Advanced Therapy Medicinal Products (ATMPs)

An analysis of research activity based on a review of patent literature

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FOREWORD

Belgium takes a very important role in the ATMP (Advanced Therapy Medicinal Products) landscape

- Belgium is one of the top players - in Europe and world-wide - when it comes to ATMP expertise and intensity per capita, and
- Belgium was the first country in Europe to have an ATMP on the market, in 2009: ChondroCelect from Tigenix

This has led us to the idea to publish a Tech Watch to inform the interested reader on this topic, and to complement information that we have from scientific literature, from white papers and from working groups in this area with a study of the patent literature in this field. Because we looked at the patent landscape world-wide and because the topic is quite broad, only high-level insights can be provided and the overview will not be complete.

When reading this Tech Watch bear in mind a few things: (i) an IP Tech Watch and conclusions drawn from it are based primarily on volumes and not so much on intensity per capita, (ii) patents may have been filed by mother companies and this may be the reason why you expect to see patents from a Belgian player but see none listed, (iii) some players do not own patents but have licensed-in technology from others, or (iv) the patent is still owned by the university in case of spin-offs, (v) it further takes 18 months for a patent application to publish and be visible to the public.

Every study starts with a particular goal in mind and depends on tools and search strategies being used. Plus the study is a snapshot in time, it was undertaken end 2023. We hope that you enjoy reading this report and that you understand the limitations it has due to its nature and because of the choices that we have made. The field of ATMPs is a fast-growing area and has many stakeholders involved, small & big, established companies and newcomers, private and public entities, specialized consortia and working groups, universities and research centra, hospitals, medical doctors, etcetera. The list is too long to name them all, but know that all play a unique and important role in the ATMP ecosystem.

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1 Executive summary

Advanced Therapy Medicinal Products (ATMPs) are a class of innovative medical products that encompass (I) Gene Therapy, (II) Cell Therapy, and (III) Tissue Engineering. These therapies are designed to treat, intercept, prevent or diagnose diseases by intervening in the body's cellular and genetic makeup. ATMPs represent a new era in medicine, offering cutting-edge approaches to address unmet medical needs.

This report provides an analysis of the innovative activities in the field of ATMPs by a review of the patent activity and of the recent patent publications on this topic, covering the period 2000-2023. Patent information often includes technical information that is not available from any other source. Because of the high number of patents in the field and the broad topic, only high level insights can be provided and the overview may not be complete.

Patent datasets were evaluated using the tool "PatentInspiration" whereby insight was obtained with respect to activity over time, main players and technologies used. Patent value analysis was used to obtain the key innovations in the respective datasets. Artificial Intelligence (AI) was used to help find trends and to advance data mining.

More information on ATMPs and their subcategories, challenges and focus on the next page.

Below an Executive Summary for the innovative activities in the field of ATMPs as a whole.

Technology Watch on ATMPs in a nutshell
– ATMP is an acronym for **Advanced Therapy Medicinal Products**
– number of inventions in the field of ATMPs has **tripled** over the last decade
– upswing in filing numbers started in the **2000s**
– steep increase in filing numbers since **2020**
– high proportion of **international patent applications**, suggesting high economic expectations with regard to the technologies in question and multinational commercialization strategy
– most active applicants in the field of ATMPs are companies and academics from the **United States and Europe**
– key players in the field of ATMPs are **academic/research centres & some small and medium-sized enterprises**
– key companies are based **in the US and in Europe**
– not only big pharma but also **small and medium-sized enterprises have ATMPs on the market**, showing the importance of biotech start-ups and scale-ups in the ATMP ecosystem.
– **Belgium takes position 15** in the international ranking of patent filings, and continues to build and show expertise around ATMPs
– Expected, as **Belgium is widely known to have a rich and dynamic ATMP sector**

2 Advanced Therapy Medicinal Products in a nutshell

2.1 A new era in medicine

Advanced Therapy Medicinal Products (ATMPs) are a class of innovative and fast growing medical products that encompass (I) Gene Therapy, (II) Cell Therapy and (III) Tissue Engineering. They are also referred to as 'Cell & Gene Therapies (CGT)', 'Advanced Regenerative Medicines (ARM)' or 'Advanced Therapies (AT)'.

Table I below provides a glimpse into the diverse applications of ATMPs across different therapeutic modalities, showcasing their potential to revolutionize the treatment landscape for various diseases.

Table I : ATMP subclasses in a nutshell

Subclass	Explanation	Example
Gene Therapy (I)	Alters the genetic material of cells for therapeutic purposes. It involves introducing, removing, or modifying genes within a patient's cells to treat or prevent disease	Luxturna - Used to treat an inherited form of blindness caused by a specific gene mutation
Cell Therapy (II)	Involves the transplantation, manipulation, or engineering of cells to restore or improve cellular function. This may include the use of stem cells or immune cells	CAR T-cell therapy (e.g., Kymriah) - Utilizes modified T-cells to target and destroy cancer cells in certain types of leukemia and lymphoma
Tissue Engineering (III)	Combines cells, scaffolds, and biologically active molecules to create functional tissues for replacement or regeneration. It aims to restore damaged tissues or organs	Trachea transplantation with a bioengineered scaffold - Used to replace damaged or diseased trachea with a synthetic or natural scaffold populated by the patient's cells

Cell & Gene Therapies (CGTs) are on the rise & have known a steady increase the past few years. By the end of 2019, over 75 ATMPs had been launched worldwide, including singular markets such as Japan, Russia and South-Korea (McKinsey, 2021). EMA[1] expects the submission or approval of 10 to 20 ATMPs per year during the next 5 years (pharma.be, 2022).

2.2 Potential to address unmet medical needs

ATMP therapies have many benefits and advantages. They offer hope to patients that suffer from serious, often rare, chronic and previously unaddressed diseases. Some therapies are able to cure/heal with a single or limited number of administrations as compared to a lifelong suffering and medication. ATMP therapies allow specific, tailored and personalized approaches.

Yet there are various downsides and challenges too. Challenges include amongst others complex manufacturing and logistics, specific storage requirements and a short shelf-life, high up-front costs, plus specific regulatory and pharmacovigilance demands (NIH, 2020).

[1] EMA: The European Medicine Agency

2.3 Key players in the field of ATMPs

Key players in the development and delivery of ATMPs appear to be academic/research centres & small and medium-sized enterprises, whereas large pharmaceutical companies seem to focus primarily on oncologic diseases using modified cytotoxic T-cells and chimeric antigen receptor (CAR) T-cells (NIH, 2020).

The unmet need for CGTs in Europe seems huge. The estimated patient population for just four indications (SMA, beta-thalassemia, diffuse large B-cell lymphoma & retinitis pigmentosa) addressed by CGTs today is 385,000, roughly three times as large as the equivalent US cohort (McKinsey 2021, Exhibit 3 therein).

Europe is publishing most of the scientific papers on CGTs, yet struggles to translate such strength in research into market leadership. Between 2005 and 2018, Europe accounted for just 16 percent of total CGT product registrations. The remaining 28 percent and 56 percent came from the United States and China, respectively (McKinsey 2021, Reference 6 therein). Less venture capital is one clear reason for the performance gap according to McKinsey. For more information on actual investments in the different regions per therapeutic approach, we kindly refer to the Alliance for Regenerative Medicine data (https://alliancerm.org/data, September 2023 data).

Looking at developers per headquarter region & per therapeutic approach, we see that the US takes the lead with 1,105 developers followed by Asia Pacific and Europe with 846 and 506 developers respectively (https://alliancerm.org/data, September 2023 data). What we further see is that the number of developers in Tissue Engineering is low, in all regions, compared to other therapies like Gene Therapy, Cell Therapy or Gene-Modified Cell Therapy and Cell-Based Immunology Therapy[2].

2.4 Innovative activities in the field of ATMPs

Now what does the ATMP patent landscape tell us. This report provides an analysis of the innovative activities in the field of ATMPs by a review of the patent activity & of the recent patent publications on this topic over the past 2 decades. Patent information often includes technical information that is not available from any other source. In some cases, a patent publication is seen before the actual product is on the market and/or before a scientific publication.

In this report we first look at patent activity & at patent literature on ATMPs as a whole. Then we look into more details at the three (3) ATMP subclasses that are listed in Table I above. Are covered separately, because of major contributions to science: mRNA technologies, CAR T-cell technologies and CRISPR technologies.

The above information was used to break down the larger patent dataset into more narrow datasets, via text pattern analysis, to gain more insights into the major ATMP technologies described in patent literature, the tendencies & the players.

We look at the global picture, then the position of Europe and of Belgium in particular, where ATMP expertise is concentrated and blooming.

Search strategies and approaches that were used to create the different patent datasets are listed in Annex III. A list of Belgian companies involved in the ATMP ecosystem is provided in Annex IV. This list includes small but groundbreaking biotech companies, specialized

[2] GMCT: Gene-Modified Cells Therapy, CBIO: Cell-Based Immunology Therapy

CDMOs[3] and CROs[4] as well as big biopharma companies expanding or building new manufacturing sites for the production of ATMPs.

[3] CDMO: Contract Development and Manufacturing Organization
[4] CRO: Contract Research Organization

3 Search strategies and Datasets

To gather relevant patent information as the basis for this report, search strategies were developed using meaningful keywords and relevant patent classification symbols. These search strategies, which are designed to strike a balance between completeness and a small fraction of unrelated documents in the result sets, were then used to create a basic dataset of relevant patent documents. The basic dataset and subsets thereof were then used for further patent analysis.

Creation of the datasets:

- In order to explore the ATMP patent landscape, a number of different patent datasets were created using the tool "PatentInspiration".
- Three different patent datasets were created for (I) Gene Therapy, (II) Cell Therapy and (III) Tissue Engineering looking for particular keywords in titles and abstracts (ti, ab). These datasets were then combined into one single dataset related to Advanced Therapy Medicinal Products in general (ti, ab).
- This single dataset related to Advanced Therapy Medicinal Products (ATMPs) in general, contains → 18,000 patent families from over the past 2 decades. This large dataset was then further cleaned out to remove irrelevant patents. A final dataset of ~ 13,000 patent families was maintained and analysed.

Text pattern analysis in title, abstract, claims and description (ti, ab, cl, d) was used to gain more in-depth insights.

Bear in mind that a patent analysis is always a snapshot in time and that the conclusions that are drawn depend on the (limitations of the) tools and the search strategies used.

More information on the Search Strategy used in this Report in Annex III.

4 The field of ATMP

This section presents the results of the analysis regarding the field of Advanced Therapy Medicinal Products (ATMPs) as a whole. For this purpose, filing trends in that field are first considered. Then, the main jurisdictions for which protection was sought are looked at. Thereafter follows an analysis of active applicants[5] in the field of ATMPs and their thematic focus. This section ends with listing the patents of the past 20 years with contribution of Belgian inventors. Focus herein is on industrial players involved.

4.1 ATMP Patent Activity

To get an idea of the patent activity in the field of ATMPs, we looked at the number of first patent publications[6] per year. We looked at patent families & not at individual patent publications, as patent families are a good indicator for the total number of inventions being filed.

Looking back in time, we find back the first patent publications on ATMPs around 1990 (~20). In 1995 this number had increased to ~200 & in 2000 we see ~300 first patent publications. In the period from 2003 till 2019 we have more or less a steady state, with the number of first patent publications per year fluctuating between ~350 and ~500.

Figure 1 shows a steep increase in the number of inventions over the past few years, with ~900 first patent publications in 2020 and ~1400 first patent publications in 2022[7]. It remains to be seen if this activity will continue to grow, or if it will stabilize until a next breakthrough or pandemic. On average, the ATMP patent activity has tripled in the last decade.

Figures 2A&B show you where most of the inventions are being filed. The graphs provide information on the strategy of the actors in the sector. They either file in their home country, or they file where production facilities of competition and key markets are. These graphs are based on first patent publication numbers and is dependent on the practices of the national/regional Patent Offices (when they publish/republish).

First, we see a high number of international (WIPO) and European (EPO) patent filings, which is indicative for the fact that applicants see an economic interest and potential in their inventions. Next, these graphs tell us where we have key players. We seem to have key players in the US, Japan, Canada and Europe, followed by South Korea and China. Figure 2A shows the top 50, Figure 2B the top 10.

Figures 3A&B give you a better indication of where most of the key players come from, by looking at the nationality or place of residence of the applicants. These figures give us a better idea of who are the key European players. In the top 10 of key players world-wide we have **Germany**, **the UK**, **France** and **Switzerland**. For the rest the same picture as in Figure 2, with the US taking a truly dominant position. **Belgium** takes position 15 in the international ranking, which is very good seen the small size of the country. Figure 3A shows the top 50, Figure 3B the top 10.

Table 1 shows the dominant positions of the US (first place, ~50%) and Europe (second place, ~25%), with Asian countries being less active in this field. By plotting the filing activity per country over the years, we see that Europe is less explosive qua filing activity in the past 3 years (compared

[5] Company or academic that started the patent registration/examination procedure
[6] Publication of he patent application 18 months after first filing of the invention
[7] We ignore 2023 numbers, as they are not complete

to the US and Asia)[8]. In Europe, the filing activity is more constant over the years. Less venture capital could be at the basis of this performance gap in Europe as a whole (see McKinsey' conclusions in the introduction, page 5, point 2.3).

