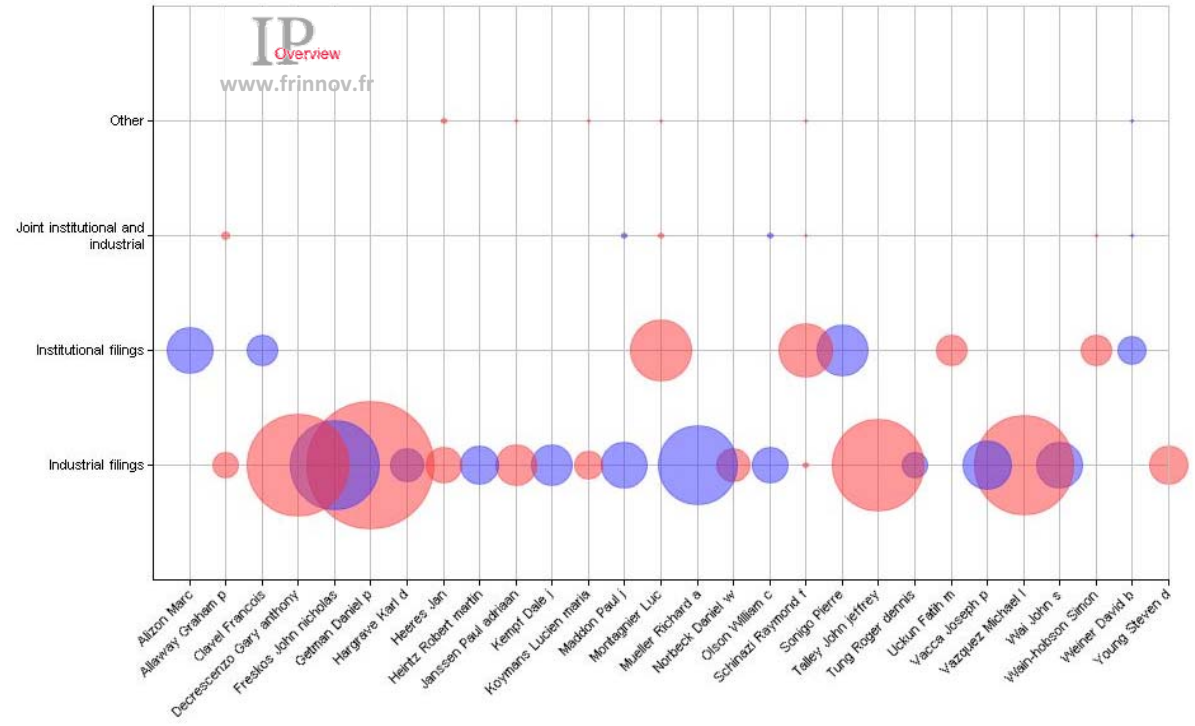


Figure 47: Industrial/institutional filings of the main inventors and/or experts

- breakdown by therapeutic target

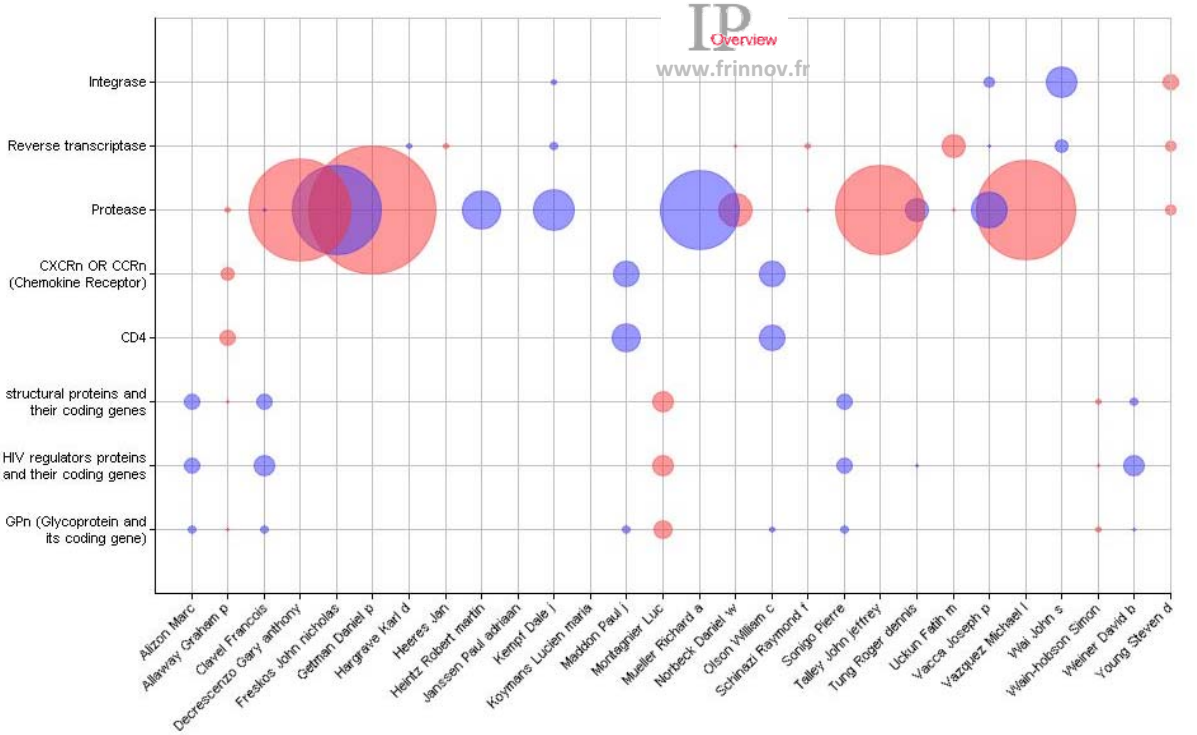


Figure 48: Therapeutic targets protected by the main inventors and/or experts

- breakdown by class of therapeutic compound

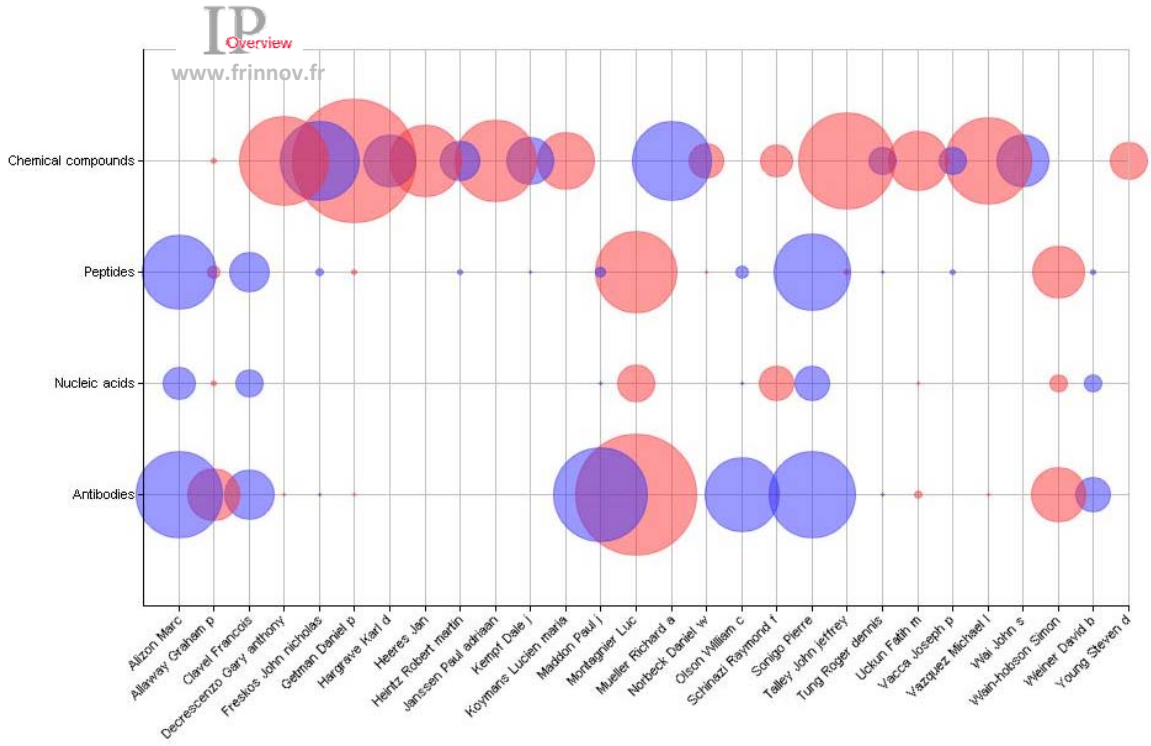


Figure 49: Classes of compounds protected by the main inventors and/or experts

- and finally the breakdown by application

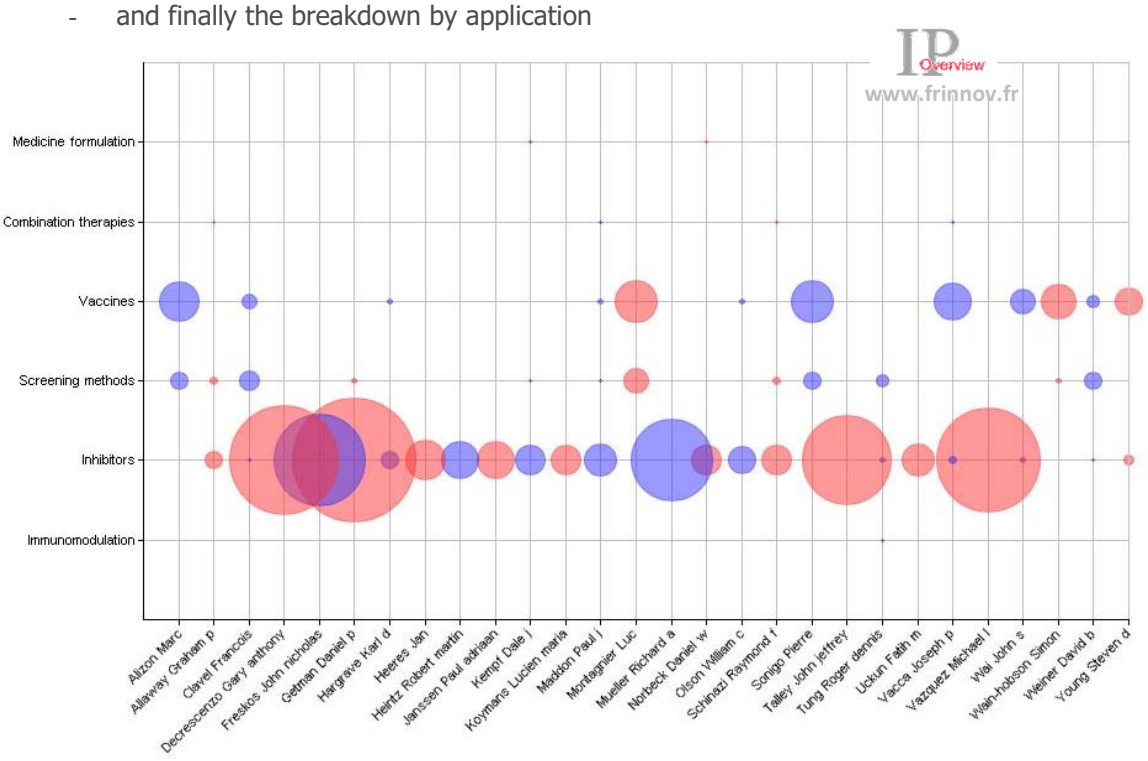


Figure 50: Applications protected by the main inventors and/or experts

These initial breakdowns give a very general picture which is difficult to interpret. This period must therefore be analyzed in greater detail.

Nevertheless it is interesting to note:

- A fairly clear separation between academic inventors and industrial inventors.
- An over-representation of chemical compounds protected by industrial inventors, especially protease inhibitors.
- On the other hand, a more global approach by institutional research teams which focus on vaccines and screening methods for structural and regulatory proteins and their coding genes.

Several research teams also emerge on this map:

- Dr Graham Allaway, Paul Maddon and William Olson's team concentrating on entry inhibition and viral fusion.
- Dr John Wai's team and Dr Steven Young's team focused on an approach targeting integrase.
- Dr Faith Uckun's team working on reverse transcriptase inhibition.
- Dr Raymond Schinazi's team working on nucleic acids.

6.1.6 Description of the main inventors

This section provides a description of a few of the most important inventors and/or experts for the entire period (1983-2006) who were not members of the same research groups.

Pr. Luc Montagnier, M.D, Ph.D., French doctor and virologist, was the pioneer inventor in HIV. Indeed, he discovered the HIV virus in 1983 with the team he led at Institut Pasteur in Paris. In 1986, Luc Montagnier and his group also isolated a second form of the HIV virus, HIV-2. Luc Montagnier was the first Director of the « AIDS and Retrovirus » Department at Institut Pasteur where he remained from 1991 to 1997. From 1997 to 2001, he was Professor and Director of the Center of Cellular and Molecular Biology at Queens College at New York University.

Dr. Raymond Schinazi is a Professor of Pediatrics at the University of Emory and of Chemistry at the University of Georgia. He is also « Senior Research Career Scientist » at the Veteran's Administration in Atlanta. He is especially known for his pioneer research on d4T (stavudine), 3TC (lamivudine), FTC (EMTRIVA), D-D4FC (reverset), AN (racivir), and than AMDX (Amdoxovir®), drugs that have been approved by the FDA or are in various stages of clinical development. He has founded several biotechnology companies focusing on the discovery and development of new antiviral drugs such as Pharmasset, Triangle Pharmaceuticals (acquired by Gilead Sciences in 2003), and Idenix Pharmaceuticals (54% acquired by Novartis in 2003). At present, he is one of the Directors of Alios Biopharma, a biotech company involved in the fight against viral infections and cancers.

Dr. Daniel P. Getman began his career in 1982 at Monsanto. With the merger of Monsanto and Upjohn Pharmacia in 2000, Pharmacia was founded and then with the merger of Pharmacia and Pfizer in 2002, Daniel Getman found his way to the number one pharmaceutical company in the world: Pfizer. He is now Vice President of Worldwide R&D at Pfizer. He has also been named President of the Committee of Exploratory Development and collaborates with different teams on the project to identify new candidate drugs for clinical trials.

Dr Joseph Vacca, an American scientist, works at Merck&co. and filed a key patent in 1998 protecting the compound Indinavir, one of the first protease inhibitors to be marketed.
From 1981 to 1988, **Paul J. Maddon**, M.D., Ph.D., did research work at the Howard Hughes Medical Institute at Columbia University. He founded Progenics Pharmaceuticals, a biopharmaceutical company that works on the development and commercialization of novel therapeutic products to treat as yet unmet medical needs of patients with debilitating or life threatening diseases. Since it was founded in 1986, he has held the positions of Chairman of the Board of Directors, Chief Executive Officer, President and Chief Scientific Officer. He also participates in two scientific examination

committees at the NIH (National Institutes of Health) and is a member of the editorial board of the review « Journal of Virology ».

Paul Adriaan Janssen (1926-2003) founded Janssen Pharmaceutica, a Belgian pharmaceutical company in 1953, which was then acquired by Johnson & Johnson in 1961. In 1995, Paul Adriaan Janssen founded the « Center for Molecular Design », specialized in research to identify candidate drugs to treat AIDS.

6.2 Pioneer inventors (1983-1992)

The main inventors and the inventors with the best expertise factors from 1983 to 1992 are shown in the tables below.

Inventors	Nb patents	Applicants	Nb patents
Getman Daniel	72	SEARLE CO	59
		MONSANTO CO	30
		PHARMACIA CORP	5
Talley John	71	SEARLE CO	57
		MONSANTO CO	32
		PHARMACIA CORP	5
Decrescenzo Gary	61	SEARLE CO	52
		MONSANTO CO	23
		PHARMACIA CORP	3
Mueller Richard	61	SEARLE CO	53
		MONSANTO CO	23
		PHARMACIA CORP	3
Vazquez Michael	61	SEARLE CO	53
		MONSANTO CO	23
		PHARMACIA CORP	3
Montagnier Luc	54	INSTITUT PASTEUR	51
		CNRS	9
		TRANSGENE	5
		US GOVERNMENT	3
		INSERM	2
Freskos John	48	SEARLE CO	38
		MONSANTO CO	19
		PHARMACIA CORP	3
Alizon Marc	40	INSTITUT PASTEUR	37
		CNRS	13
		US GOVERNMENT	2
		TRANSGENE	1

Table 13: List of the main inventors (1983-1992)

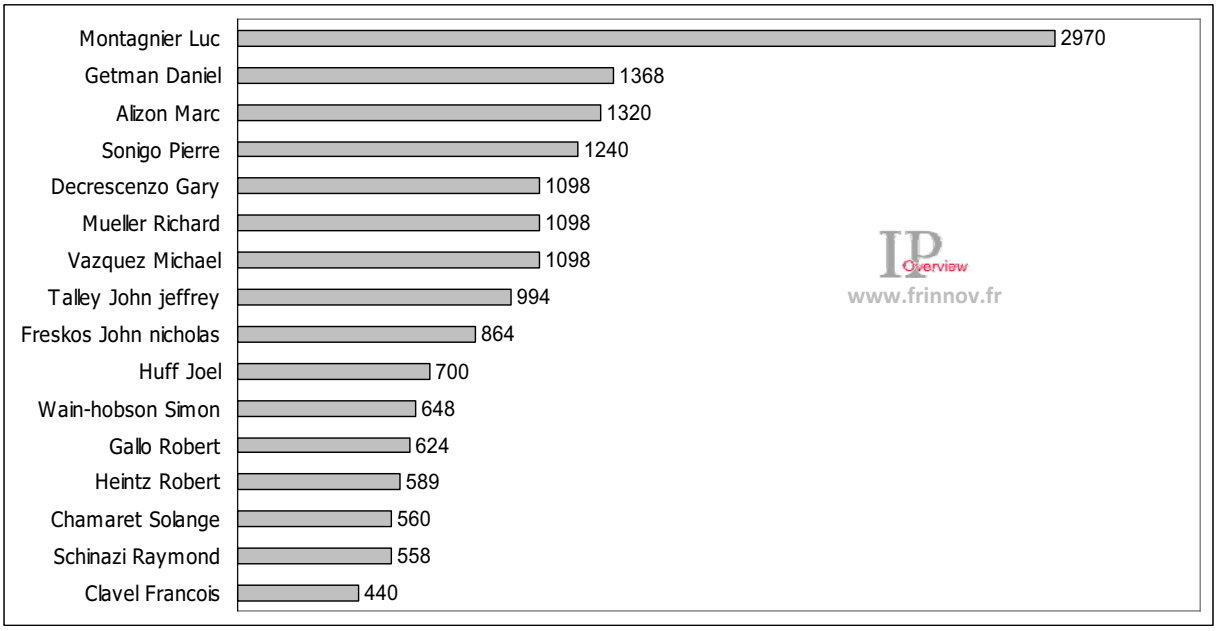


Figure 51: List of experts (1983-1992)

Pr. Luc Montagnier is clearly the top collaborator of all the other experts in this field.

The figure below shows the major research groups during this period (with at least 6 joint filings). Several pioneer research teams emerge in the field, in particular two important groups:

- The group including the inventors Luc Montagnier, Marc Alizon and Pierre Sonigo, at Institut Pasteur, which mainly filed patents describing the HIV-1 and HIV-2 virus (structural and regulatory proteins and their coding genes) for diagnostic applications (not taken into account for the analysis), biomarkers/screening methods and vaccines.
- And the group including the inventors Daniel Getman, John Talley, Richard Muller, Michael Vazquez, Gary Decrescenzo, John Freskos and Robert Heintz, first with Monsanto (before joining Pfizer) which mostly focused its research on chemical compound inhibiting protease.

Raymond Schinazi at the University of Emory and the University of Georgia, whose patents mostly protect nucleotide compounds with no specific target should also be mentioned as well as Joel Huff, Steven Young and Joseph Vacca who have protected chemical and peptide compounds inhibiting protease and reverse transcriptase.

It should also be noted that most companies only work with 1 or 2 research groups, except for Merck&co which is associated with 5 different research teams.

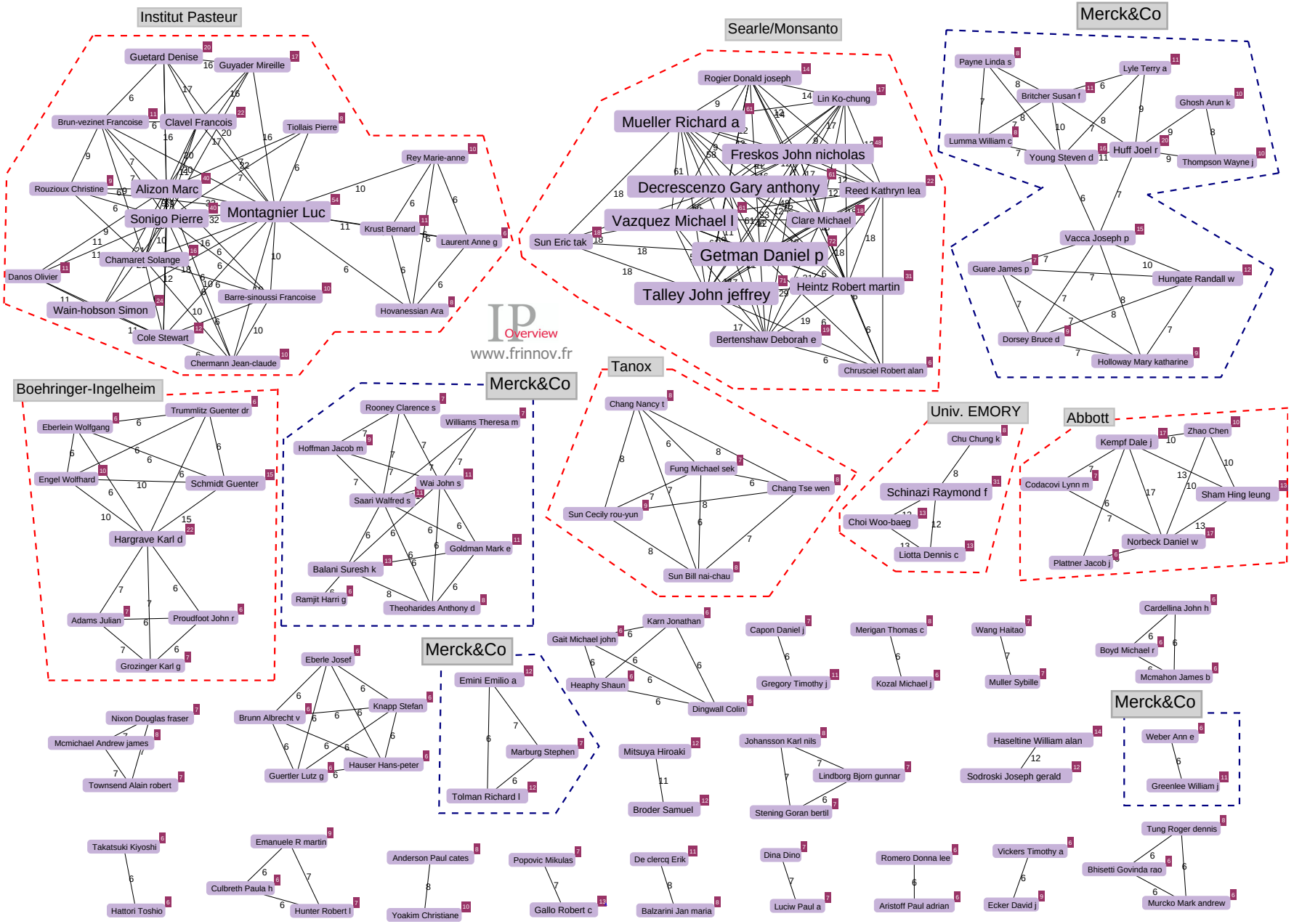


Figure 52: The major collaborations among inventors (1983-1992)