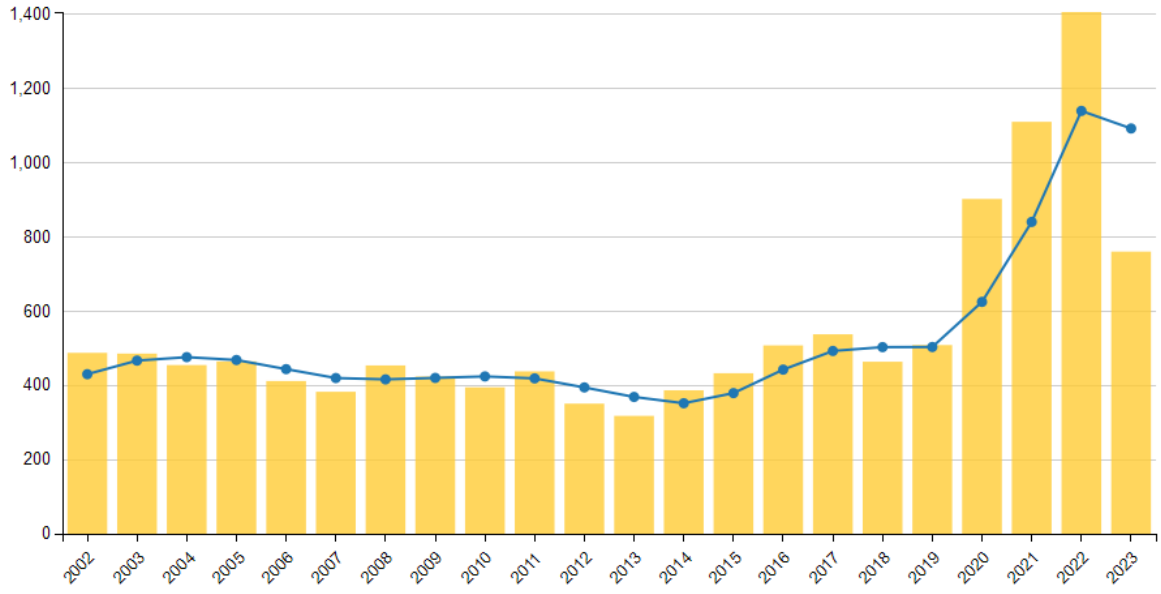

Figure 1: Number of ATMP first patent publications by publication year (period 2002-2023)

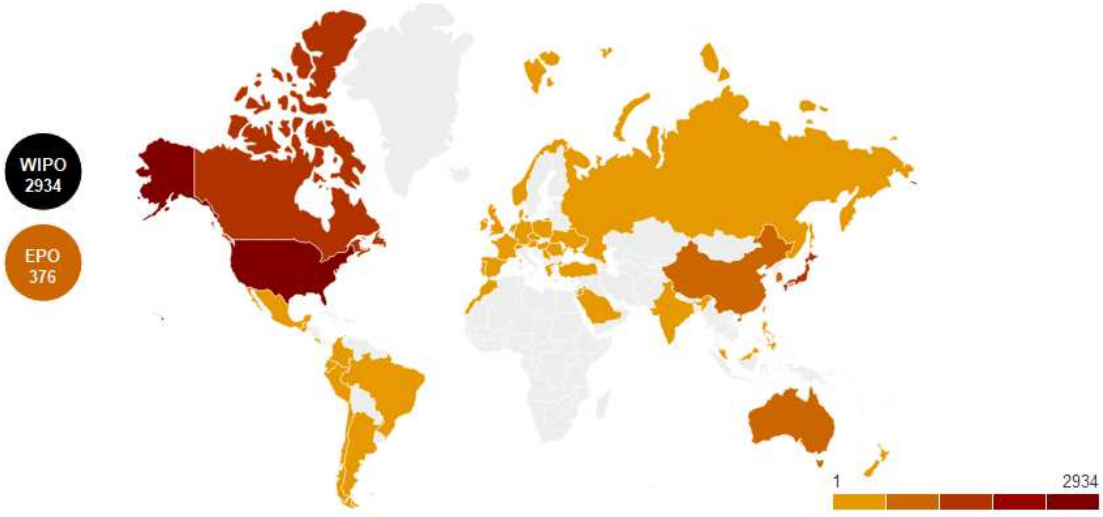

Figure 2A: Top 50 ATMP publication countries (based on country prefix)

[8] The latter is true for Europe as a whole but not for individual countries like the UK, France, Germany, Swiss and Belgium

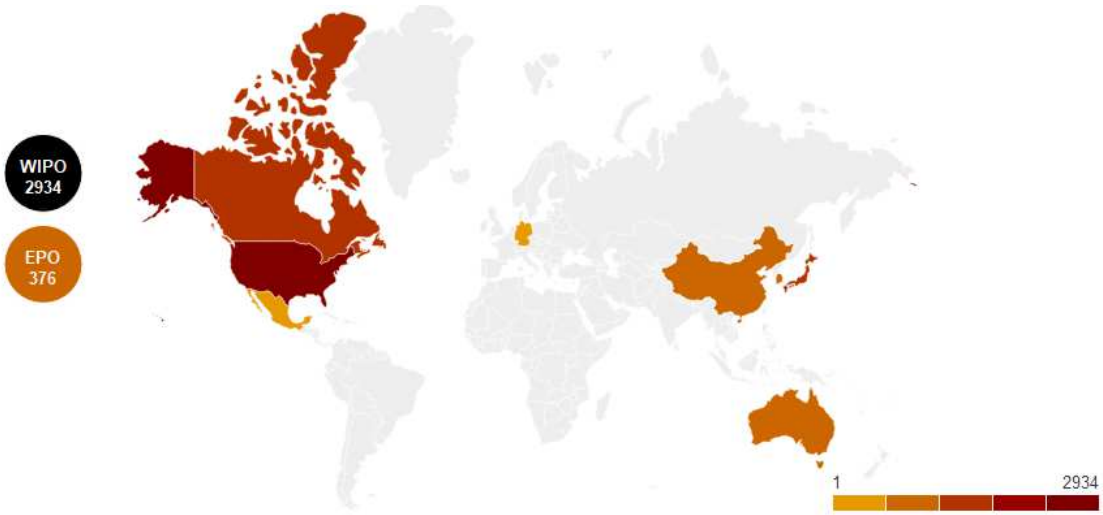

Figure 2B: Top 10 ATMP publication countries (based on country prefix)

Figure 3A: Top 50 ATMP publication countries (based on nationality/place of residence of the applicant)

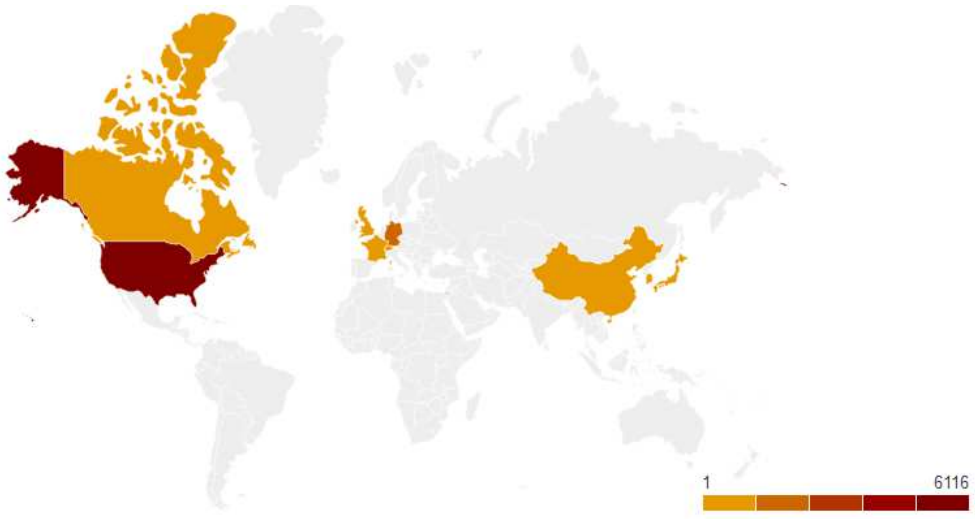

Figure 3B: Top 10 ATMP publication countries (based on nationality/place of residence of the applicant)

Table 1 below lists the number of first patent publications by applicant country. These numbers give an indication of where the top applicants (companies + academics) are based (in which country/region).

Applicant Country	No. of first patent publications	% (total =12,893)
US	6116	47
Europe (total of)	3297	26
Japan	533	4
Korea	489	4
China	411	3
Canada	335	3
Belgium (15th)	~140	1

Table 1: ATMP first patent publications by applicant country

We see that the US takes the fist place, with ~50% of the inventions stemming from the US. Europe (total of countries) comes second, accounting for 26% of the inventions. Japan, Korea and China together account for 11%. Belgium, which comes at the 15th place, accounts for 1%.

Figure 4 gives us an idea of the patent activity (via first patent publication numbers) of the different players over the years. Overall we see a drastic increase in patent activity as of 2000, but this trend is less obvious overall in European countries (compared to for instance the US and Asia). Japan and Korea show a remarkable growth the past few years.

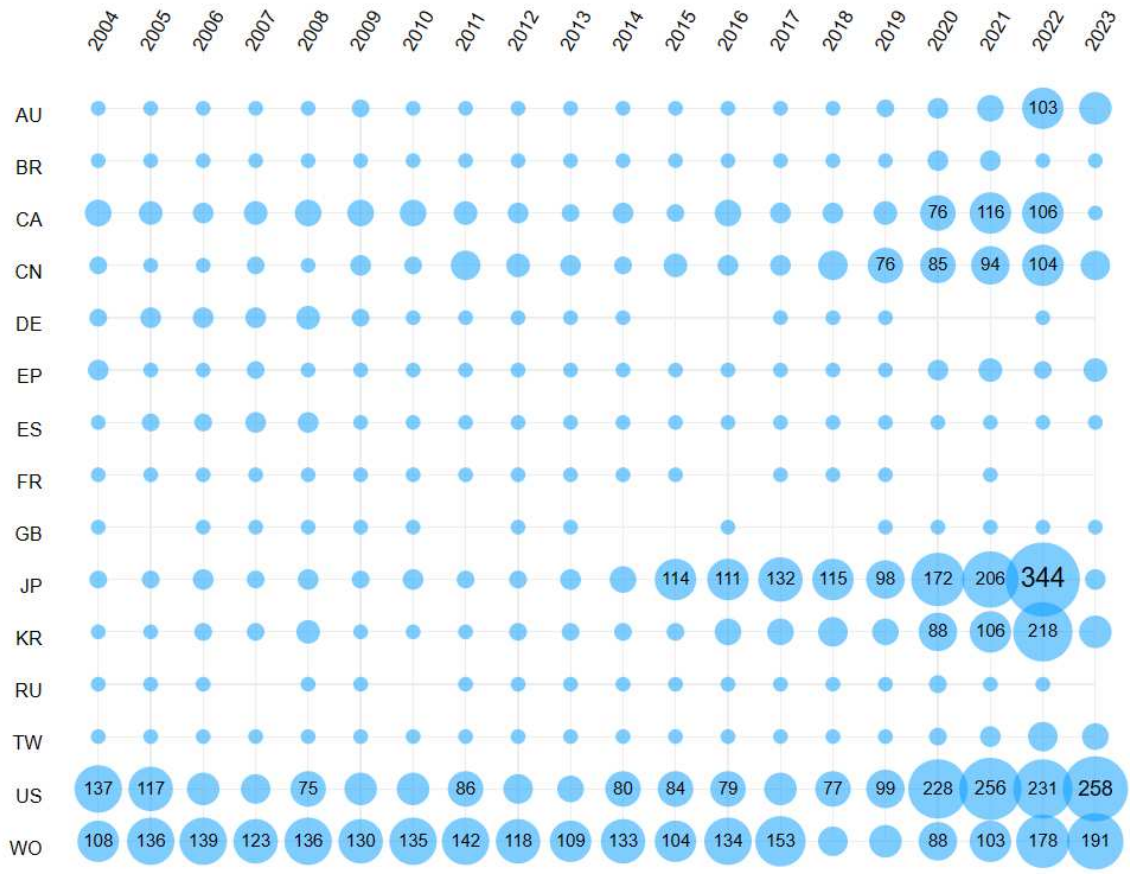

Figure 4: ATMP patent activity (via the country prefix) over the years (period 2004-2023). Patent activity is based on the number of first patent publications

Overall, the ATMP patent landscape is scattered. There are over 10,606 applicants (filing entities) of which most have filed 1 patent only. Only 2% of the applicants have 10 or more patent families on their name, and only 0,4% of the applicants have 30 or more patent families on their name in this field.

4.2 Top 10 ATMP applicants

The ATMP patent landscape is largely dominated by academics (> 75%), which include Universities, Research Centra but also Governments and Hospitals. This is not surprising in view of the technology and the way it develops and is picked up. Big pharmaceutical companies tend to be risk-adverse and pick up on promising technologies once the potential is clear and production and logistics are feasible.

The top 10 list of applicants (companies + academics): is dominated by academic players. We find back four (4) US Universities and two (2) **French** Research Centra. The only companies that we find in the top 10 are: NOVARTIS (**CH**[9]) and JUNO THERAPEUTICS (US), which take the 9th and 10th place respectively. Most of the companies in this list appear to focus on Cell and Gene Therapies (CGT) (Table 2).

[9] We use 2-letter codes for countries wherein e.g. CH stands for Switzerland

Top	Applicant	Country	No. of patent families	Collaboration with
1	UNIVERSITY OF CALIFORNIA	US	194	
2	UNIVERSITY OF TEXAS	US	174	
3	UNIVERSITY OF PENNSYLVANIA	US	123	
4	HARVARD COLLEGE	US	109	
5	INST NAT SANTE RECH MED	**FR**	97	GENETHON
6	UNIVERSITY JOHNS HOPKINS	US	93	Few companies
7	UNIVERSITY LELAND STANFORD JUNIOR	US	88	CATALYST BIOSCIENCES
8	CENTRE NAT RECH SCIENT	**FR**	85	REGENXBIO & GENETHON
9	NOVARTIS	**CH**	75	
10	JUNO THERAPEUTICS	US	70	

Table 2: Top 10 ATMP applicants (companies + academics)

The top 10 of ATMP filing companies is dominated by the US and by European Companies (Table 3). Top filers in Europe come from **France**, **Switzerland** and **Germany**. Most companies in the top 10 are biotech companies, some of which are young companies (JUNO THERAPEUTICS & IMMATICS BIOTECHNOLOGIES) ,and some of which are small to mid-sized companies with less than 500 employees (BLUEBIRD BIO, GENETHON and CELLECTIS).

Top	Company	Country	No. of patent families
1	NOVARTIS	**CH**	75
2	JUNO THERAPEUTICS	US	70
3	GENZYME CORP	US	61
4	AVENTIS PHARMA	**FR**	46
5	GENENTECH	US	46
6	IMMATICS BIOTECHNOLOGIES	**DE**	33
7	BLUEBIRD BIO INC	US	33
8	GENETHON	**FR**	31
9	CELLECTIS	**FR**	31
10	SMITHKLINE BEECHAM CORP	US	30

Table 3: Top 10 ATMP companies

Figure 5: Patent activity of the top 10 ATMP companies over the years

Filing entities were then plotted against the timeline to see how their filing activity evolves/evolved over time (Figure 5). First, we see a first peak in activity near 2004-2005 and a second peak in activity near 2020-2021 (evident by plotting all applicants over time, results not shown). Next, we notice that some companies seem to have stopped their activities in this area (at least for now), whereas others only started recently (after 2010, or even after 2015). Top applicant of the past 3 years: JUNO THERAPEUTICS (US), with 46 first patent publications between 2020 and 2022 and with a continued high activity. The focus of JUNO THERAPEUTICS is on cell-based immuno-oncology (CBIO).

Various of the above listed companies have ATMPs on the market or in the registration process (Table 4). Between brackets, the year that the ATMP entered the market. These data show the absolute strength & successfulness of small to midsized biotech companies in this area. These data further show the intense collaboration and licensing in this area.

Company Name	ATMP (on the market or pending) and Use
NOVARTIS (CH)	• **KYMRIAH™** (2017), CAR-T cell therapy for cancer; developed in collaboration with the University of Pennsylvania
TAKEDA PHARMACEUTICAL (JP)	• **ALOFISEL™** (2018), Allogeneic stem cell therapy for complex perianal fistulas in Crohn's disease; Alofisel was developed by the Belgian biotech **TiGenix**
NOVARTIS (CH)	• **LUXTURNA™** (2017), Gene therapy for inherited retinal disorders; Luxturna was developed and is commercialized in the US by Spark Therapeutics
BLUEBIRD BIO (US)	• **ZYNTEGLO™** (2022), Gene therapy for transfusion-dependent β-thalassemia. • **LENTI-D** (2018), for cerebral adrenoleukodystrophy.
CELLECTIS (FR)	• **UCART19™**, CAR T-cell technology pending for acute lymphoblastic leukemia, licensed to Servier
SMITHKLINE BEECHAM (US)	• **STRIMVELIS™** (2016), Gene therapy for adenosine deaminase deficiency (ADA-SCID), developed at San Raffaele Telethon Institute for Gene Therapy and developed by GlaxoSmithKline

Table 4: ATMPs pending and on the market by Top 10 companies

4.3 Belgian ATMP players

In the following section we look at Belgian players in particular. What we note is that most Belgian ATMP players are active in the field of Cell and Gene Therapy and that, as mentioned before, academics appear to play an important role in the ATMP ecosystem. Most ATMPs as we know are born in a university lab.

Table 5 below gives an idea of Belgian companies involved in ATMP. The list was extracted from the general dataset of 12,893 patents studied and covering the past 20 years. The list contains about 100 inventions.

Qua companies we have BONE THERAPEUTICS (now BIOSENIC), CELYAD, ETHERNA IMMUNOTHERAPIES, JANSSEN PHARMACEUTICA, NOVADIP BIOSCIENCES, PROMETHERA BIOSCIENCES (NOW CELLAÏON) and UCB (BIO)PHARMA as most active players.

- JANSSEN PHARMACEUTICA, GLAXOSMITHKLINE BIOLOGICALS and UCB (BIO)PHARMA are well-established pharmaceutical multinationals.
- TIGENIX, active in the field of Tissue Engineering, has been acquired by Takeda (a Japanese multinational) in 2018. TIGENIX was the fist company in Europe to have an ATMP on the market: CondroCelect (in 2009).
- HENOGEN, a viral vector manufacturer, has been acquired by THERMO FISHER SCIENTIFIC (a US multinational) in 2021.

Other companies in the list are small to medium-sized companies that were founded after the year 2000.

- CELYAD, located in Mont-Saint-Guibert/Wallonia and founded in 2007, focuses on CAR-T cell therapies for cancer.
- PROMETHERA BIOSCIENCES (now CELLAÏON), located in Mont-Saint-Guibert/Wallonia and founded in 2009, focuses on cell therapeutic products, including human liver cells, to treat liver diseases.
- NOVADIP BIOSCIENCES, located in Mont-Saint-Guibert/Wallonia and founded in 2013, focuses on stem cell therapies.
- ETHERNA IMMUNOTHERAPIES, located in Niel/Flanders and founded in 2013 as a spin-off of the VUB, develops products for the treatment of cancer and infectious disease.
- REVATIS, located in Liège/Wallonia and founded in 2013 as a spin-off of the University of Liège, is dedicated to advanced regenerative medicine and cell therapy.
- PDC*LINE PHARMA, located in Liège/Wallonia and founded in 2014, FR/BE company providing off-the-shelf cancer immunotherapies based on a proprietary Plasmacytoid Dendritic Cell line (PDC*line) pre-loaded with peptides that are derived from target tumor antigens
- XPRESS BIOLOGICS, located in Herstal/Wallonia and founded in 2014, is a Biologics CDMO[10] providing development and manufacturing services of plasmid DNA (pDNA) and proteins.
- ALLEGRO, located in Antwerp/Flanders and founded in 2021, has developed ground-breaking nanotechnology and focuses on degenerative diseases and tissue engineering.

The above demonstrates that Research & Development in Cell and Gene Therapy and in Regenerative Medicines is booming both in Flanders and in Wallonia. Belgium has established itself on the map as a true "Biotech and Health Valley" thanks to its tradition of scientific and

[10] CDMO: Contract Development and Manufacturing Organization

industrial excellence and the strength of its ecosystem, which brings together leading players in every stage of the innovation chain[11].

[11] BioWin, 2016. Wallonia – a cell therapy and regenerative medicine powerhouse. www.biowin.org; bio.be/essenscia belicht troeven van Belgische farma en biotech tijdens Wereld Economisch Forum in Davos - essenscia

Table 5: List of ATMP patents of the past 23 years with contribution of Belgian inventors (focus is on industrial players)

Applicant	Title / Content	Pub. Year[12]	Pub. No.
ALLEGRO	Composition and Scaffold Material to Regenerate Cartilages =→ nanocrystalline cellulose scaffold to support cell growth	2022	NL1044345
BETA CELL	Method for the treatment of diabetes mellitus based on encapsulated pancreatic cells	2015	WO2015040176A1
BETA CELL	Method for encapsulated therapeutic products and uses thereof	2012	WO2012130567A1
BONE THERAPEUTICS (now BIOSENIC)	Osteogenic differentiation of bone marrow stem cells and mesenchymal stem cells using a combination of growth factors	2009	WO2009087213A
BONE THERAPEUTICS (now BIOSENIC)	Pharmaceutical composition for use in the treatment and/or the prevention of osteoarticular diseases comprising stem cells	2009	WO2009101194A1
BONE THERAPEUTICS (now BIOSENIC)	Pharmaceutical composition for use in the treatment and/or the prevention of osteoarticular diseases comprising stem cells	2009	WO2009101210A1
BONE THERAPEUTICS (now BIOSENIC)	Human bone-forming cells in the treatment of conditions and bone diseases associated with immunodeficiency or immunosuppression	2009	WO2009135914A1
BONE THERAPEUTICS (now BIOSENIC)	In vitro preservation of therapeutic cells	2016	WO2016170112A1
BONE THERAPEUTICS (now BIOSENIC)	Method of differentiation of mesenchymal stem cells	2019	WO2019076591A1
BONE THERAPEUTICS (now BIOSENIC)	Method of differentiation of mesenchymal stem cells	2020	WO2020064791A1
BONE THERAPEUTICS (now BIOSENIC)	Osteogenic differentiation of bone marrow stem cells and mesenchymal stem cells using a combination of growth factors	2020	WO2020227679A1
BONE THERAPEUTICS (now BIOSENIC)	Methods for differentiating mesenchymal stem cells	2021	TW202104591
CELYAD	Nkg2d car cells expressing il-18 for adoptive cell therapy	2023	WO2023001774A1
CELYAD	Improved chimeric and engineered scaffolds and clusters of multiplexed inhibitory RNA	2022	WO2022233982A1
CELYAD	Cd52-deficient cells for adoptive cell therapy	2020	WO2020254528A1

[12] Pub. Year: Year of first publication

Applicant	Title / Content	Pub. Year[13]	Pub. No.
CELYAD	Car t-cells targeting bcma and uses thereof	2020	WO2020221873A1
CELYAD	Reducing fratricide of immune cells expressing nkg2d-based receptors	2019	WO2019110667A1
CELYAD	Compositions and methods for improving persistence of cells for adoptive transfer	2019	WO2019110693A1
CELYAD	Cells with multiplexed inhibitory RNA	2020	WO2020221939A1
CELYAD	Pooling signaling and costimulatory domains in flexible car design	2019	WO2019115818A2
CELYAD ONCOLOGY	Improved scaffolds for multiplexed inhibitory rna	2021	WO2021224278A1
ETHERNA IMMUNOTHERAPIES	Method for large-scale production of large-sized lipid nanoparticles (LNPs)	2023	WO2023118450A1
ETHERNA IMMUNOTHERAPIES	Use of lipid nanoparticles (LNPs) for immunogenic delivery of nucleic acid molecules, specifically mRNA	2023	TW202304505A
ETHERNA IMMUNOTHERAPIES	Method for large-scale production of large-sized lipid nanoparticles (LNPs) =→ GMP-compliant scalable method to produce large volumes of LNP's with minimal diameter of 140 nm quickly	2023	WO2023118450A1
ETHERNA IMMUNOTHERAPIES	Method for large-scale production of large-sized lipid nanoparticles (LNPs) =→ physicochemical properties of the reaction mixture are monitored in order to timely stop the reaction and/or to add fresh reagents to allow the reaction to continue under optimal conditions	2023	WO2023275217A1
ETHERNA IMMUNOTHERAPIES	Lipid nanoparticles (LNPs) =→ comprising an ionizable lipid, a phospholipid, a sterol, a C14-PEG2000 PEG lipid and one or more nucleic acids, preferred amount of said PEG lipid defined	2023	TW202304505A
ETHERNA IMMUNOTHERAPIES	Methods for storing mRNA compositions =→ adding a metal binding chelator to prevent/reduce aggregation upon freeze-thawing	2022	WO2022248566A1
ETHERNA IMMUNOTHERAPIES	Method to reduce double stranded RNA by-product formation =→ adding magnesium to prevent/reduce dsRNA formation during in vitro transcription	2022	WO2022248565A1
ETHERNA IMMUNOTHERAPIES	Lipid nanoparticles (LNPs) =→ comprising an ionizable lipid, a phospholipid, a sterol, a C14-PEG2000 PEG lipid and one or more nucleic acids, preferred amount of said PEG lipid defined	2021	WO2021250263A1
ETHERNA IMMUNOTHERAPIES	Intranasal mRNA vaccines =→ with one or more immunostimulatory molecules next to one or more pathogenic antigens and a specifically designed delivery system	2021	WO2021160881A1
ETHERNA IMMUNOTHERAPIES	Lipid nanoparticles (LNPs) =→ comprising an ionizable lipid, a phospholipid, a sterol, a C18-PEG2000 PEG lipid and one or more nucleic acids, preferred amount of said PEG lipid defined	2021	WO2021148511A1