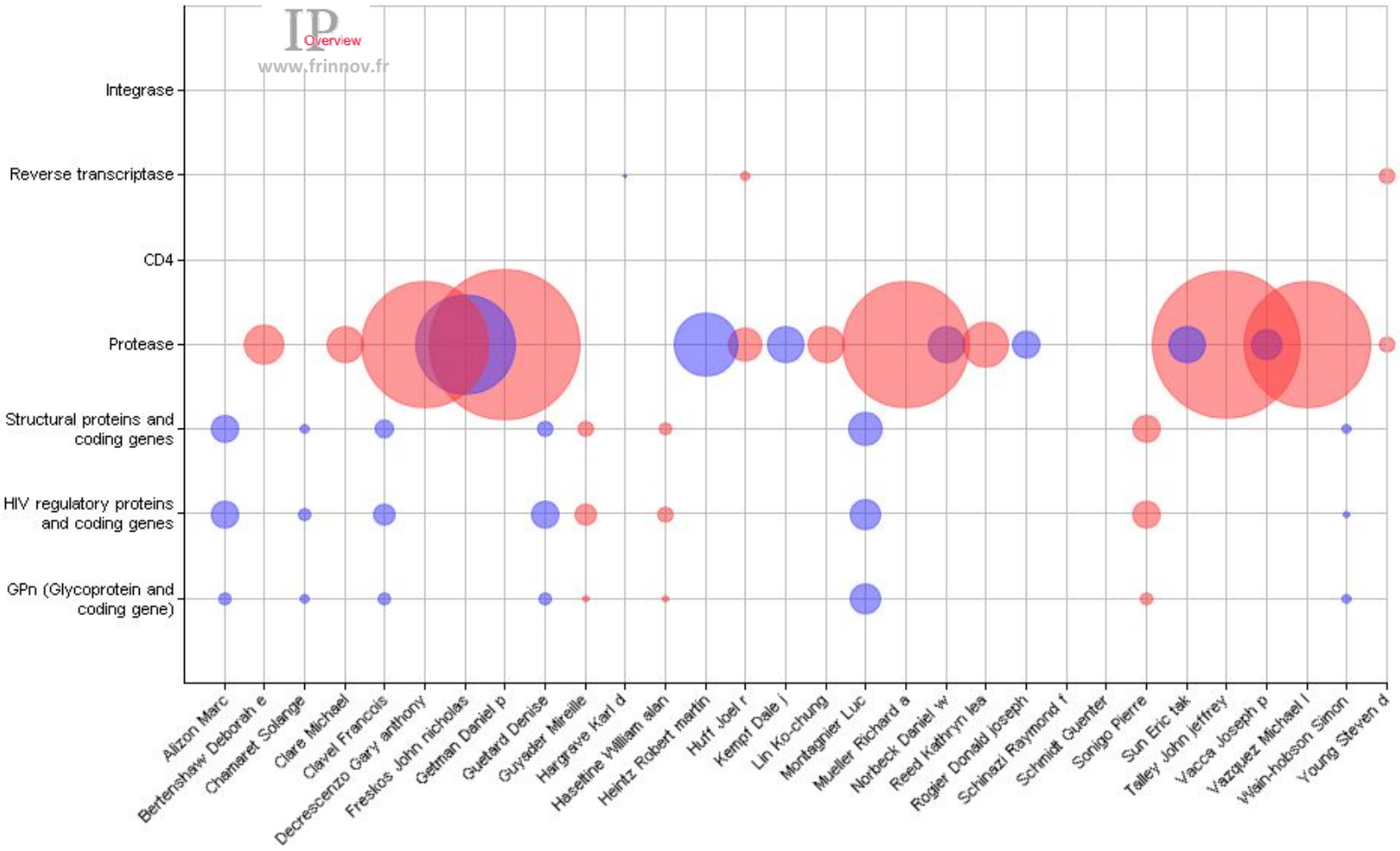


Figure 53: Therapeutic targets of the main inventors (1983-1992)

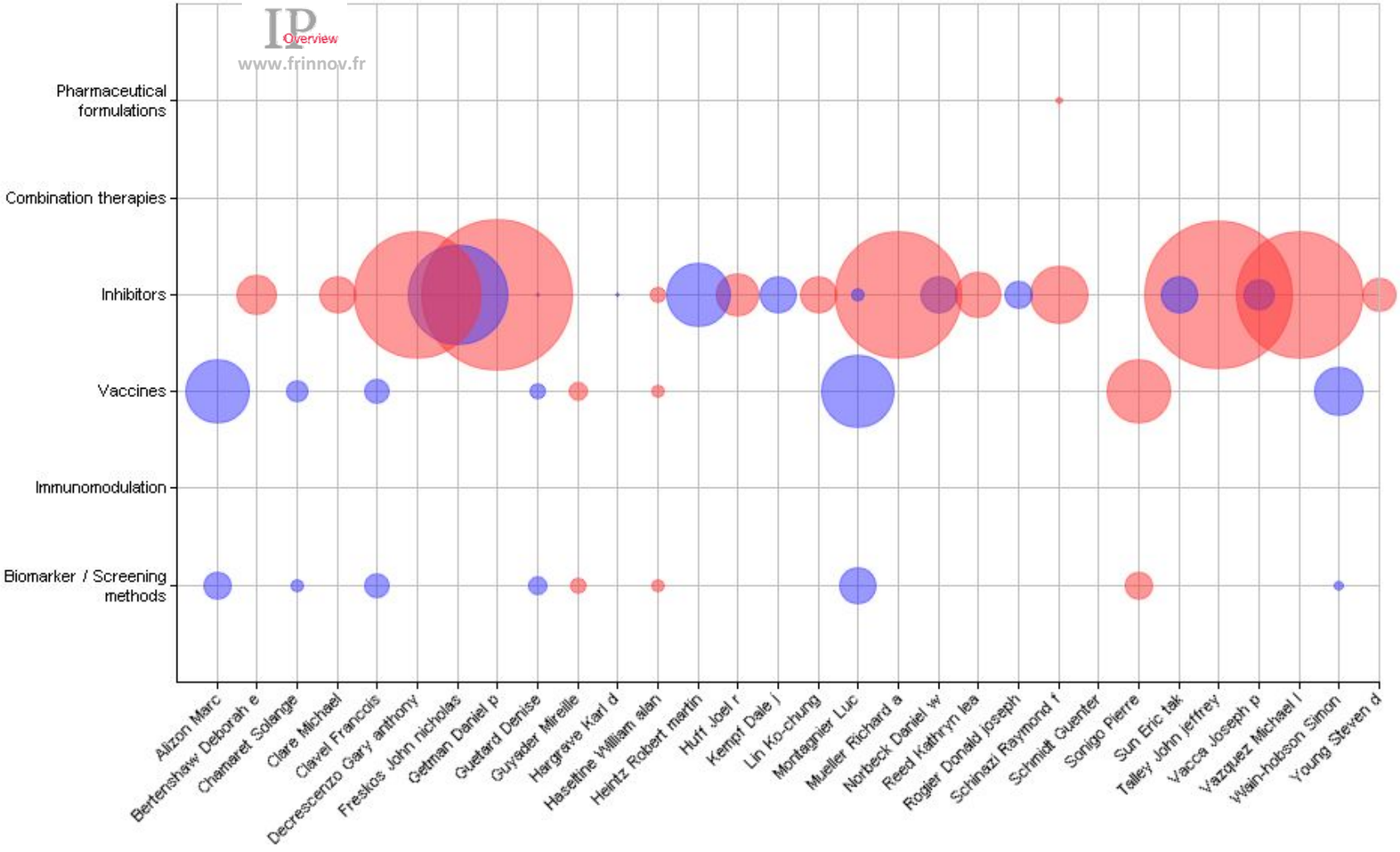


Figure 54: Applications of the main inventors (1983-1992)

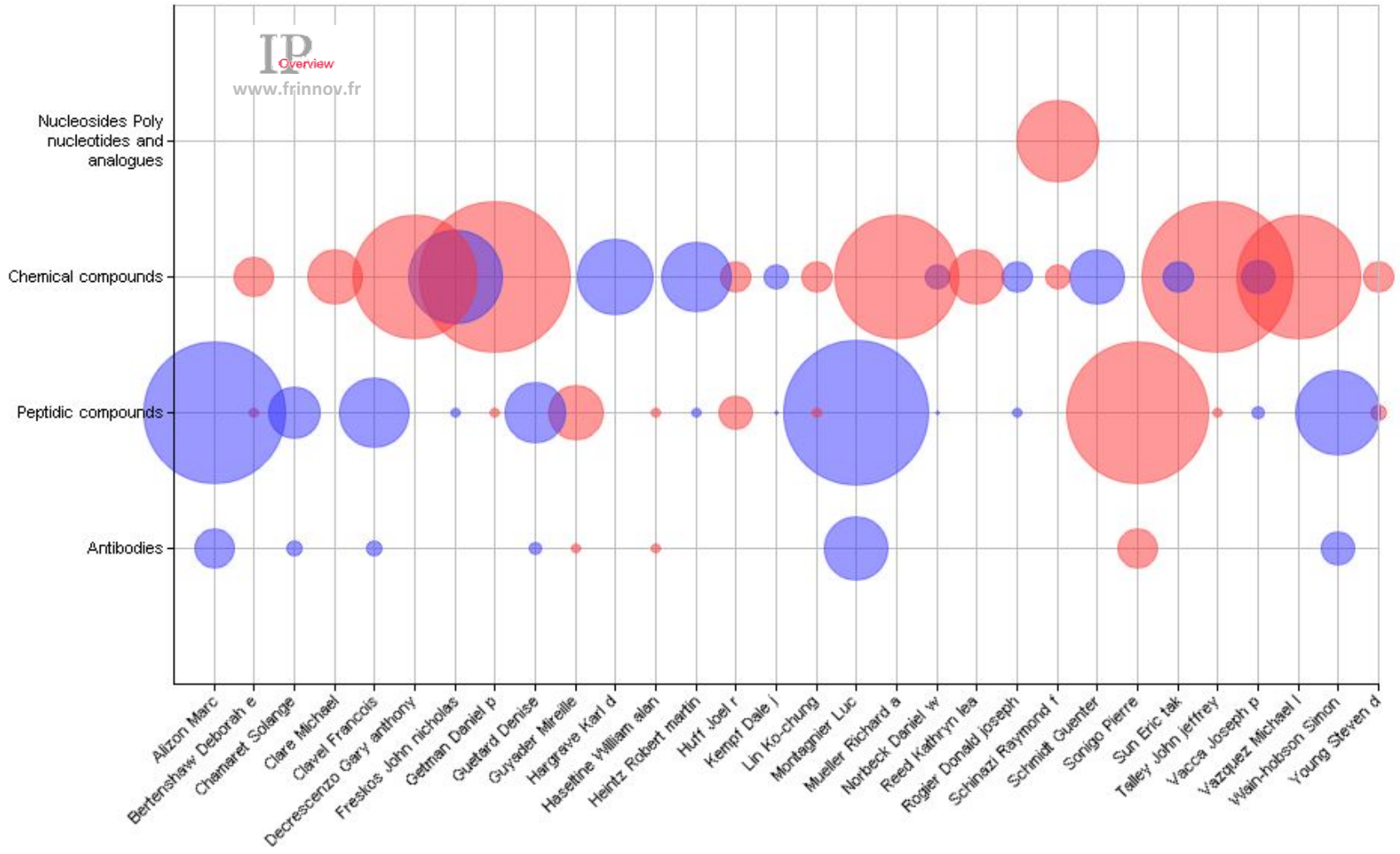


Figure 55: Classes of compounds of the main inventors (1983-1992)

6.3 Main inventors from 1993 to 2000

The main inventors and the inventors with the best expertise factors from 1993 to 2000 are shown in the tables below.