[13] Pub. Year: Year of first publication

Applicant	Title / Content	Pub. Year[14]	Pub. No.
ETHERNA IMMUNOTHERAPIES	Method for RNA manufacturing =→ filtration step performed on RNA samples containing ssRNA, dsRNA and at least one salt in the absence of cellulose	2021	WO2021255297A1
ETHERNA IMMUNOTHERAPIES	Lipid nanoparticles (LNPs) =→ combination of one or more mRNA molecules encoding functional immunostimulatory proteins and one or more mRNA molecules encoding an antigen	2020	WO2020216911A1
ETHERNA IMMUNOTHERAPIES	Combination therapy =→ combination of mRNA molecules encoding functional immunostimulatory proteins with mRNA molecules encoding tumor-associated antigens for use as therapeutic vaccine in the treatment of metastatic cancer patients	2020	WO2020260685A1
ETHERNA IMMUNOTHERAPIES	mRNA vaccines =→ combination of an mRNA molecule encoding a functional immunostimulatory protein and a CTLA4 pathway inhibitor	2020	WO2020182993A1
ETHERNA IMMUNOTHERAPIES	mRNA vaccines =→ combination of mRNA molecules encoding functional immunostimulatory proteins and a PD-1 pathway inhibitor	2020	WO2020141212A1
ETHERNA IMMUNOTHERAPIES	Lipid nanoparticles (LNPs) =→ comprising an ionisable lipid, a phospholipid, a sterol, a PEG lipid and one or more nucleic acids, minimal diameter is 140 nm for a more potent immune response	2019	WO2019141814A1
GSK BIOLOGICALS	Replication competent adenoviral vectors =→ superior replication and expression of exogenous immunogens, for prophylactic, therapeutic vaccines and for use in gene therapy	2019	WO2019076877A1
HENOGEN	Sealant or tissue generating product =→ based on a (coagulated) plasma matrix, one or more growth factors, at least one phospholipid and a protein scaffold	2005	US2005244393A1
HENOGEN	Sealant or tissue generating product =→ based on a (coagulated) plasma matrix, one or more growth factors, at least one phospholipid and a protein scaffold	2004	WO2004002539
HENOGEN	Sealant or tissue generating product =→ based on a (coagulated) plasma matrix, one or more growth factors, at least one phospholipid and a protein scaffold	2004	WO2004002539A2
INTREXON ACTOBIOTICS	Reduced colonization of microbes at the mucosa = recombinant microbe that has reduced capacity of colonizing the mucosa in comparison to its wild type ancestor by having an inactive thymidylate synthase gene	2010	WO2010034844A1
JANSSEN PHARMACEUTICA[15]	Compositions and methods for quantifying integration of recombinant vector nucleic acid =→ particular primers and probes, for performing the quantitation	2021	WO2021180665A1
JANSSEN PHARMACEUTICA	Preparation of inactivated artificial antigen presenting cells and their use in cell therapies =→ inactivated aAPCs are generated through crosslinking, such as via a photoreaction involving a psoralen derivative, and UVA irradiation	2008	WO2008045286A2

[14] Pub. Year: Year of first publication

[15] Janssen Pharmaceutica, or Johnson & Johnson Medicines

Applicant	Title / Content	Pub. Year[16]	Pub. No.
JANSSEN PHARMACEUTICA	Cancer treatment combining lymphodepleting agent with CTLs and cytokines =→ autologous CD8+ T cells are obtained from a patient, activated ex vivo by contacting them with xenogenic antigen presenting cells loaded with selected peptide antigen, thereby generating antigen- specific activated cytotoxic T lymphocytes	2008	WO2007103009A2
JANSSEN PHARMACEUTICA	Modulation of smooth muscle cell proliferation by vegf-x or antagonists thereof =→ vegf-x, and a cub domain can be used in tissue engineering applications to increase the number of smooth muscle cells within specific tissue to restore that tissue function or architecture	2003	WO2002072127A2
LEGEND BIOTECH[17]	Methods of minimizing neurotoxicity associated with chimeric antigen receptor (car) t cell therapy	2022	WO2022238901A1
NOVADIP BIOSCIENCES	Cellular and/or extracellular extracts for preventing and/or treating cancer and/or inflammation	2022	WO2022112528A1
NOVADIP BIOSCIENCES	Biomaterials for the prevention and treatment of tissue disorders =→ sterile and desiccated biomaterials comprising devitalized differentiated cells having tissue regenerating and/or repairing properties, and a particulate material, the cells and the particulate material being embedded in an extracellular matrix. The particulate material is often gelatin, a ceramic material, or a demineralized bone matrix (DBM)	2021	WO2021105404A1
NOVADIP BIOSCIENCES	miRNA-based pharmaceutical compositions and uses thereof for the prevention and the treatment of tissue disorders	2021	WO2021105407A1
NOVADIP BIOSCIENCES	Biomaterial comprising adipose-derived stem cells and gelatin and method for producing the same	2020	WO2020058511A1
NOVADIP BIOSCIENCES	Biomaterial comprising adipose-derived stem cells and method for producing the same	2019	WO2019057862A1
NOVADIP BIOSCIENCES	Biomaterial comprising adipose-derived stem cells and method for producing the same	2019	WO2019057861A1
NOVADIP BIOSCIENCES	Biomaterial comprising adipose-derived stem cells and method for producing the same	2019	US2019083680
NOVADIP BIOSCIENCES	Methods for assesing the purity of a mesenchymal stem cells preparation	2017	WO2016180788A1
ONCODNA[18]	A RNA vaccine comprising a RNA pool generated from a double stranded DNA pool =→ useful as personalized cancer vaccine	2023	WO2023037000A2
PDC*LINE PHARMA	Genetically modified PDC (plasmacytoid dendritic cell) line for secreting a cytokine, and its use for increasing the expansion of antigen-specific cells in immunotherapy	2022	WO2020083974A1

[16] Pub. Year: Year of first publication
[17] LEGEND BIOTECH has a very high number of patents around Cell therapy and the use of CAR-T cells in particular but only one with a Belgian inventor
[18] ONCODNA has many patents filed around disease profiling and the generation of a plurality of neoantigens based on a patient's sample

Applicant	Title / Content	Pub. Year[19]	Pub. No.
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Use of liver progenitor or stem cells in disorders characterized by vascular hyperpermeability	2021	WO2021069553A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Cell composition comprising hepatic progenitor cells expressing HLA-E	2020	WO2020120664A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Preparation of human allogeneic liver-derived progenitor cells	2020	WO2020221843A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Adult liver progenitor cells for treating acute-on-chronic liver failure	2020	WO2020193714A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Method for producing adult liver progenitor cells	2016	WO2016030525A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Mobile facility for preparing and distributing cell-based medicinal products	2014	WO2014049151A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Encapsulated liver cell composition	2011	WO2010124837A2
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Cryopreservation of hepatocytes	2007	WO2007059855A1
PROMETHERA BIOSCIENCES (NOW CELLAÏON)	Storage medium for cells	2007	WO2007003382A2
REGENESYS	Biocompatible scaffolds for culturing post natal progenitor cells	2021	WO2021176420A1
REGENESYS	Expansion of stem cells in hollow fiber bioreactors	2012	WO2012168295A1
REVATIS	Culturing of stem cells, such as muscle stem cells	2021	WO2021165451A1
REVATIS	Method for obtaining differentiated cells from muscle derived progenitor cells	2018	WO2018189124A1

[19] Pub. Year: Year of first publication

REVATIS	New uses of mammalian muscle-derived stem cells	2018	WO2018189121A1
Applicant	Title / Content	Pub. Year[20]	Pub. No.
TIGENIX	Methods and compositions for use in intralymphatic cellular therapies= → stem cell, regulatory T-cell and/or fibroblast cell for the treatment or repair of damaged tissue	2014	WO2012095743A2
TIGENIX	Methods to maintain, improve and restore the cartilage phenotype of chondrocytes =→ regulatory cells, which are capable of restoring, maintaining or improving the stable cartilage phenotype of expanded and passaged chondrocytes	2007	WO2007107330A2
TIGENIX	Isolation of precursor cells and their use for tissue repair =→ cartilage-derived morphogenetic protein CDMP-1 or a transforming growth factor β having at least 80 % homology with CDMP-1, used as a marker of skeletal precursor cells	2001	WO2001025402A1
UCB BIOPHARMA	Gene therapy =→ nucleic acid constructs comprising methyl CpG binding protein 2 (MeCP2) promoter sequences	2022	WO2022034130A1
UCB BIOPHARMA	Modulation of cftr expression =→ CRISPR/Cas9-based epigenome editing tools for repression or activation of CFTR gene expression and provides the regions of the CFTR gene that can be targeted by such system to increase the CFTR expression	2022	WO2022008557A2
UCB BIOPHARMA	Viral particles for use in treating synucleinopathy such as Parkinson's disease with gene therapy	2022	WO2022029322A2
UCB BIOPHARMA	Gene therapy using nucleic acid constructs comprising methyl cpg binding protein 2 (mecp2) promoter sequences	2022	WO2022034130A1
UCB BIOPHARMA	Viral particles for use in treating synucleinopathy such as Parkinson's disease with gene therapy	2021	WO2021028299A1
UCB BIOPHARMA	Endosomolytic agents for gene therapy	2018	WO2018060280A1
XPRESS BIOLOGICS	Automated process for extracting a peptide of interest located in periplasmic space and/or comprising an acidification step	2023	WO2023175190
XPRESS BIOLOGICS	Method for discontinuous plasmid extraction from a microorganism and for purifying a plasmid of interest	2022	WO2023275406A1
XPRESS BIOLOGICS	Method for producing a periplasmic form of the protein crm197	2022	WO2022180265A2
ZIPHIUS VACCINES	Lipid nanoparticles for oligonucleotide delivery	2023	WO2023078954A1
ZIPHIUS VACCINES	Lipid nanoparticles for oligonucleotide delivery	2023	WO2023078946A1
ZIPHIUS VACCINES	Lipid nanoparticles for oligonucleotide delivery	2023	WO2023078950A1
ZIPHIUS VACCINES & UGHENT[21]	Self-replicating RNA molecules comprising a sequence encoding nonstructural alphavirus proteins and a sequence encoding a SARS-CoV-5 2 protein antigen	2021	WO2021255270A1

[20] Pub. Year: Year of first publication
[21] UGhent: University of Ghent

4.4 Major Technologies, Major CPC codes and Major topics covered

Before diving deeper into the Advanced Therapy Medicinal Products (ATMP) patent landscape, it is worth looking at the Major Technological Areas wherein ATMP patents are filed & at the major CPC[22] codes attributed to them.

4.4.1 Major Technologies

Figure 6 below depicts an analysis of the Technological Areas that we find back within the patent pool of ~13,000 ATMP patents studied. Not surprisingly, the ATMP patents fall primarily in the area of Pharmaceuticals and of Biotechnology (purple), and for a small part in the area of Medical Instruments and of Analysis of Biological materials (yellow).

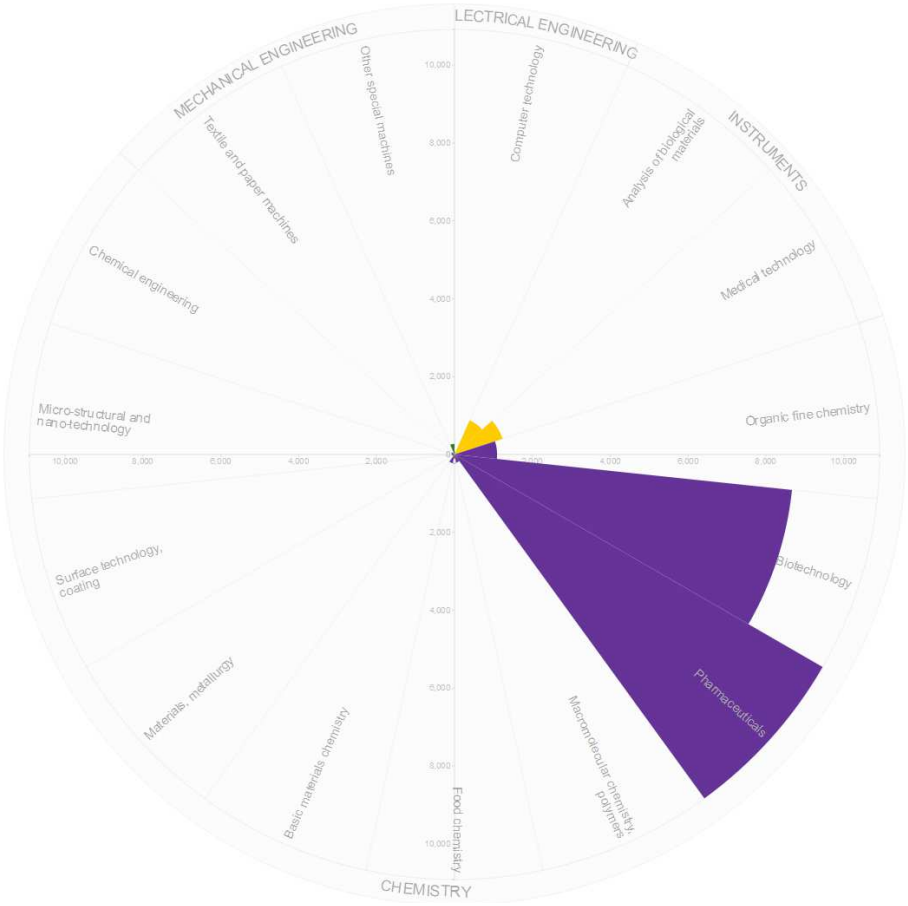

Figure 6: Technological Areas covered by ATMP patents

[22] CPC stands for Cooperative Patent Classification, a joint effort of the EPO (European Patent Office) and the USPTO (US Patent & Trademark Office)

4.4.2 Major ATMP Codes

Patent Classification Codes (IPC and CPC codes) are another way to get a quick insight into the technology behind patents. Classification codes are assigned by Patent Officers at filing, in order to classify patents according to their technical content.

Figure 7 below depicts the Major CPC [23] Full codes (top 10) attributed to patent families that are filed within the field of ATMP.

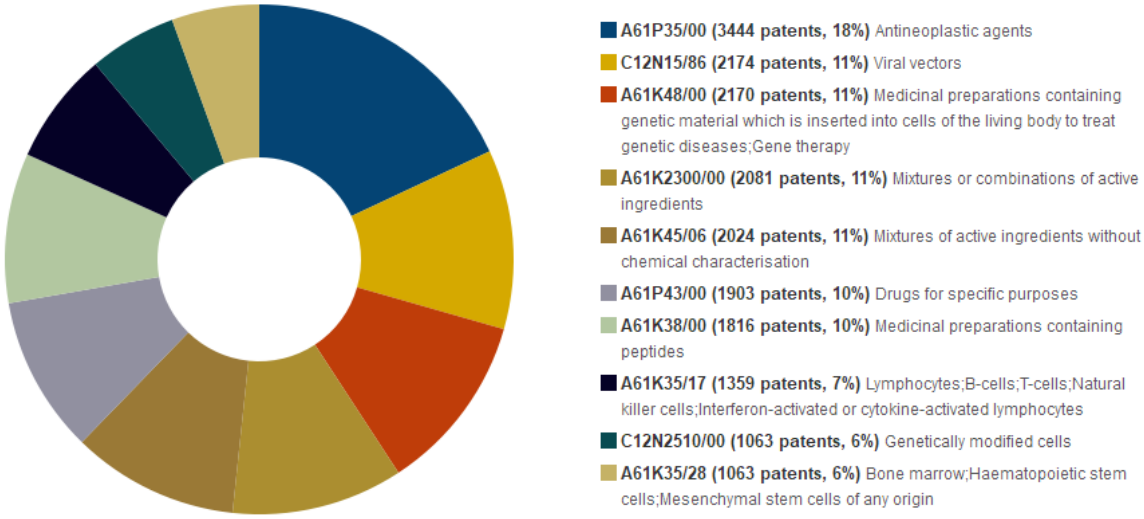

Figure 7: CPC Full Codes (Top10) associated with ATMP

Figure 7 shows that most of the ATMP patents deal with Gene Therapy (A61P35, A61P43, A61K38, A61K45, A61K48, A61K2300 and C12N15) and then with Cell Therapy (A61K35 and C12N2510). Tissue Engineering patents do not figure in the Top 10. This corresponds to what is seen in scientific literature and what is reported by those that follow up the key players (https://alliancerm.org/data/, therapeutic developers data, September 2023).

A few interesting side notes: Full CPC code A61P35 relates to cancer therapy (oncology) using ATMPs. A61K48/0075 is an interesting CPC sub-class that focuses on the GTMP[24] delivery systems. A61P43 is yet another interesting CPC code as patents are classified herein with respect to the diseases/disorders being treated. The subcategories within this CPC class can be used later to see what diseases/disorders are being focused on the last years (Table 6).

[23] CPC stands for Cooperative Patent Classification, a joint effort of the EPO (European Patent Office) and the USPTO (United States Patent & Trademark Office) to classify patents in a same way

[24] GTMP: Gene Therapy Medicinal Products

Subcategory	Drug type
1/00	Drugs for disorders of the alimentary tract or the digestive system
3/00	Drugs for disorders of the metabolism (of the blood or the extracellular fluid)
5/00	Drugs for disorders of the endocrine system
7/00	Drugs for disorders of the blood or the extracellular fluid
9/00	Drugs for disorders of the cardiovascular system
11/00	Drugs for disorders of the respiratory system
13/00	Drugs for disorders of the urinary system
15/00	Drugs for genital or sexual disorders (for disorders of sex hormones)
17/00	Drugs for dermatological disorder
19/00	Drugs for skeletal disorders
21/00	Drugs for disorders of the muscular or neuromuscular system
25/00	Drugs for disorders of the nervous system
27/00	Drugs for disorders of the senses
35/00	Antineoplastic agents
37/00	Drugs for immunological or allergic disorders
43/00	Drugs for specific purposes, not provided for in the other groups

Table 6: A61P35 subcategories and diseases/disorders being treated

4.4.3 Major topics covered

Some of the Technologies that are used in the field of Advanced Therapy Medicinal Products (ATMPs) and their Activity Over Time are depicted in Figure 8. This Figure gives us an idea of when the first patents around a certain technology were published, and if the technology has further evolved or not. In the second place, this mapping can provide an insight into mature certain technologies are, in particular when patent insights are combined with commercial or with literature insights.

Following Techniques were looked at: (I) Gene Therapy, (II) Cell Therapy and (III) Tissue Engineering. The time period covered: 2000-2023. Text pattern analysis was done in: Title, Abstract, Claims and Description (t, a, cl, d).

Gene Therapy is dominating the picture, followed by Cell Therapy. There are much less patent publications around Tissue Engineering. What we further see is that Gene therapy was a hot topic beginning of the 21th century that regained a lot of interest the past few years. Cell therapy on the other hand is a more recent topic that continues to grow.

Mapping the same text patterns in title, abstract, claims and description (ti, ab, cl, d) against companies, provided the following insights (Figure 9, cleaned figure): Few top filing Companies are involved with Tissue Engineering (though various Academic players have been filing patents in this area, results not shown).

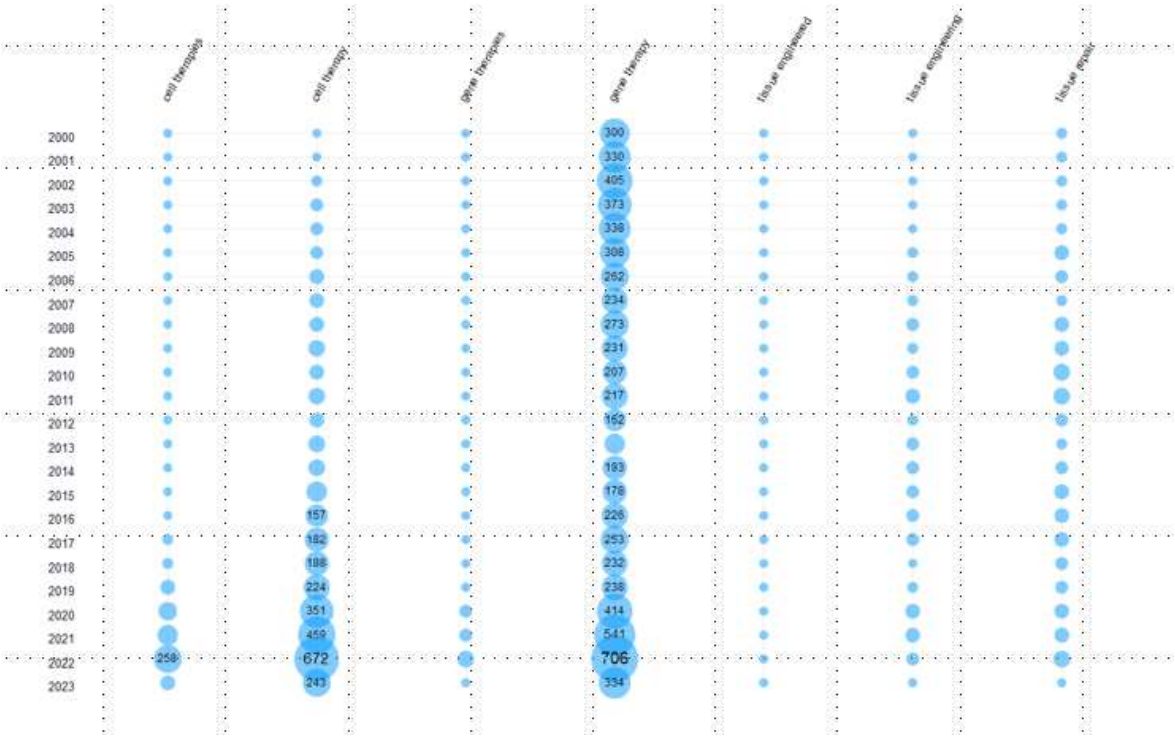

Figure 8: Different ATMP main categories and focus over the years (2004-2023)

Figure 9: Top 20 companies plotted versus ATMP main categories
(Cell Therapy, Gene Therapy and Tissue Engineering, in alphabetical order)

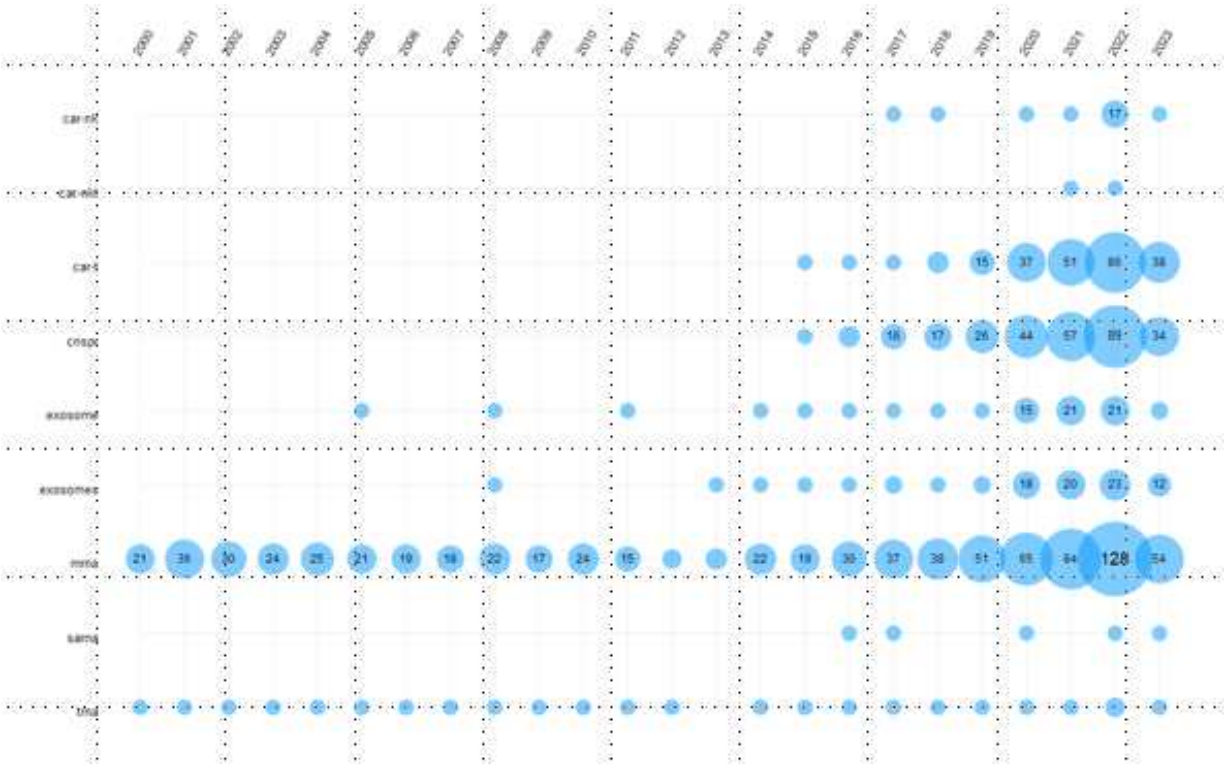

Figure 10: Recent technologies of interest and when they took off (period covered: 2000-2023) On the Y-axis (topdown): CAR-NK, CAR-NKT, CAR-T, CRISPR, EXOSOME, EXOSOMES, mRNA, saRNA, tRNA

Figure 10 above shows us that mRNA technologies and tRNA technologies are older technologies, whereas other technologies that are listed herein took off ~2015 or later. Within the area of Chimeric Antigen Receptor Technologies (CAR), focus is in particular on CAR T-cell Immunotherapy, more than on CAR NK[25]-cell Immunotherapy. Withing the area of RNA Technologies, mRNA Technologies are more established and advanced than tRNA and saRNA[26] Technologies. Exosome-based Technologies are taking on too. Highest number of first patent publications the past three years are found to deal with mRNA Technologies, CAR-T Technologies and CRISPR Technologies (the latter being a real Break Through Technology that was rewarded with a Nobel Prize).

In the next Chapter we look in more details at the major ATMP Technologies. We start with Gene Therapy, then Cell Therapy, and then Tissue Engineering. For each of these Technologies we also look in more detail at some of the Major Technologies and Trends of the Past Few Years.

[25] NK cell: natural killer cell
[26] mRNA: messenger RNA, tRNA: transfer RNA, saRNA: self-amplifying RNA

5 Selection of topics

In this last section, we dive into some topics that (i) either are important for the sector, that (ii) gained momentum or that (iii) cover recent trends.

- We start with Gene and Cell Technologies, and cover under this heading the following topics in more detail: mRNA technologies (with focus on mRNA vaccines), then CAR T-cell Immunotherapy and CRISPR-Cas technologies.
- Next we cover Tissue Engineering, and discuss herein to a limited extent some of the novel trends.
- For the major technologies, we also look at valuable patents in the domain that were (i) either rolled out broadly and/or that (ii) have been cited multiple times in other patents, and that for that reason are considered important.

5.1 Gene Therapy Medicinal Products (GTMPs)

Most patents in the field of Advanced Therapy Medicinal products (ATMPs) deal with Gene Therapy, not surprisingly as this is the oldest technology. We created a separate patent dataset containing ~3,500 patents on this topic to study the overall field, top technologies and some recent trends.

- Gene therapy involves the introduction, alteration, or correction of genetic material within a patient's cells to treat or prevent diseases. It can be used to replace faulty genes, insert new genes, or modify existing ones.

5.1.1 Overall: 2000-2023

Looking at the entire period covered (from 2000-2023) and at the entire set of GTMP patents, we note the following: Same top 10 applicants as for ATMPs in general. We identify three (3) categories of applicants: (i) those that have been filing patents on GTMPs throughout the years, (ii) those that have been active primarily in the years 2000-2006 and (iii) those that started filing actively in this field the past 3-5 years (data not shown).