Inventors	Nb patents	Applicants	Nb patents
Getman Daniel	30	MONSANTO CO	30
		PHARMACIA CORP	1
Freskos John nicholas	27	MONSANTO CO	26
		PHARMACIA CORP	1
		UPJOHN CO	1
		ELAN INC	1
Elshourbagy Nabil	26	SMITHKLINE BEECHAM CORP	26
Maddon Paul	26	PROGENICS PHARM INC	25
		AARON DIAMOND AIDS RES CENTER	6
		AROGENICS PHARMACEUTICALS INC	1
Decrescenzo Gary	25	MONSANTO CO	25
Mills Sander	25	MERCK & Co	25
Sikorski James	25	MONSANTO CO	25
Uckun Fatih	25	PARKER HUGHES INSTITUTE	23
		WAYNE HUGHES INST	3
		UNIV MINNESOTA	2
		HUGHES INST	2
Maccoss Malcolm	23	MERCK & Co	23
Vazquez Michael	23	MONSANTO CO	23
Devadas Balekudru	22	MONSANTO CO	22
Mcdonald Joseph	22	MONSANTO CO	22
Nagarajan Srinivasan	21	MONSANTO CO	21
Vacca Joseph	20	MERCK & Co	20
		TULARIK INC	2

Table 14: List of the main inventors (1993-2000)

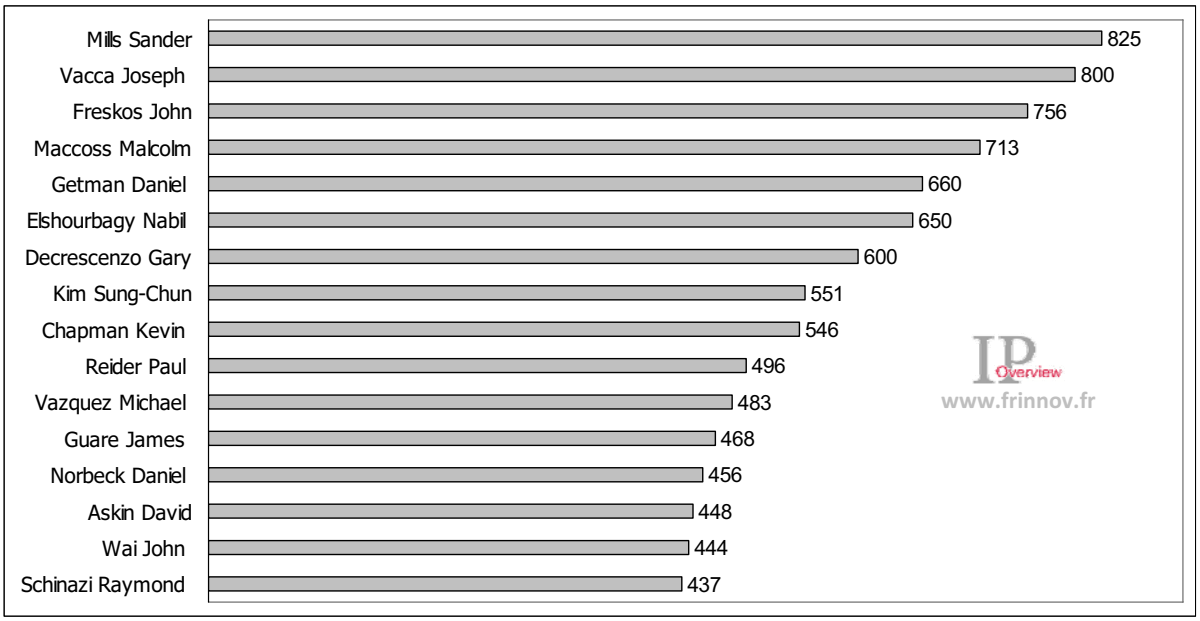


Figure 56: List of experts (1993-2000)

Sander Mills, Joseph Vacca and John Freskos clearly top the list of experts during this period.

The figure below shows the main research groups during this period (with at least 6 joint filings), with two large teams filing a significant number of patents (≥9):

- The group working with Daniel Getman at Monsanto, which continues to protect chemical compounds inhibiting protease.
- The team working with Adriaan Janssen at Johnson&Johnson mainly protecting chemical compounds inhibiting reverse transcriptase.

Numerous other research teams have increased their filing during this period. For example:

- The team at Progenics Pharmaceuticals led by Paul Maddon, working mostly on developing peptide, nucleosides/(poly)nucleotides & analog compounds and antibodies to inhibit viral entry into the cell and develop a vaccine,
- The team at SmithKline Beecham led by Nabil Elshourbagy, focusing on peptide and nucleosides/(poly)nucleotides & analogs inhibiting protease and biomarker/screening methods.
- The team at Merck&co working with the inventors/« experts » Sander Mills and Malcom Maccoss, mainly filing patents protecting immunomodulators and chemical compounds antagonists of chemokine receptors,
- Another team at Merck&co working with Steven Young and Joseph Vacca who have diversified their research and are focusing on chemical compounds (and peptide compounds for Joseph Vacca) inhibiting reverse transcriptase and integrase (and protease for Joseph Vacca and vaccines for Steven Young),
- A third team at Merck&co working with David Askin and Paul Reider on chemical compounds inhibiting protease,

- The team at the Parker Hugues Institute working with Uckun Faith mainly on chemical compounds, nucleosides/(poly)nucelotides and analogs inhibiting reverse transcriptase and protease and on antibodies.
- And finally the team at the University of Emory with Raymond Schinazi working on chemical compounds, nucleosides/(poly)nucleotides & analogs inhibiting protease, reverse transcriptase and integrase and biomarkers/screening methods. He is the only major inventor to specifically develop pharmaceutical formulations.

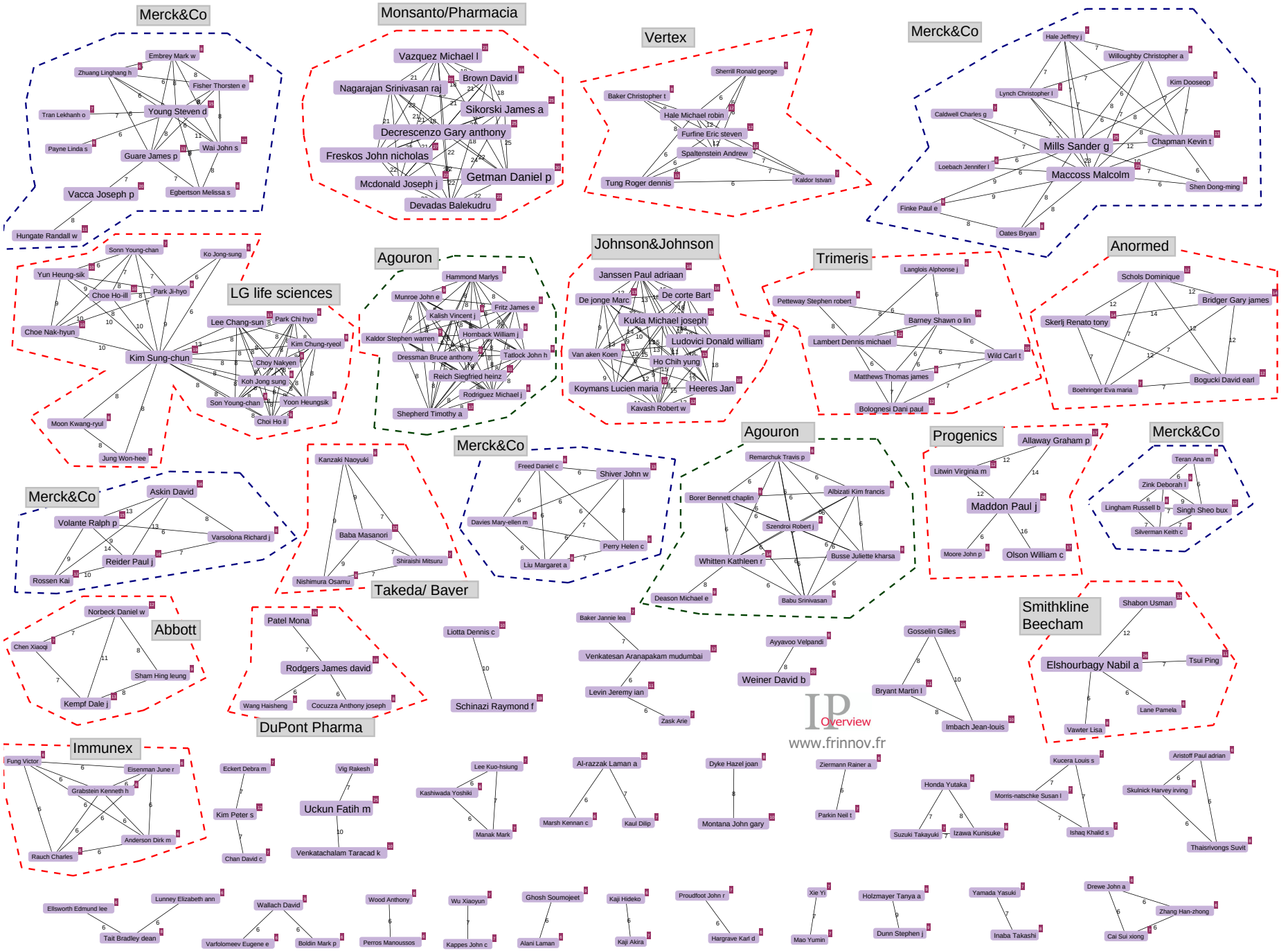


Figure 57: The major collaborations among inventors (1993-2000)

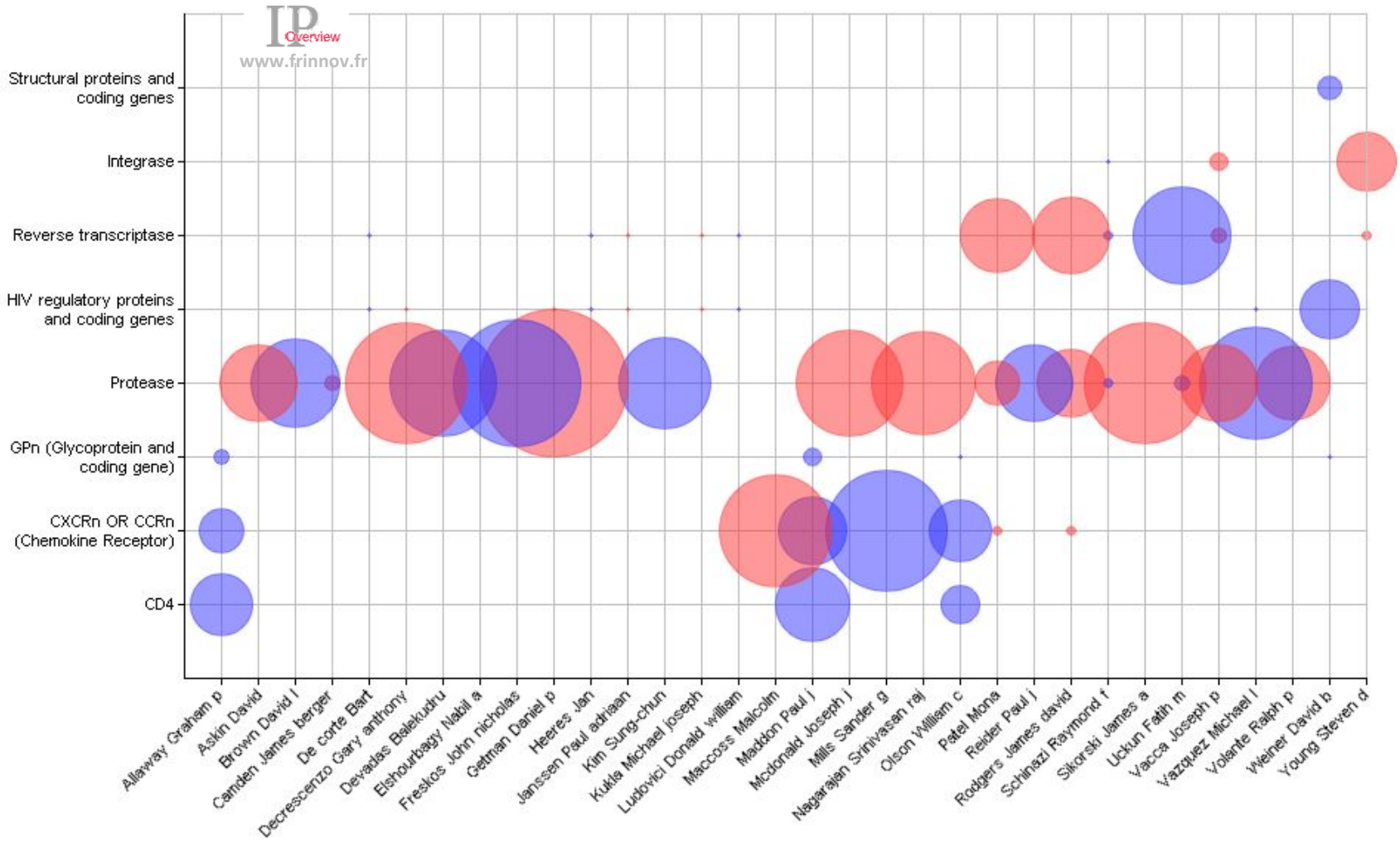


Figure 58: Therapeutic targets of the main inventors (1993-2000)