In a next step we focus primarily on the newcomers and their innovation partners in this area by looking at the past five (5) years.

5.1.2 Recent years: 2019-2023

a. Top 10 GTMP applicants (companies and academics):

The Top 10 of GTMP Applicants of the past few years: is dominated by US & European players, and again most patents are being filed by academics. **France** has been a very active filer the past 5 years and we have one (1) **Belgian** company listed in the top 10: ETHERNA IMMUNOTHERAPEUTICS (Table 7). In this list, we looked at companies as well as at academics.

b. Top 10 GTMP companies:

The Top 10 of GTMP Companies of the past few years: GENETHON **(FR)**, REGENXBIO (US), ETHERNA IMMUNOTHERAPIES **(BE)**, CUREVAC **(DE)**, PREVAIL THERAPEUTICS (US), GENZYME (US), UCL BUSINESS **(UK)**, BLUEBIRD BIO (US), and UNIQURE IP **(NL)**. In this top 10 of filing companies, we find back five (5) European companies, from **Belgium**, **France**, **Germany, the Netherlands** & **the UK**

respectively: ETHERNA IMMUNOTHERAPIES, GENETHON, CUREVAC, UNIQURE IP, and UCL BUSINESS. Other companies in this list are US-based.

Belgian entities that have been filing in this domain the past few years: ETHERNA IMMUNOTHERAPIES, GLAXOSMITHKLINE BIOLOGICALS, plus various universities and research institutions.

Top	Applicant	Country	No. of patent families
1	INST NAT SANTE RECH MED	**FR**	44
2	UNIV PENNSYLVANIA	US	29
3	RES INST NATIONWIDE CHILDRENS HOSPITAL	US	26
4	UNIV FLORIDA	US	26
5	GENETHON	**FR**	25
6	UCL BUSINESS	US	23
7	REGENXBIO	US	22
8	UNIV CALIFORNIA	US	22
9	UNIV DEVRY VAL DESSONNE	**FR**	20
10	**ETHERNA IMMUNOTHERAPIES**	**BE**	**18**

Table 7: Top 10 GTMP applicants (companies + academics) in the period 2019-2023

5.1.3 Valuable GTMP patents

Using a patent value analysis, GTMP patents were scored based on the size of the patent family and on the number of forward patent citations. A high score is obtained if the Family Size is large, which would be an indicator of the market significance of the patent, and if the Number of Forward Citations is large, which is an indicator of the significance of the technology described. From the analysis done, the patents with a high value score as well as patents that have a large number of citations, were selected and listed in Table 8 below. Figure 11 shows that a significant number of recently published inventions are believed to have a high market potential, in view of the Family Size (lower right of the figure, large circles).

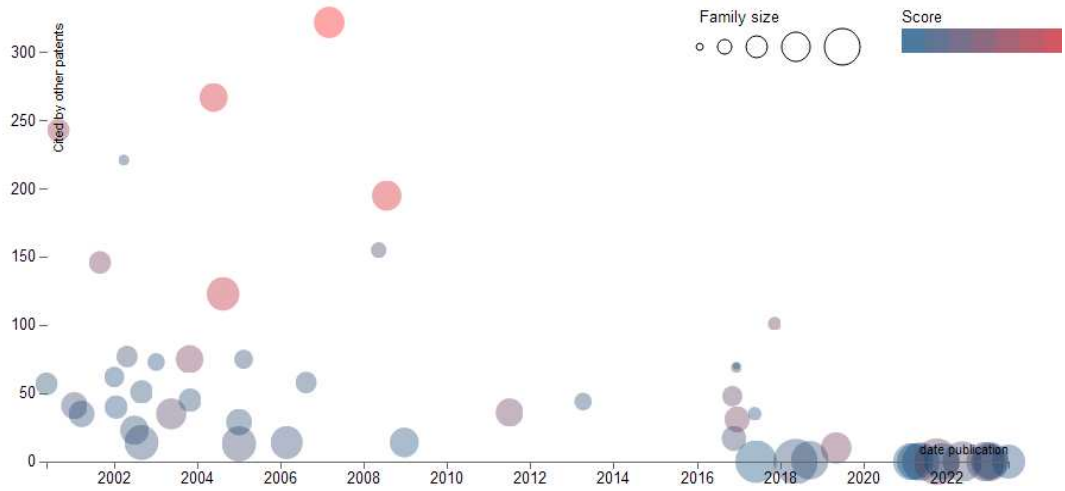

Figure 11: Importance of GTMP patents based on Recency, Family Size and Forward Citations Size

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
WO2007024708A2	71	01/03/2007	25	322
WO2008083949A2	67	17/07/2008	22	159
WO2004067753A2	65	12/08/2004	31	123
US6110490A	60	29/08/2000	10	273

Table 8: Most valuable GTMP patents that published in the period 2000-2018

- **WO2007024708A2** (UNIVERSITY OF PENNSYLVANIA, US) relates to RNA molecules comprising pseudouridine to reduce the immunogenicity of those molecules
- **WO2008083949A2** (CUREVAC, **SE**) relates to RNA-coded antibodies
- **WO2004067753A2** (CELLECTIS, **FR**) relates to the use of meganucleases for inducing homologous recombination ex vivo and in toto
- **US6110490A** (US Health, US) relates to a liposomal delivery system for biologically active agents

European companies dominate this list (Table 8). When we look at recent GTMP patent publications (of the past 5 years), then we find back primarily US academics and US companies, and one (1) **Slovakian** company that is working on Alzheimer, that have rolled out their inventions in a large number of countries[27,28] (Table 9).

[27] Roll out in many countries translates into a large Family Size
[28] Because filed only recently, the Size Forward Citations is low. This size is expected to increase the coming years

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
US20190016759A1	57	17/01/2019	25	10
US20220023427A1	56	27/01/2022	116	0
US20220054657A1	53	24/02/2022	55	0
US20210284980A1	53	13/05/2022	64	0
US20220010004A1	52	13/01/2022	57	0

Table 9: Most valuable GTMP patents that published in the period 2019-2023[29]

- **US20190016759A1** (UNIVERSITY OF FLORIDA, US) relates to AAV vectors with high transduction efficiency and uses thereof for gene therapy. They have a modification in the AAV capsid proteins
- **US20220023427A1** (ARBUTUS BIOPHARMA, US) relates to lipid delivery systems
- **US20220054657A1** (GENZYME, US) relates to gene therapy for retinitis pigmentosa
- **US20210284980A1** (PRECISION BIOSCIENCES, US) relates to rationally-designed meganucleases with altered sequence specificity and DNA-binding affinity
- **US20220010004A1** (AXON NEUROSCIENCE, **SK**) relates to protein-based therapy and diagnosis of TAU protein-mediated pathologies in alzheimer's disease

5.2 Cell Therapy Medicinal Products (CTMPs)

Another important subcategory in the field of ATMP technologies concerns Cell Therapy Medicinal Products (CTMPs). We created a separate patent dataset containing ~3,000 patents on this topic to study the overall field, top technologies and some recent trends.

- Cell therapy involves the transplantation or infusion of cells into a patient to treat a wide range of diseases and conditions, often involving the use of stem cells, immune cells, or other specialized cell types.

5.2.1 Overall: 2000-2023

In the field of CTMPs, the patent activity has been steadily increasing since 2002 (data not shown). Few applicants were actively filing in 2004 already, most started filing after 2014 only.

In a next step we focus primarily on the newcomers and their innovation partners in this area.

5.2.2 Recent years: 2019-2023

a. Top 10 CTMP applicants (companies and academics):

The Top 10 of CTMP Applicants of the past few years: is fully dominated by the US, with JUNO THERAPEUTICS as top filer in this area (Table 10). In this list we looked at companies as well as academics.

[29] Family member published in 2019-2023, though some are derived from earlier filed international patent applications

Top	Applicant	Country	No. of patent families
1	JUNO THERAPEUTICS	US	72
2	UNIVERSITY OF CALIFORNIA	US	31
3	KITE PHARMA	US	28
4	MEMORIAL SLOAN KETTERING CANCER CENTER	US	26
5	MAGENTA THERAPEUTICS	US	24
6	UNIVERSITY OF TEXAS	US	24
7	UNIVERSITY OF PENNSYLVANIA	US	24
8	UNIVERSITY OF LELAND STANFORD JUNIOR	US	23
9	HARVARD COLLEGE	US	20
10	INNOVATIVE CELLULAR THERAPEUTICS HOLDINGS	US	15

Table 10: Top 10 CMTP applicants (companies + academics) in the period 2019-2023

b. Top 10 CTMP companies:

The Top 10 of CTMP Companies of the past few years: JUNO THERAPEUTICS (US), KITE PHARMA (US), MAGENTA THERAPEUTICS (US), INNOVATIVE CELLULAR THERAPEUTICS (US), 2SEVENTY BIO (US), BLUEBIRD BIO (US), CELLECTIS (**FR**), NOVARTIS (**CH**), CELGENE (US) and POSEIDA THERAPEUTICS (US). Though the US dominates also this list, we have two (2) European companies represented herein, from France and Switzerland respectively: CELLECTIS and NOVARTIS.

Belgian entities that have been filing in this domain the past few years: CELYAD, UCB BIOPHARMA, plus various universities and research institutions.

5.2.3 Valuable CTMP patents

Using a patent value analysis, CTMP patents were scored based on the size of the patent family and on the number of forward patent citations. A high score is obtained if the Family Size is large, which would be an indicator of the market significance of the patent, and if the Number of Forward Citations is large, which is an indicator of the significance of the technology described. From the analysis done, the patents with a high value score as well as patents that have a large number of citations were selected and listed in Table 10 below. Figure 12 shows which recent patents are believed to have high potential, in view of the family size.

Overall CTMP scores are lower than for GTMP patents, and in general we have less patents with a high Forward Citation Size. Yet again, recent inventions are rolled out in a high number of countries (Large Family Sizes) which means that the applicants see a lot of potential and economic interest in their developments (lower right of the figure, large circles).

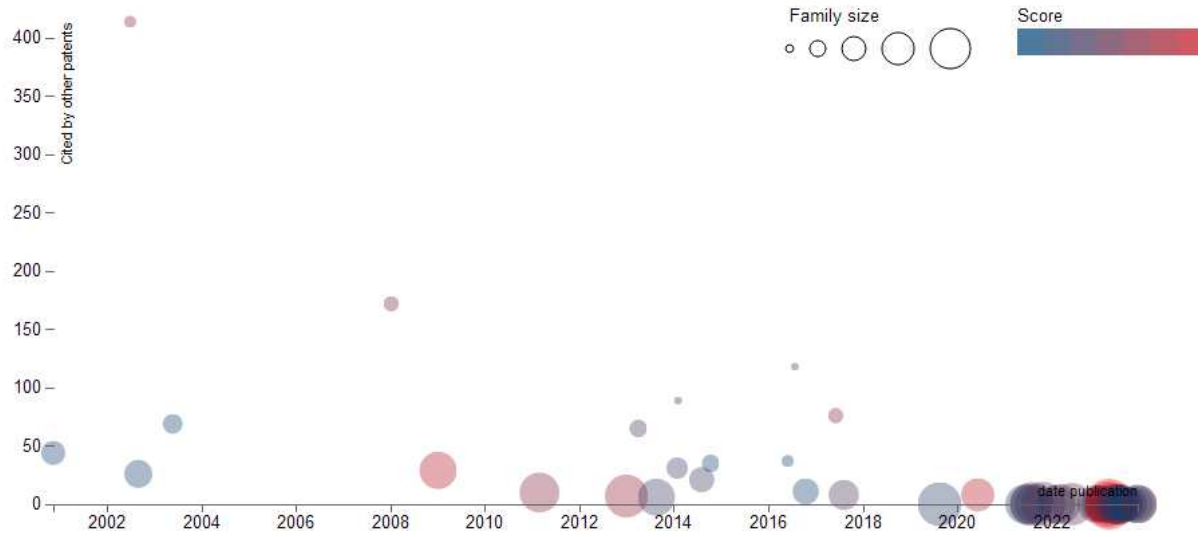

Figure 12: Importance of CTMP patents based on Recency, Family Size and Forward Citations Size

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
WO2009006997A1	56	31/12/2008	31	29
WO2000023573A2	54	25/06/2002	3	414
WO2011103470A1	54	26/12/2012	52	7
WO2009143411A2	53	23/02/2011	39	10
US2008003683A1 [30]	52	03/01/2008	4	172

Table 11: Most valuable CTMP patents that published in the period 2000-2018

- **WO2009006997A2** (IZUMI BIO, US) relates to human pluripotent stem cells inducible from human postnatal tissue, and to methods for inducing them
- **WO2000023573A2** (CITY OF HOPE, US) relates to Cd20-specific redirected t cells and their use in cellular immunotherapy of cd20+ malignancies
- **WO2011103470A1** (OSIRIS THERAPEUTICS, US) relates to therapeutic products comprising vitalized placental dispersions
- **WO2009143411A2** (SIWA CORPORRATION, US) relates to apparatuses, compositions and methods for removing cells which interfere with regenerative processes. Partially active or non-active cells are killed
- **US2008003683A1** (CITY OF HOPE, US) relates to Ce7-specific redirected immune cells

US companies fully dominate this list (Table 12). When we look at recent CTMP patent publications then we see the same: US academics and US companies only (Table 13).

[30] Not filed outside of the US

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
WO2015157391A1	60	17/03/2023	108	0
WO2020112687A2	56	04/06/2020	21	8
WO2014201167A1	55	09/03/2023	64	0
WO2017123644A1	53	18/04/2023	48	0
WO2016073602A2	52	26/05/2023	43	0

Table 12: Most valuable CTMP patents that published in the period 2019-2023[31]

- **WO2015157391A1** (SEATTLE'S CHILDREN HOSPITAL, US) provides materials and methods to bring immune responses mediated by cellular immunotherapy. This may be done for instance via the transfer of CD8+ central memory T-cells or via a combination of central memory T-cells and CD4+ T-cells that are genetically modified to express a chimeric receptor
- **WO2020112687A2** (FORTY SEVEN, US) relates to antibodies specifically binding to c-Kit and to methods of using such antibodies in stem cell replacement and cancer treatment
- **WO2014201167A1** (HARVARD COLLEGE, US) relates to materials and methods for inducing β cell maturation, and to isolated populations of SC-β cells for use in cell therapy
- **WO2017123644A1** (RUBIUS THERAPEUTICS, US) relates to materials and methods for multimodal therapies, e.g., for treating immune conditions. This means that one administers a plurality of agents that function in a coordinated manner to provide a therapeutic benefit
- **WO2016073602A2** (JUNO THERAPEUTICS, US) provides for transduction methods, in which cells and virus are incubated under conditions that result in transduction of the cells with a viral vector

In the next few sections we focus on a couple of technologies that helped advance CGTP[32] developments. We start with mRNA technologies, next CAR-T technologies, and then CRISPR-Cas technologies. mRNA technologies made possible mRNA vaccines but also played a big role in the development of amongst other CAR-T technologies and Genome editing.

5.3 mRNA technologies

mRNA technologies have made an important contribution to modern health care and continue to be on the rise. The application of mRNA based drug for disease therapy include (a) Vaccines, (b) Genome editing, (c) Cell therapy, (d) Therapeutic protein production and (e) Protein replacement (Wang et al.[33], figure 3A therein). Wang et al. report that more than 720 mRNA and interfering/modulating RNA candidate therapeutics for many medical conditions are under development by companies and academics worldwide.

In October 2023, thus only recently, the European Patent Office (EPO) has published a very comprehensive patent insight report on mRNA technologies, with focus on mRNA-based vaccines. This patent insight report and the data/search strategy used, are available from the EPO

[31] Family member published in 2019-2023, though some are derived from earlier filed international patent applications
[32] Cell and Gene Therapy Products
[33] Wang et al. mRNA-based vaccines and therapeutics: an in-depth survey of current and upcoming clinical applications. Journal of Biomedical Science (2023) 30:84 (Open Access)

website. Here, we take over the highlights of this report & go a bit more into detail on the European players.

- mRNA-based therapies use messenger RNA (mRNA) to instruct cells to produce specific proteins which may be useful for a variety of medical applications.

mRNA-based vaccines are a particularly dynamic sub-area of mRNA technologies. The rapid development of mRNA-based vaccines against SARS-CoV-2[34] would not have been possible without the extensive research into mRNA over the past few decades.

mRNA technology presents several advantages that makes it an attractive alternative over traditional immunotherapies[35].

- mRNA is precise: only a specific antigen is expressed
- improved protection: both humoral and cellular immune responses are promoted, plus the innate immune system is induced
- safer compared to DNA vaccines: no danger of integration into the genome
- flexible platform: quick adaption to antigen variants is possible

By incorporating modified nucleosides, providing a 5' cap and a longer poly(A) tail one has been able to increase the mRNA stability. And the development of mRNA carriers such as liposomes, lipid nanoparticles, lipoplexes, polyplexes and polymeric nanoparticles helped overcome the problems with cell entry.

Today, mRNA vaccines are used in the treatment of cancer (therapeutic vaccines) & in the prevention of viral, bacterial and malaria infections (prophylactic vaccines).

5.3.1 Overall: 2000-2023

Most active applicants in the field of mRNA vaccines are: companies and academics from the US, Europe and China. Top filing companies are MODERNA (US), CUREVAC (**DE**), BIONTECH (**DE**), GSK (**UK**), GILEAD SCIENCES (US), SANOFI (**FR**) JOHNSON & JOHNSON (US), ENANTA PHARMACEUTICALS (US), VICAL (US) and BAYER (**DE**). Many European companies are found in this list. Worth noting is that the vaccine against malaria was developed in Belgium.

5.3.2 Recent years: 2019-2023

GSK (**UK**) and SANOFI (**FR**) have been active in this area as of the beginning (since before 2000). GILEAD SCIENCES (US) and ETHERNA IMMUNOTHERAPIES[36] (**BE**) are amongst the newcomers in this field. What is worth noting, is that the US Government has played an active role and has been amongst the top filing entities of the past decade. What is further worth nothing, is the extensive collaboration between companies and academics in this field, leading to big steps forward[37].

The EPO has provided in its patent insight report a very comprehensive Table that shows which companies/players have been focusing on what (Table 13, pages 32-33 of this report). That Table shows that some players focus on particular diseases only, whereas other players focus on a variety of diseases and work in diverse fields.

[34] SARS-CoV-2: coronavirus 2, virus that caused the COVID-19 pandemia
[35] Based on the EPO Patent Insight report, p13
[36] ETHERNA IMMUNOTHERAPIES patents are listed in Table 5
[37] Partly fueled by the COVID-19 pandemia and partly by the establishment of ecosystems that help advance developments in this area

Belgian entities that have been filing in this domain the past few years: CELYAD, IMCYSE, ITEOS BELGIUM, ORIONIS BIOSCIENCES, UCB BIOPHARMA, plus various universities and research institutions.

5.3.3 Valuable mRNA patents

The EPO identified the following influential patents in the field of mRNA vaccines (patent insight report, Table on page 9)

Influential inventions in the field of mRNA-based vaccines:		
Structure and production of mRNA	**Formulation of mRNA for delivery**	**mRNA-based drug applications e.g. mRNA vaccines**
EP2305699 Stabilised mRNA with increased G/C content which is optimised for translation in its coded areas for the vaccination against sleeping sickness, leishmaniosis and toxoplasmosis EP1905844 Stabilised mRNA tumour vaccines EP2578685 RNA containing modified nucleosides and methods of use thereof EP3329941 RNA-coded bispecific antibody EP2603590 Nucleic acid comprising or coding for a histone stem-loop and a poly(a) sequence or a polyadenylation signal for increasing the expression of an encoded protein EP3134131 Nucleic acid vaccines	EP1905844 Stabilised mRNA tumour vaccines EP2590626 Liposomes with lipids having an advantageous PKA-value for RNA delivery EP3623361 Lipids and lipid compositions for the delivery of active agents EP3134131 Nucleic acid vaccines	EP1905844 Stabilised mRNA tumour vaccines EP3329941 RNA-coded bispecific antibody EP2331129 Composition comprising a complexed (m)RNA and a naked mRNA for providing or enhancing an immunostimulatory response in a mammal and uses thereof EP3134131 Nucleic acid vaccines

5.4 CAR T-cell immunotherapy

In December 2019, the European Patent Office (EPO) has also published a patent insight report on Chimeric Antigen Receptor T-cell Immunotherapy (CAR T-cell Immunotherapy). This patent insight report and the data/search strategy used are available from the EPO website. We have used this report and its insights as a basis, and have updated it to include more recent insights (including the period 2019-2023 as well).

- Chimeric Antigen Receptor T-cell (CAR-T) Immunotherapy is a form of cell therapy that enhances a patient's own T-cells to target and destroy cancer cells more effectively, often used in the treatment of certain blood cancers.
- T-cells are (i) extracted from a blood sample, (ii) genetically re-programmed to produce CAR (chimeric antigen receptors) and then (iii) (re-)introduced into the patient. The modified T-cells recognize and kill the tumor. The T-cells can be the patient's own cells (autologous cells), or donor cells (allogeneic cells) can be used.

5.4.1 Overall: 2000-2023

CAR T-cell patenting took off from 2013 and has been increasing ever since. Applicants from the US are the most productive, followed by Chinese applicants and Swiss (mainly NOVARTIS), British,

French and German applicants. What is interesting to see is that the participation of China is much higher than we have seen in other areas discussed so far. Interesting also is that near 50% of the patents in this area have been filed by companies.

In the Top 10 of CAR-T academics we find: primarily US players besides one (1) European player (UNIVERSITY COLLEGE OF LONDON, UK) and one (1) Chinese player (CHINESE PLA GENERAL HOSPITAL, CN). In the Top 5 of CAR-T companies figure NOVARTIS (**CH**), CELLECTIS (**FR**), SUZHOU PULUODA SCIENCE AND TECH (CN), BLUEBIRD BIO (US) and EUREKA THERAPEUTICS (US).

5.4.2 Recent years: 2019-2023

In the Top 5 of CAR-T applicants (companies and academics) we find: the UNIVERSITY OF PENNSYLVANIA (US), NOVARTIS (**CH**), JUNO THERAPEUTIS (US), AUTOLUS (US) and HOPE CITY (US). In the Top 5 of CAR-T companies we have: JUNO THERAPEUTIS (US), NOVARTIS (**CH**), AUTOLUS (US), CELECTIS (**FR**) and CRISPR THERAPEUTICS (**CH**). NOVARTIS (**CH**) and CELLECTIS (**FR**) are collaborating with various companies & research institutions to advance their inventions in the field.

Belgian entities that have been filing in this domain the past few years are: CELYAD, UCB BIOPHARMA, plus some universities.

5.4.3 Valuable CAR T-cell patents

The EPO identified the following influential patents in the field of CAR-T technologies (patent insight report, data provided in the Powerpoint presentation) for the period 2000-20019:

Top 5 cited CAR T-cell patents, period 2000-2018:

- **WO2012079000** (UNIVERSITY OF PENNSYLVANIA, US) – 101 citations: relates to the use of chimeric antigen receptor-modified T cells to treat cancer.
- **WO2015031687** (FRED HUTCHINSON CANCER RESEARCH CENTER & SEATTLE CHILDREN'S HOSPITAL, US) – 39 citations: relates to methods and compositions for cellular immunotherapy.
- **WO2011059836** (DARTMOUTH COLLEGE, US) – 36 citations: relates T cell receptor-deficient T cell compositions.
- **WO2014153270** (NOVARTIS & UNIVERSITY OF PENNSYLVANIA, US) – 29 citations: relates to the treatment of cancer using humanized anti-cd19 chimeric antigen receptor.
- **WO2015142675** (NOVARTIS & UNIVERSITY OF PENNSYLVANIA, US) – 27 citations: relates to the treatment of cancer using chimeric antigen receptor.

  The patent from the UNIVERSITY OF PENNSYLVANIA is not only the one with the most family extensions but also the most cited, followed by a patent that is in co-ownership from the FRED HUTCHINSON CANCER RESEARCH CENTER & SEATTLE CHILDRENS HOSPITAL, both US.

Top 5 CAR T-cell patents with most family members, period 2000-2018:

- **WO2012079000** (UNIVERSITY OF PENNSYLVANIA, US) – > 60 family members: relates to the use of chimeric antigen receptor-modified T cells to treat cancer.
- **WO2015157386** (UNIVERSITY OF WASHINGTON & SEATTLE CHILDRENS HOSPITAL, US) – ~60 family members: relates to the production of engineered t-cells by sleeping beaty transposon coupled with methotrexate selection.

- **WO2015075468** (UNIVERSITY COLLEGE LONDON, UK) – ~30 family members: relates to cells which co-express two different chimeric antigen receptors (CAR) at the cell surface.
- **WO2013176916** (CELLECTIS, **FR**) – ~30 family members: relates to the use of pre t alpha and its functional variants for expanding tcr alpha deficient t cells.
- **WO2011119979** (MEMORIAL SLOAN-KENTERING, US) – ~25 family members: relates to muc16 antibodies and their use

Top 5 patents with most family members, that means more than one application for the same invention filed with different patent authorities. This is an important indicator for the value of the patents since the applicant is willing to absorb the corresponding high cost of patenting in multiple countries.

We identified the following as valuable, for the period 2019-2023:

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
US9944702B2	67	03/01/2019	15	7
WO2019030240A1	67	14/02/2019	19	6
US2020055948A1	67	20/02/2020	3	16
US2019048085A1	65	14/02/2019	27	4
US2019169637A1	65	06/06/2019	12	7

Table 13: Most valuable CAR-T patents that published in the period 2019-2023[38]

- **US9944702B2** (CELLECTIS, **FR**) relates to d33 specific chimeric antigen receptors for cancer immunotherapy
- **WO2019030240A1** (NBE-THERAPEUTICS, **CH**) relates to antibodies binding to a linear human cs1 epitope
- **US2020055948A1** (NOVARTIS, **CH**) relates to cells expressing a bcma-targeting chimeric antigen receptor, and combination therapy with a gamma secretase inhibitor
- **US2019048085A1** (CELL MEDICA SWITZERLAND, **CH**) relates to modified cells for immunotherapy
- **US2019169637A1** (JULIUS MAXIMILANS UNIVERSITY OF WURTZBURG, **DE**) relates to a method for high level and stable gene transfer in lymphocytes

The top 5 of valuable CAR T-cell patents in the period 2019-2023 is dominated by Europe. Figure 13 below shows the impact of recently filed patents in this domain. Though young, they are being picked up and cited by others quickly. Plus, recently filed patents are rolled out widely (evident from the Large Sizes of the patent families, Lower right of the figure: large circles).