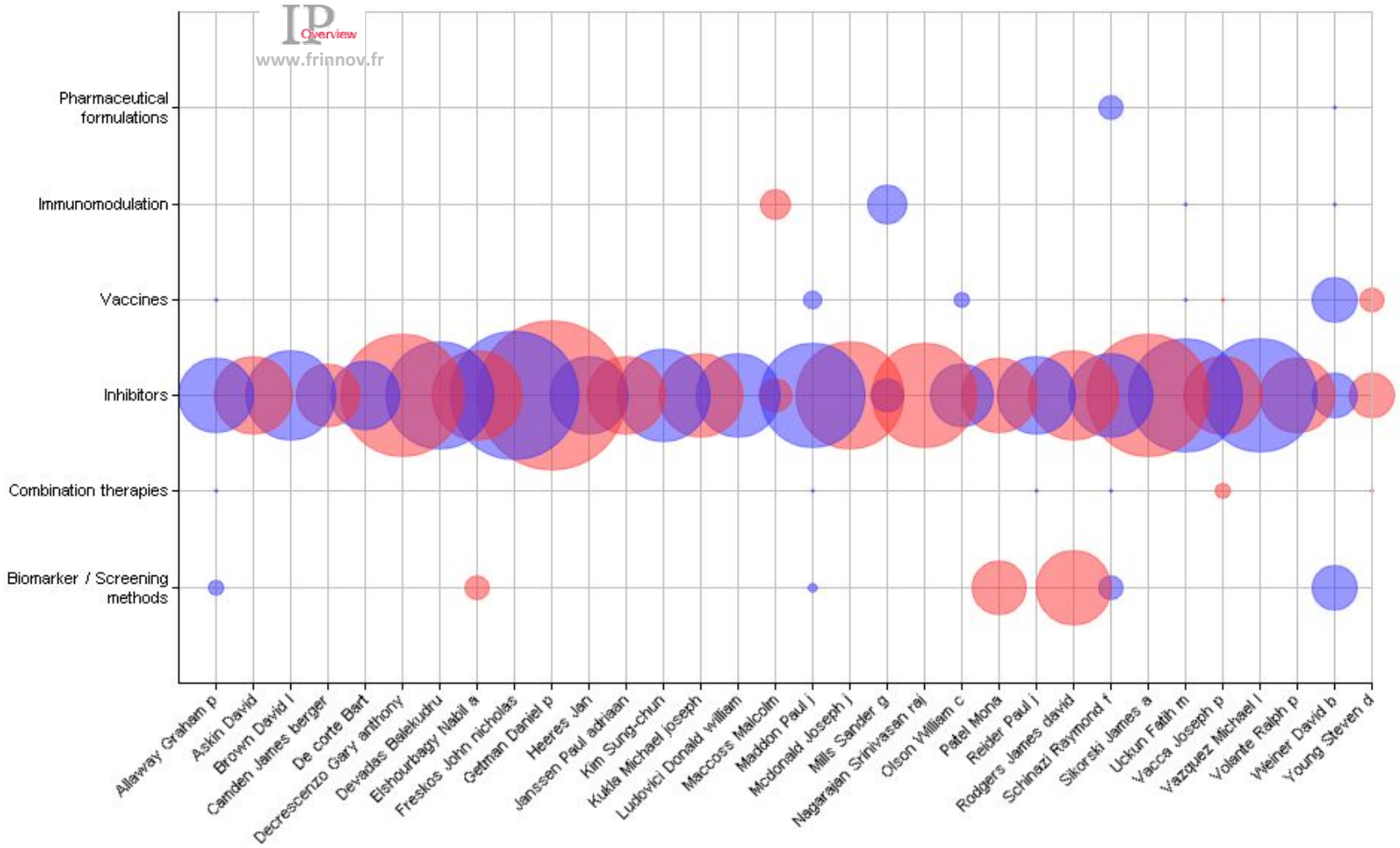


Figure 59: Applications of the main inventors (1993-2000)

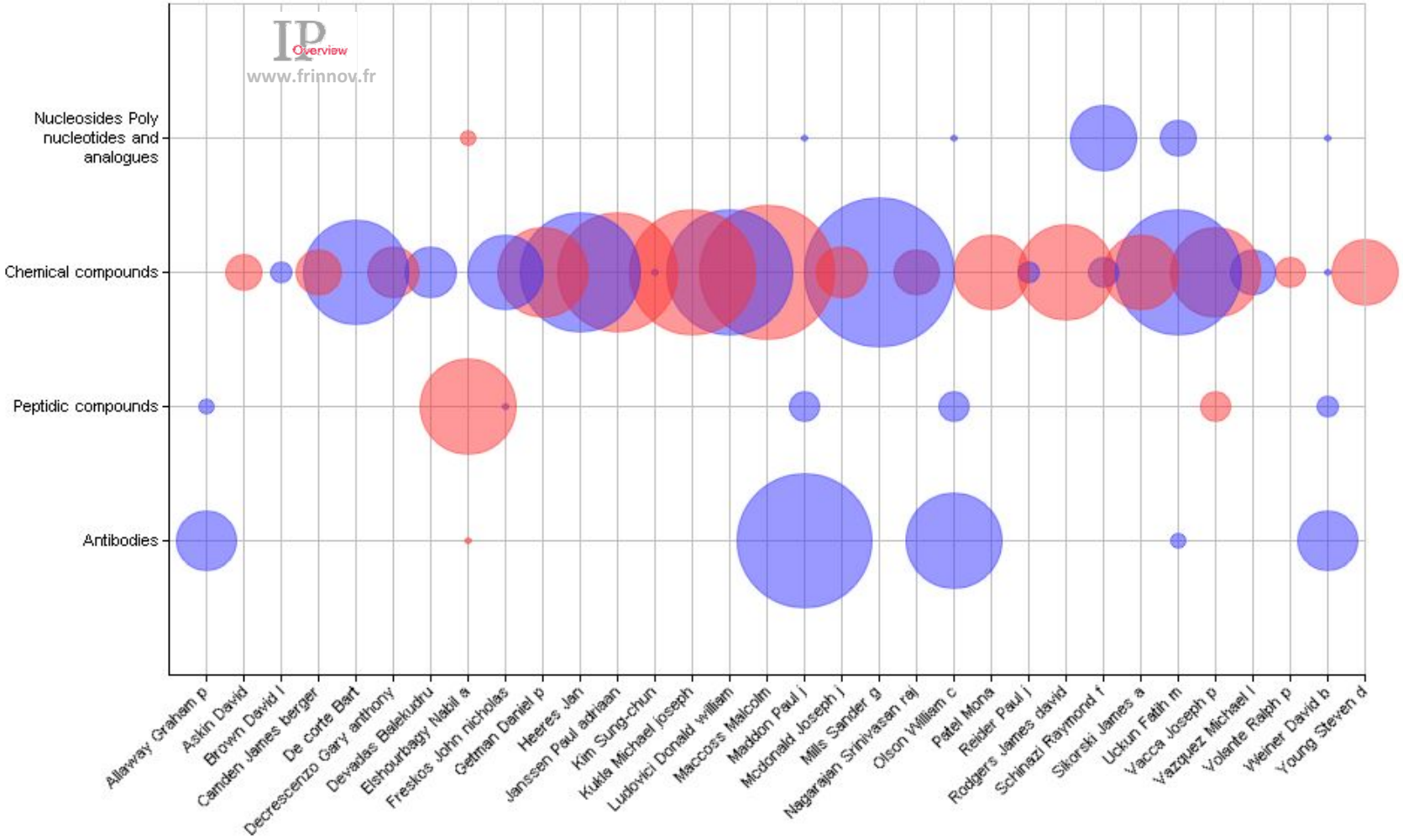


Figure 60: Classes of compounds of the main inventors (1993-2000)

6.4 Main inventors from 2001 to 2006

Inventors	Nb Patents	Applicants	Nb patents
Wigerinck Piet	23	TIBOTEC INC	23
Kadow John	22	BMS	20
		PHARMACOPEIA	1
		SCHERING PLOUGH CORP	1
Surleraux Dominique	22	TIBOTEC INC	21
Meanwell Nicholas	19	BMS	16
		PHARMACOPEIA	1
		SCHERING PLOUGH CORP	1
		PHARMACIA CORP	1
Olson William	18	PROGENICS PHARM INC	15
		CORNELL FOUNDATION INC	4
		PDL BIOPHARMA INC	3
		MERCK & Co	1
		AARON DIAMOND AIDS RES CENTER	1
Parkin Neil	18 18	MONOGRAM BIOSCIENCES INC	18
		VIR0LOGIC INC	1
Guillemont Jerome	17	TIBOTEC INC	10
		JOHNSON & JOHNSON	5
Heeres Jan	17	JOHNSON & JOHNSON	7
		TIBOTEC INC	7
		IDENIX PHARMACEUTICALS INC	1
Naidu Narasimhulu	17	BMS	17
De bethune Marie-pierre	15	TIBOTEC INC	12
Kim Choung	15	GILEAD	14
		KRICT (KR)	1
Lewi Paulus Joannes	15	JOHNSON & JOHNSON	7
		TIBOTEC INC	7
Taveras Arthur	15	SCHERING PLOUGH CORP	13
		PHARMACOPEIA	8
		INST SUPERIORE SANITA	1
Wai John	15	MERCK & Co	15
Wang Tao	15	BMS	13
		PHARMACOPEIA	1
		SCHERING PLOUGH CORP	1

Table 15: Main inventors (2001-2006)

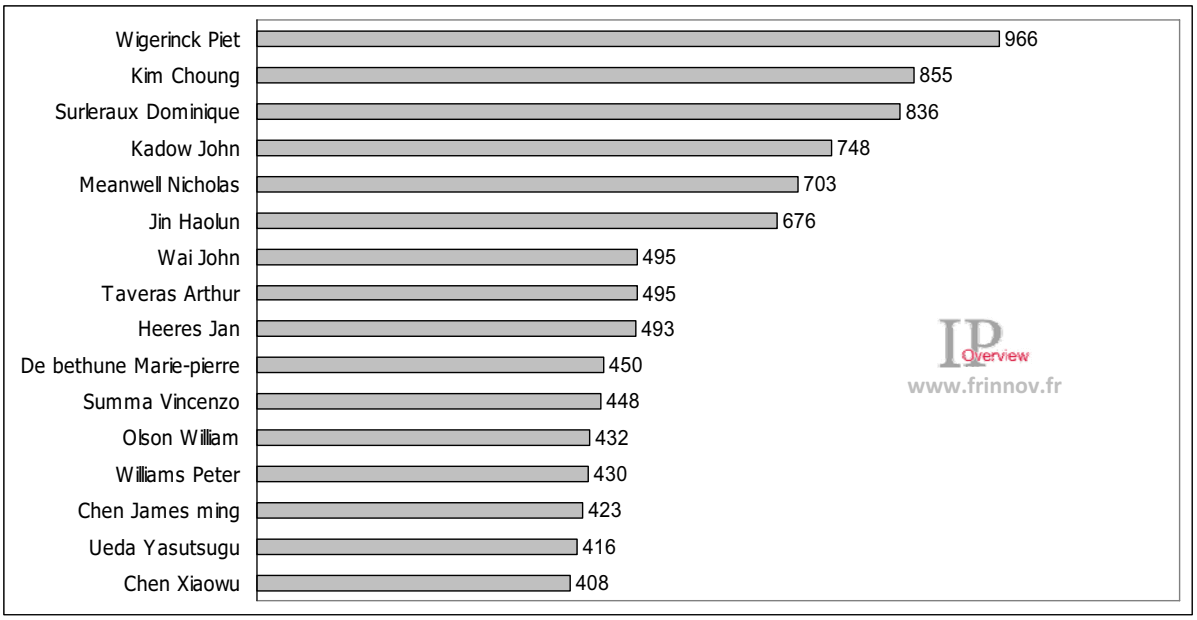


Figure 61: List of experts (2001-2006)

The classification of experts remains very close to that of the most prolific inventors during this period. Only the inventors Choung Kim and Haolun Jin improve their position as a result of their collaborations.

The figure below shows the major research groups during this period (with a minimum of 6 joint filings). Two large teams emerge as the most prolific applicants (≥8):

- The team at Tibotec led by Piet Wigerinck and Dominique Surleraux mainly protecting chemical compounds (and nucleosides/(poly)nucleotides & analogs for Piet Wigerinck) inhibiting protease and reverse transcriptase as well as methods to evaluate these compounds.
- A second Tibotec / Johnson & Johnson team led by Jan Heeres and Jérôme Guillemont that protects chemical compound inhibiting reverse transcriptase.
- The team at Schering Plough Corp working with Robert Merrit and Arthur Taveras, mainly protecting immunomodulators and chemical compounds antagonists of chemokine receptors.

Other teams with inventors filing a significant number of patents during this period include:

- The team at BMS working with the « experts » John Kadow and Nicholas Meanwell focusing on chemical compounds inhibiting viral entry (chemokine receptors, CD4 and glycoproteins) and integrase for Nicholas Meanwell.
- A second team at BMS working with the inventor Naidu Narasimhulu mainly protecting chemical compounds antagonists of chemokine receptor and inhibiting integrase, reverse transcriptase and protease.
- The group at Merck&co with John Wai protecting only chemical compounds inhibiting integrase.
- The team at Chiron led by Susan Barnett should also be mentioned for its work on vaccine research.

- Finally the team at Progenics with William Olson and Paul Maddon working on antibodies and peptide compounds for vaccine applications and viral entry inhibitors.

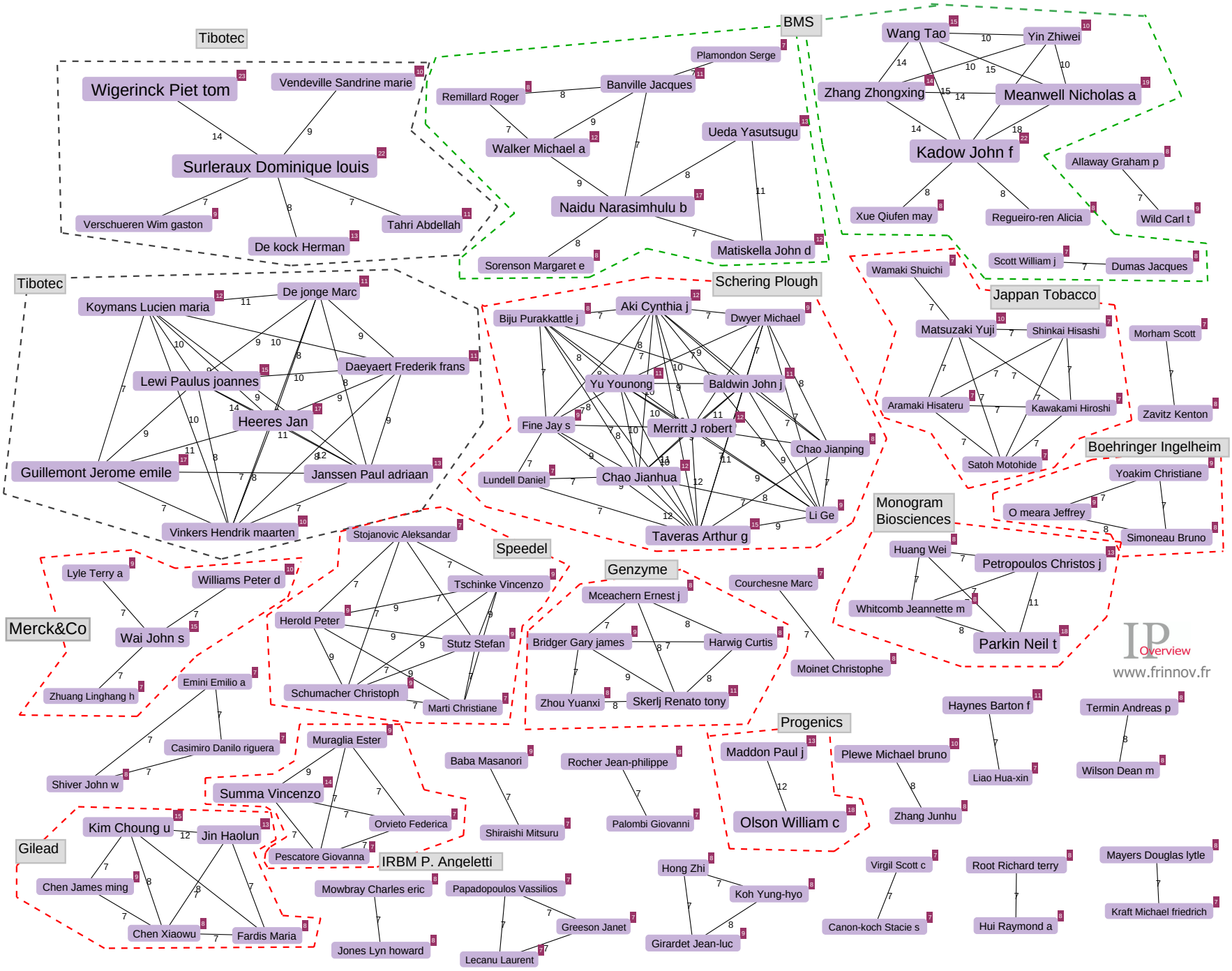


Figure 62: The major collaborations among inventors (2001-2006)

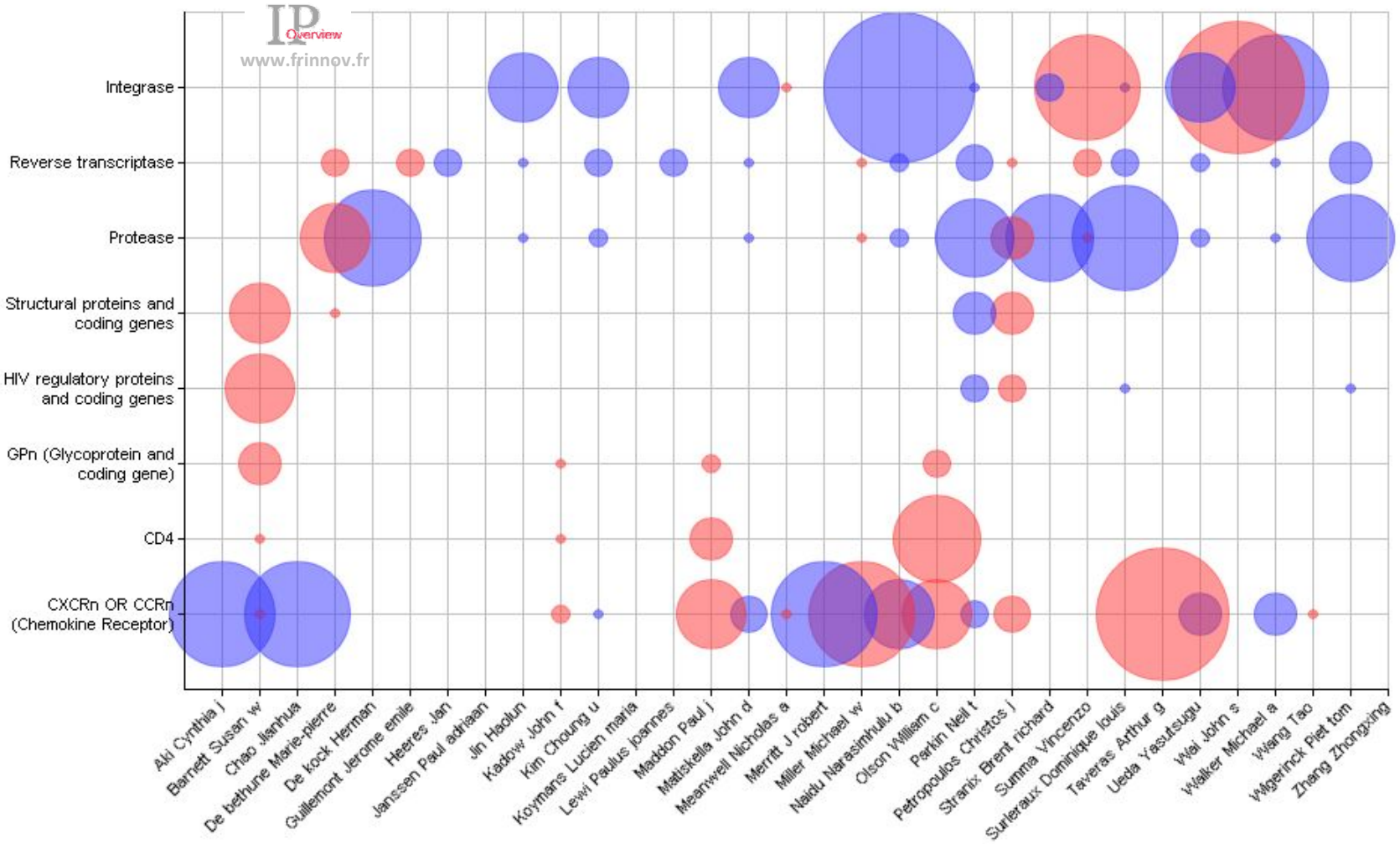


Figure 63: Therapeutic targets of the main inventors (2001-2006)

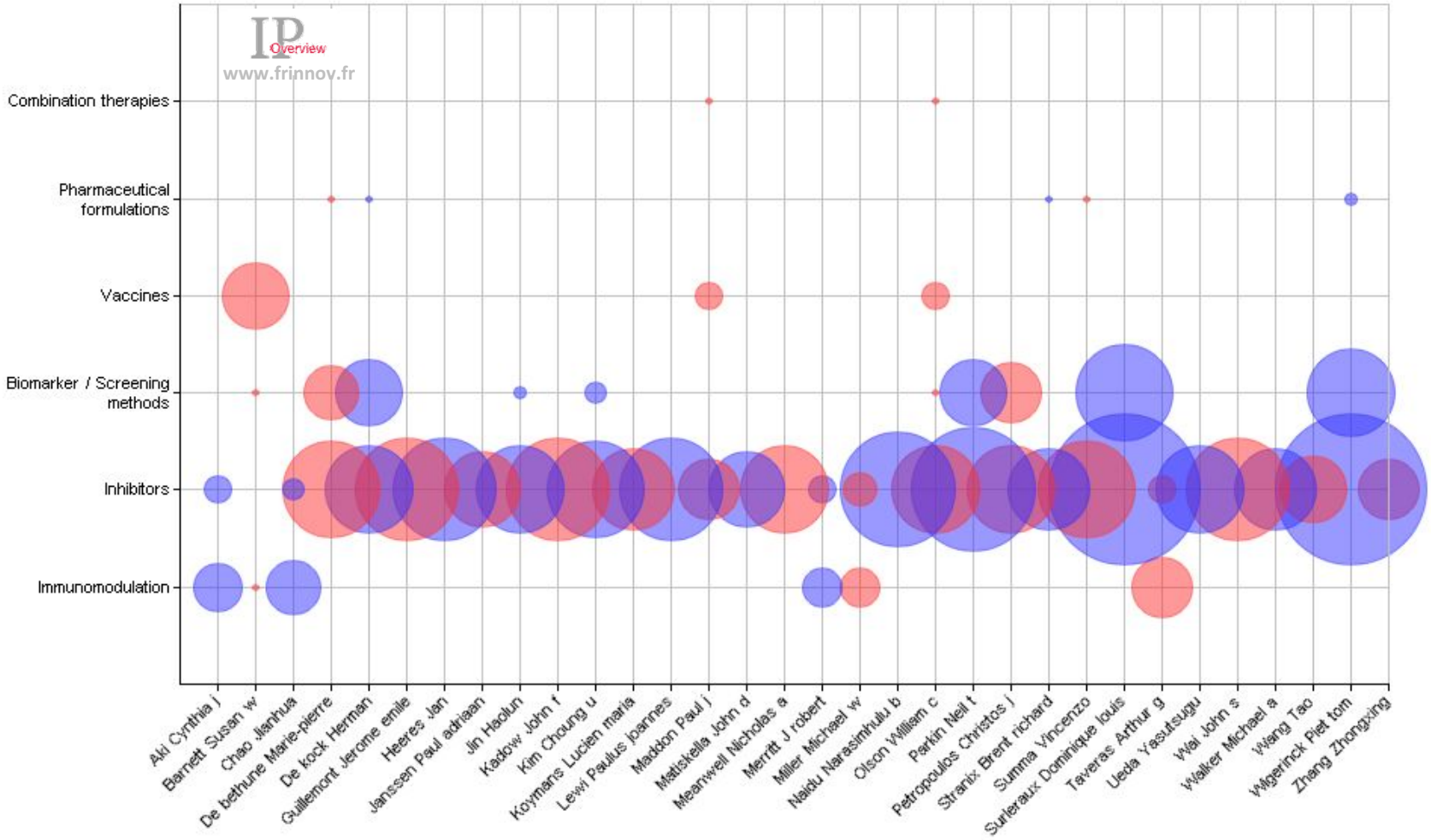


Figure 64: Applications of the main inventors (2001-2006)

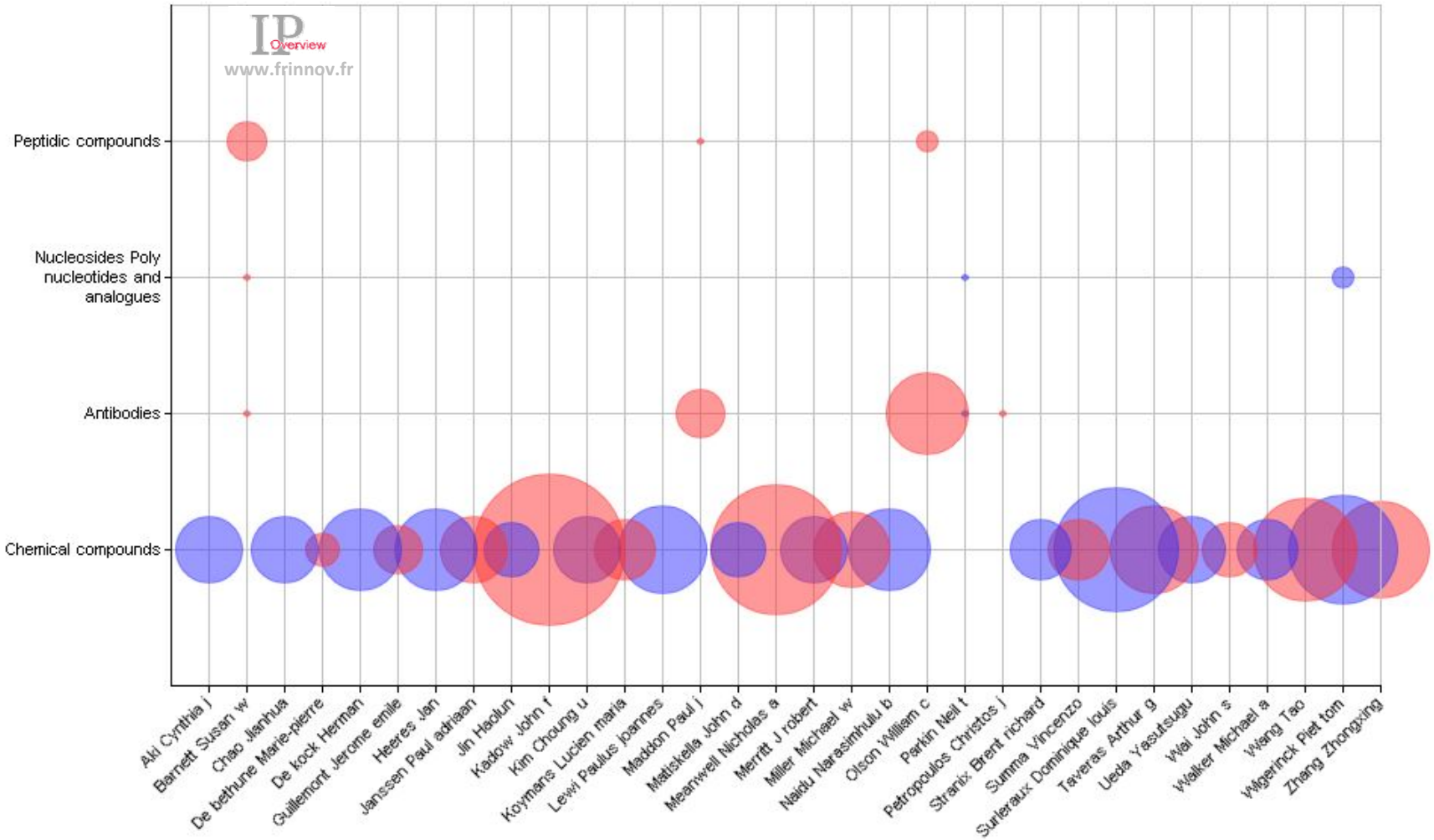


Figure 65: Classes of compounds of the main inventors (2001-2006)

6.5 Emerging inventors

The table below shows the inventors with the strongest emergence factor. This corresponds to the increase in the number of filings per inventor in 2004, 2005 and 2006.

2006 was the last year when all the data were available. In other words, this table presents the inventors who have a strong potential of becoming future experts in the field of HIV therapy.

Emerging inventors	Nb patents	Applicants	Nb patents	Topics (nb patents)
Schumacher Christoph	9	Speedel Experimenta AG	9	Chemical compounds (7) Protease inhibitors (9)
Herold Peter				
Stutz Stefan				
Tschinke Vincenzo				
Marti Christiane	7		7	
Stojanovic Aleksandar				
Mah Robert	6		6	
Quirmbach Michael	5		5	
Joshi Pramod	6	Vertex Pharma	6	Chemical compounds (6) Ion-channel modulator (6) HIV-associated neuropathy (6)
Palombi Giovanni	6	Addex Pharmaceuticals	6	Chemical compounds (6) Modulators of metabotropic glutamate receptors (6) HIV-associated neuropathy (6)
Le Poul emmanuel	5		5	
Gagliardi Stefania	4		4	
Kawasuji Takashi	6	Shionogi & Co	6	Chemical compounds (6) Integrase inhibitors (6)
		GSK	4	
Spaltenstein Andrew	6	GSK	6	Chemical compounds (6) Integrase inhibitors (6)
Jonckers Tim	5	Tibotec	5	Protease inhibitors (5) Biomarker / Screening methods (4) Chemical compounds (3)
		Univ Massachussetts	1	
Gelbard Harris	5	Univ Rochester	5	HIV-associated neuropathy (5)
Raman Prakash	4	Millenium Pharm Inc	1	Inhibitors (5) of protease (2) and chemokine receptors (1)
		Novartis	4	
Rigollier Pascal	4			
Desai Manoj	4	Gilead	4	Chemical (2) and peptide compounds (1) for pharmaceutical formulations (1) and inhibitors (4) of protease (3)

Table 16: List of emerging inventors

7 Conclusion

Since 1996, the marketing of protease and reverse transcriptase inhibitors and their many combinations has significantly reduced mortality and improved the quality of life for AIDS patients. As a result, a severe and deadly epidemic has now become a long term pandemic creating a colossal market which will reach the astronomical sum of 15 billion US dollars in revenue in the upcoming years.

7.1 No novel therapies in sight

Nearly all the HIV therapeutics on the market today for mono-, bi- or tritherapy are protease and/or reverse transcriptase inhibitors. The commercialization of several novel therapies, including viral entry inhibitors (enfurvitide, 2003), chemokine receptor antagonists (Maraviroc, 2007) and integrase inhibitors (Raltegravir, 2007) has only occurred very recently.

The industrial pipeline is seriously drying up in certain areas. Preclinical research now rarely provides candidate drugs for clinical studies, especially for the important therapeutic targets of protease and reverse transcriptase.

Our analysis of patenting strategies, which is the heart of this study, clearly shows the significant downturn (40% fewer) in the number of filings. This downturn is true for all the targets and topics in the study and is part of an overall tendency of the players to turn away from research and development as well as a sign of reaching the limit of traditional approaches.

Fewer filings means fewer new molecules entering clinical trials and thus fewer chances for new drugs on the market in the future.

We are seeing a real need for radical change in approach to HIV therapy, in particular the need to develop novel therapeutic targets and gain further understanding of the interaction between the virus and the immune system.

This situation is a unique opportunity for academic research because it reflects the need to get "back to the basics" of fundamental research. In this context, academic research should remain dynamic, driven by the need for industrials to exploit the expertise of public research, compensating somewhat for the withdrawal of private research programs in this sector.

Thus fundamental academic research will probably be closely monitored by industry to watch for the emergence of novel therapeutic approaches which could represent the future of HIV therapy.

Emerging topics that were identified include maturation inhibitors and treatments targeting key cell proteins that interact with HIV replication (cf. appendices).

7.2 Repositioning of the major industrial players

Today, several companies dominate the field of HIV therapy, but they have each used different strategies to obtain market penetration. Some have focused their research on specific fields and others have pursued several directions. Some companies have purchased and developed promising drug candidates discovered in academic research laboratories or Biotech companies, (Gilead and Roche). Others have acquired licenses while still exploiting the results of their own research (GSK, BMS, Tibotec, Abbott). Finally, others have only developed anti-virals from their own laboratories (Boehringer-Ingelheim, Merck&co).

Thus, the major market players are not necessarily those that have invested in and protected innovation (ie the main applicants) but those that seems to have had a pertinent medium-term strategy.

Gilead, today's recent market leader, only filed 44 patents between 1991 and 2006. Their position as leader is therefore not a result of an intellectual property strategy but is based on the acquisition of key molecules (promising candidates or drugs already approved by reglementary administrations) (emtricitabine - collaboration between IOCB and Leuven Katholic University and tenofovir - Emory University) and the development of combination therapies with these molecules.

Thanks to the acquisition of Tibotec, Johnson&Johnson, a recent player in this field, seems to be an up and coming major market player. They have achieved this by having an innovative strategy which includes having a strong position in the most popular therapeutic target inhibitors (reverse transcriptase and protease) while at the same time developing new molecules against the resistances that develop to existing treatments.

Among the other major market players, BMS, Abbott and Boehringer-Ingelheim have invested substantially and concentrated their research on specific targets, mostly the discovery of chemical compounds inhibiting reverse transcriptase, protease and integrase.

GSK, on the other hand, took the risk of diversifying its approach by expanding the scope of its research to cover all therapeutic targets and all classes of compounds so that they now have a large

spectrum of complementary molecules on the market. Although this « diversified » strategy has assured its position as leader for a long period of time, it may be reaching its limit and need to be redefined. With so many of its own molecules being commercialized, any new compound merely cuts into GSK's sales. Today, GSK seems to lack promising anti-viral products to compensate the serious slowdown in their market position.

Finally, Merck&co and Pfizer find themselves in the paradoxical position of being the pioneers in the field, the most prolific applicants and the market players in the most difficulty. These two companies have had diametrically opposed strategies.

Pfizer is known for massively buying out other market players: Warner Lambert, Parke & Davis, Agouron, Pharmacia, Upjohn, Searle: all companies with active research & development and substantial patent portfolios, which have been built thanks to major collaborations, such as that between Japan Tobacco and Agouron. However, this massive acquisition strategy seems to have disorganized the acquired companies which have not sufficiently exploited the significant potential of their experts and their research and development. The commercialization of maraviroc, the first viral entry CCR5 antagonist could be Pfizer's last chance to maintain a position in the market unless it decides to buy another Big Pharma or curve the company's policy and massively license-in drug candidates already in clinical trials. It should be noted that the purchase of Wyeth was not for the purpose of improving Pfizer's market position in HIV Therapy since it has never been a major player in this field and has mainly pursued vaccine research.

Merck&co, on the other hand, began concentrating its research very early on promising therapeutic targets gaining a lead of several years on its competitors. Although it is a pioneer in inhibitors of protease, reverse transcriptase, integrase (as early as 1990) and chemokine receptor antagonists, Merck&co has often been beaten to the finish or been surpassed by other companies that have managed to market either more effective compounds or to do it more rapidly. The outcome of the substantial financial investment by this company in numerous therapeutic approaches with several research teams reflecting an R&D strategy covering all topics, has not been conclusive. The marketing of the first integrase inhibitor is nevertheless an important opportunity. However, these drugs must still prove their efficacy and sales potential because other novel integrase inhibitors may prove to be more effective.

This general research strategy could have given Merck&co a serious advantage for the development of a vaccine – a topic which it supported and focused upon for many years. The withdrawal of the candidate vaccine V520 in 2007 after a large phase II trial in South Africa was a difficult blow that might have pushed Merck&co out of the market of HIV Therapy. However, the recent acquisition of the company Schering Plough with its large portfolio of chemokine receptor antagonists, is an indicator of Merck&co's intention to continue to invest in this field.

Although Merck&co and GSK seems to be in a difficult position, it should be noted that their long-term investment and their general research strategy are important assets in the "back-to-basics" period occurring today.

7.3 Market players to redefine their strategies

In the next five years, several HIV treatments will go off-patent, forcing industrial partners to protect new, more effective molecules (in particular against resistances) with fewer side effects and formulations that are easier for the patient to use.

The absence of new potential therapeutic targets is going to result in a major slowdown in research efforts in the next 5 years. While waiting for this situation to turn around, the market players will probably change strategies, with certain industrial players completely abandoning their position in HIV Therapy.

The example of Roche, which announced its withdrawal in July 2008, is symptomatic of this general tendency. It should be noted that internal research at Roche was inconclusive and that the molecules under development in this company have been licensed-in from academic research (license with the National Cancer Institute and Duke University / Trimeris).

The internal research of players that wish to remain in the field should strongly focus on certain specific topics, in particular:

- Integrase inhibitors and chemokine receptor antagonists, the only therapeutic targets whose potential has not been fully exploited,
- Reducing side effects of existing therapies
- Drug delivery of active ingredients
- Treatment of opportunistic diseases
- Prevention of viral transmission

The medium term strategy of several industrial players will also certainly include renewing contact with the most successful academic research laboratories via new collaborations, strategic acquisition of specialised Biotech companies, licensing-in and/or hiring experts. It will be up to the academic laboratories to convince these companies of the interest of these new approaches.

Research and development in HIV is at an important crossroads. Both large pharmaceutical groups and the other market players must redefine their strategies if they are to carve out a future in this field.

Appendix

Emerging topics

	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06
TRIM5alpha																	3		
APOBEC3G															1	4	3		3
TSG 101														10	2	2			1
LEDGF/p75														1	2				1
HDAC														2	1	1	1	1	3
DC-sign													1		4	3		2	
RNAi									1		1			6	9	3	2	1	
Cyclophilin			4				1	1	2	2	1		2	1		1	3		1
Radiation therapy	1	1	1										1	2	1	3	2	2	1

Table 17: Evolution of fillings by emerging topics

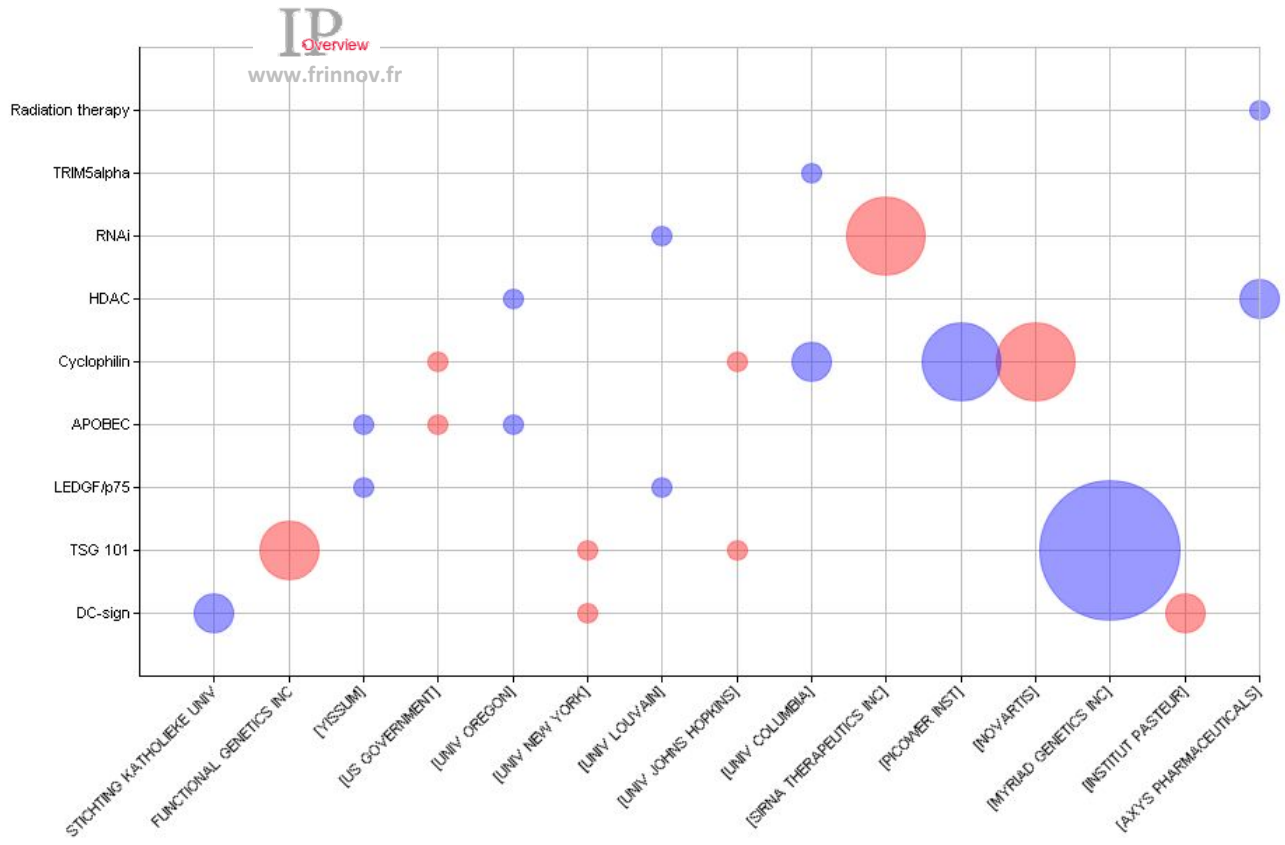


Figure 66: Emerging topics by applicants

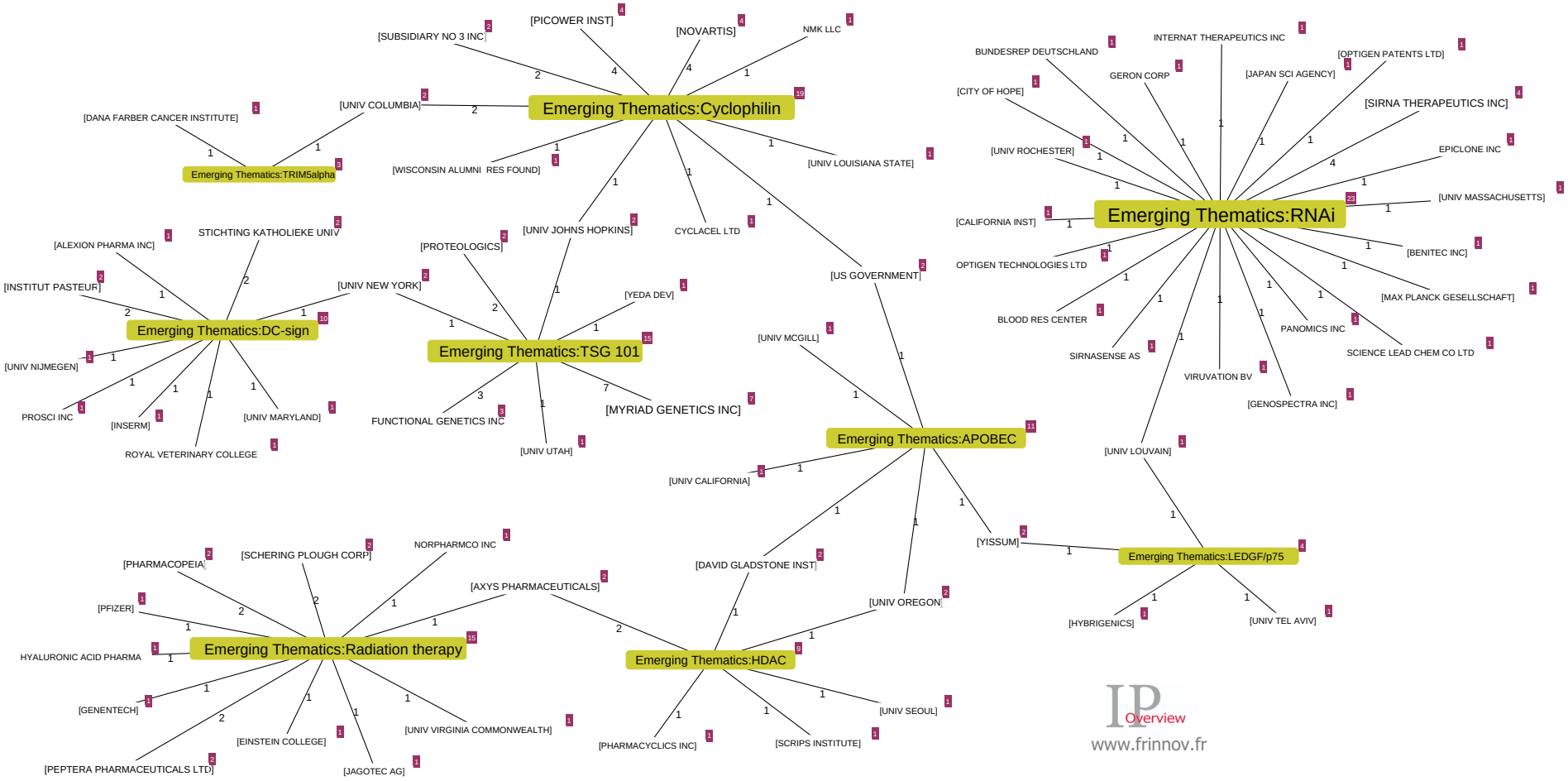


Figure 67: Applicants for emerging thopics

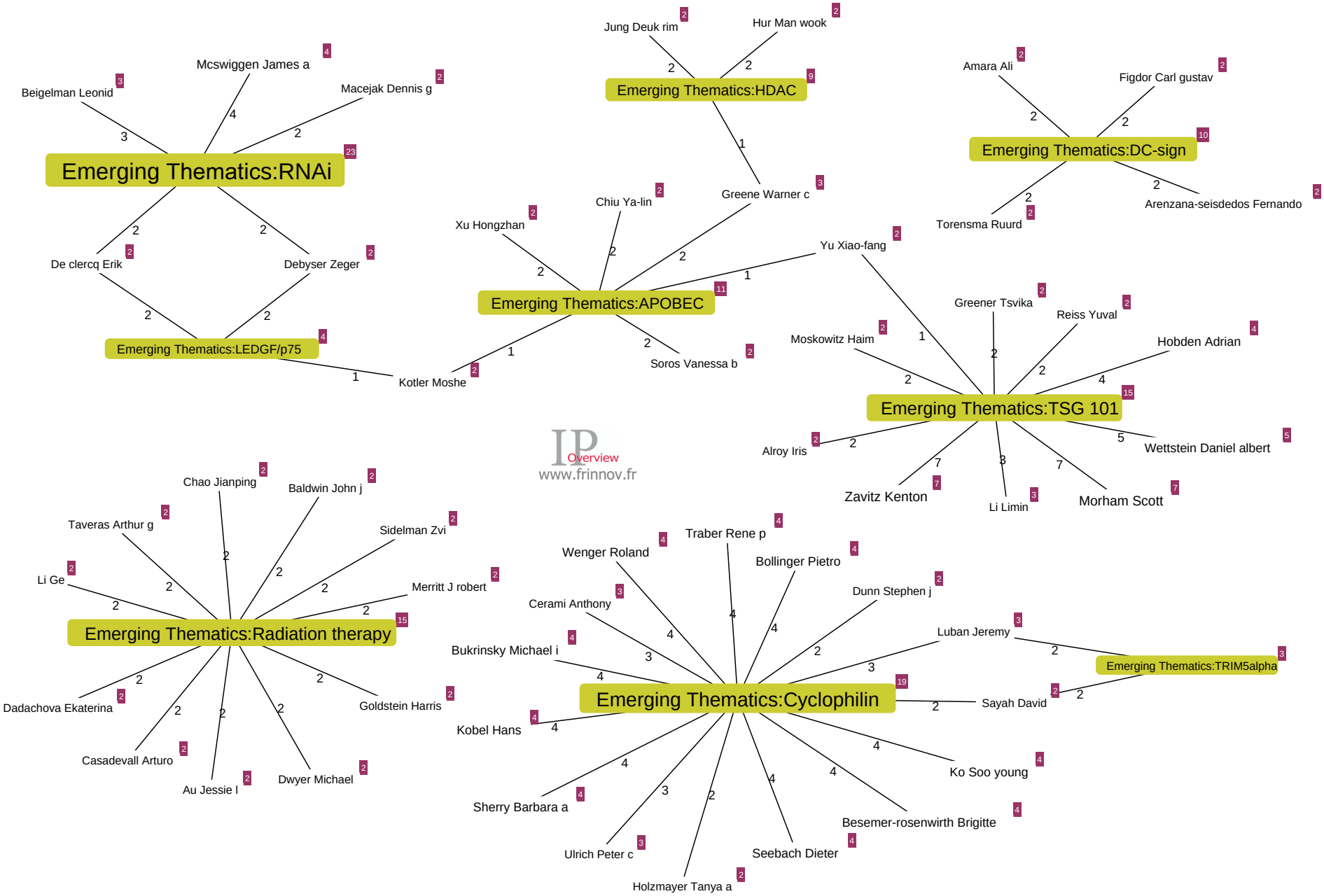


Figure 68: Autors for emerging topics

FRINNOV
83 Boulevard Exelmans
75016 PARIS
Tél.: +33 (0)1 40 51 00 90
Fax: +33 (0)1 40 51 78 58
www.frinnov.fr