[38] Family member published in 2019-2023, though some are derived from earlier filed international patent applications

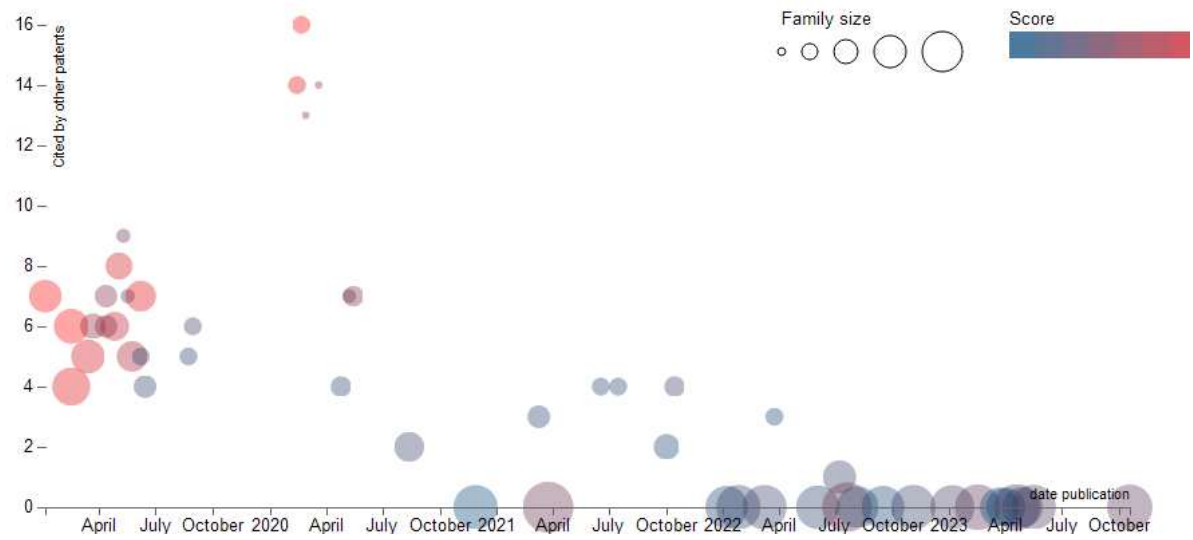

Figure 13: Importance of recently filed CAR T-Cell patents based on Recency, Family Size and Forward Citations Size (period 2019-2023)

5.5 CRISPR TECHNOLOGIES

It is also worth looking at CRISPR[39] technologies, as an important technology within Cell and Gene Therapies (CGT), as this technology can be considered as a break through technology that was rapidly picked up by many. For CRISPR technologies, a separate patent dataset was created and analysed.

In 2012, Jennifer Doudna from the University of California (US) & Emmanuelle Charpentier from the Max-Planck Institute (**DE**) published a ground breaking article on the re-engineering of the CRISPR-Cas9 endonuclease into a workable single stranded RNA compound. This contribution to science was so significant that it was recognized by the **Nobel Prize** in Chemistry in 2020[40].

- CRISPR (which stands for "Clustered Regularly Interspaced Short Palindromic Repeats") is a family of DNA sequences that are found in the genomes of prokaryotic organisms (bacteria and archaea). Cas9 (or "CRISPR-associated protein 9") is an endonuclease that uses CRISPR sequences as a guide to recognize & open up specific strands of DNA that are complementary to the CRISPR sequence.
- CRISPR-Cas technology is a powerful gene editing technology that allows precise modification of DNA sequences, enabling the correction of genetic mutations or the targeted disruption of disease-causing genes.

5.5.1 Overall: 2000-2023

CRISPR-Cas patenting took off as from 2014-2015 and has been increasing ever since. China is by far the most active player in this field, followed by the US and then Europe and Korea. The percentage of international filings in this field is lower than for other technologies discussed so far, perhaps due to the high percentage of Chinese applicants that only file in their home country. Chinese applicants

[39] CRISPR: acronym for "Clustered Regularly Interspaced Short Palindromic Repeats"

[40] *Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E (August 2012). "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity". Science. **337** (6096): 816–821*

often file 1 patent only per invention. When we look at top filing applicants & companies, then we see that these lists are dominated by the US.

Top 10 CRISPR applicants (companies and academics) are: MASSACHUSETTS INST TECHNOLOGY (US), BROAD INST INC (US), HARVARD COLLEGE (US), UNIVERSITY OF CALIFORNIA (US), EDITAS MEDICINE (US), MASSACHUSETTS GEN HOSPITAL (US), UNIVERSITY OF DUKE (US), UNIVERSITY OF TEXAS (US) and CARIBOU BIOSCIENCES (US).

Top 10 CRISPR companies are: BROAD INST INC (US), EDITAS MEDICINE (US), PINOBNEER HI BRED (US), CARIBOU BIOSCIENCES (US), REGENERON PHARMA (US), PAIRWISE PLANTS SERVICES (US), EMENDOBIO (US), ARBOR BIOTECHNOLOGIES (US), INTEGRATED DNA TECH (US) and SCRIBE THERAPEUTICS (US).

5.5.2 Recent years: 2019-2023

In the Top 5 of CRISPR applicants (companies and academics) we find: the MASSACHUSETTS INSTITUTE OF TECHNOLOGY (US) & BROAD INSTITUTE (US): both top filers, and then HARVARD COLLEGE (US), the UNIVERSITY OF CALIFORNIA (US) and EDITAS MEDICINE (US). Only US entities in this list.

In the Top 5 of CRISPR companies we have: BROAD INSTITUTE (US): top filer, and then EDITAS MEDICINE (US), CARIBOU BIOSCIENCES (US), EMENDOBIO (US), INTEGRATED DNA TECHNIQUES (US) and CRISPR THERAPEUTICS (**CH**). Hence, one (1) European company in this Top 5: CRISPR THERAPEUTICS, as Swiss company. The other companies in this list are US-based.

Exa-cel, which belongs to VERTEX PHARMACEUTICALS & CRISPR THERAPEUTICS, has just been approved for the treatment of sickle cell disease[41]. It is to be seen if a patent war will follow after this approval, as we have for mRNA-based vaccines against SARS-CoV-2.

A Belgian company that has been filing in this domain the past few years is UCB BIOPHARMA.

5.5.3 Valuable CRISPR-Cas patents

We identified the following as valuable, in the period 2000-2018:

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
WO2014093718A1	69	19/06/2014	20	291
WO2014093694A1	64	19/06/2014	7	373
WO2018119447A2	63	28/06/2018	14	100
WO2014124226A1	61	14/08/2014	11	158
WO2014204727A1	59	24/12/2014	5	257

Table 14: Most valuable CRISPR patents that published in the period 2014-2018

- **WO2014093718A1** (BROAD INSTITUTE & MASSACHUSETTS INSTITUTE OF TECHNOLOGY, US) relates to methods and systems for identifying target sequences for Cas enzymes or CRISPR-Cas systems for target sequences

[41] FDA approval December 2023, UK regulatory approval November 2023

- **WO2014093694A1** (BROAD INSTITUTE, MASSACHUSETTS INSTITUTE OF TECHNOLOGY & HARVARD COLLEGE, US) relates to CRISPR-Cas nickase systems for sequence manipulation in eukaryotes
- **WO2018119447A2** (10X GENOMICS, US) relates to methods and systems for processing polynucleotides
- **WO2014124226A1** (ROCKEFELLER UNIVERSITY, US) relates to materials and methods for selectively reducing the amount of antibiotic resistant and/or virulent bacteria in a mixed bacteria population
- **WO2014204727A1** (BROAD INSTITUTE & MASSACHUSETTS INSTITUTE OF TECHNOLOGY, US) relates to functional genomics using CRISPR-Cas systems

We identified the following as valuable, in the period 2019-2023:

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
JP2023123755A	60	05/09/2023	204	0
JP2022115994A	52	09/08/2022	94	0
JP2023061983A	51	02/05/2023	69	0
JP2022106717A	49	20/07/2022	62	0

Table 15: Most valuable CRISPR patents that published in the period 2019-2023[42]

- **JP2023123755A** (UNIVERSITY OF WIEN & UNIVERSITY OF CALIFORNIA, **AT** & US) relates to methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription
- **JP2022115994A** (SIGMA ALDRICH, US) relates to CRISPR-based genome modification and regulation
- **JP2023061983A** (GENERAL HOSPITAL, US) relates to RNA-guided targeting of genomic & epigenomic regulatory proteins to specific genomic loci
- **JP2022106717A** (SNIPR TECHNOLOGIES, US) relates to altering microbial populations and modifying microbiota

5.6 TISSUE ENGINEERING

Another separate patent dataset was created for Tissue Engineering Products (TEPs) containing ~2,500 patents on this topic to study the overall field, top technologies and some recent trends. As mentioned before, there is less patenting activity around Tissue Engineering (compared to Cell and Gene Therapies, CGT). Yet the amount of patents on this topic is not non-substantial.

The terms "tissue engineering" and "regenerative medicine"[43] have become largely interchangeable, as the field hopes to focus on cures instead of treatments for complex, often chronic, diseases.

- Tissue Engineering combines cells, scaffolds & biologically active molecules to create functional tissues for replacement or regeneration. It aims to restore damaged tissues or organs.

[42] Family member published in 2019-2023, though some are derived from earlier filed international patent applications
[43] Though Regenerative Medicine is a wider field that includes Tissue Engineering & Self Healing

Currently, tissue engineering plays a relatively small role in patient treatment. Yet, the field of tissue engineering (TE) has made tremendous progress in the past decade and is still evolving. In particular the use of existing scaffolds holds great promise as human tissue discarded during surgery can be used therefore. When combining it with a patient's own cells to make customized organs, one can reduce or overcome donor organ shortages & morbidity due to organ rejection[44].

5.6.1 Overall: 2000-2023

Tissue Engineering patenting took off as from 1996 (~40) and increased over the years till 2012 (~140) after which the activity dropped a bit. It took off again in 2020, with more first patent publications in 2023 (~170) already than in 2022. The US is by far the most active player in this field, followed by Europe and then Japan, China and Korea. The percentage of international filings in this field is high. In Europe, big filers are Germany, Switzerland, the UK and France.

Top 10 TEP applicants (companies and academics) are: the UNIVERSITY OF CALIFORNIA (US), the MASSACHUSETTS INSTITUTE OF TECHNOLOGY (US), the CENTRE NAT RECH SCIENT (**FR**), the GENETICS INSTITUTE (US), HARVARD COLLEGE (US), the CHILDRENS MEDICAL CENTER (US), the UNIVERSITY OF TEXAS (US), the INST NAT SANTE RECH MED (**FR**), SMITH & NEPHEW (US) and the UNIVERSITY LELAND STANFORD JUNIOR (US). The top 10 list of applicants is dominated by academics, most US-based, but two (2) are based in France.

Top 10 TEP companies are: SMITH & NEPHEW (US), HUMAN GENOME SCIENCES (US), DEPUY MITEK (US), ETHICON (US), CHONGQING RUNZE PHARMACEUTICAL (CN), ALLERGAN (US), REGENETECH (US), SYNTHESIS (**DE**), WARSAW ORTHOPEDIC (US), the MUSCULOSKELETAL TRANSPLANT FOUNDATION (US) and ONO PHARMACEUTICAL (JP). Mainly US companies in this list, but also one (1) German, one (1) Chinese and one (1) Japanese company: SYNTHESIS, CHONGQING RUNZE PHARMACEUTICAL and ONO PHARMACEUTICAL respectively.

Belgian entities that have been filing in this domain: NOVADIP BIOSCIENCES, REGENESYS, plus various universities and research institutions.

5.6.2 Recent years: 2019-2023

Top 10 of recent TEP applicants (companies and academics) are listed in Table 16. Besides US players, we have two (2) French Research centra and two (2) Asian Universities, one from China and one from Japan: the UNIVERSITY OF SICHUAN and of TOHOKU.

Top 10 of recent TEP companies (companies and academics) are: the MUSCULOSKELETAL TRANSPLANT FOUNDATION (US), HARVARD COLLEGE (US), MEDOS INTERNATIONAL (**CH**), LIFECELL (US), DSM IP ASSETS (**NL**), STEMRIN (US), TELA BIO (US), GEISTLICH PHARMA (**CH**), the ASSOCIATION FOR THE ADVANCEMENT OF TISSUE ENGINEERING AND CELL BASED TECHOLOGY (**PT**), LIFE SCIENCE INST PROSIDYAN (US), ACERA SURGICAL (US) and ARTHREX (US). Four (4) European companies in this list, two (2) from Switzerland, one (1) from the Netherland and one (1) from Portugal: MEDOS INTERNATIONAL, GEISTLICH PHARMA, DSM IP ASSETS and the ASSOCIATION FOR THE ADVANCEMENT OF TISSUE ENGINEERING AND CELL BASED TECHOLOGY.

[44] Tissue Engineering and Regenerative Medicine (nih.gov)

Top	Applicant	Country	No. of patent families
1	UNIV CALIFORNIA	US	12
2	CENTRE NAT RECH SCIENT	**FR**	11
3	UNIV JOHNS HOPKINS	US	10
4	HARVARD COLLEGE	US	10
5	MUSCULOSKELETAL TRANSPLANT FOUNDATION	US	8
6	UNIV SICHUAN	CN	8
7	UNIV LELAND STANFORD JUNIOR	US	8
8	UNIV PITTSBURGH COMMONWEALTH SYS HIGHER EDUCATION	US	7
9	INST NAT SANTE RECH MED	**FR**	7
10	UNIV TOHOKU	JP	6

Table 16: Top 10 TEP applicants (companies + academics) in the period 2019-2023

5.6.3 Valuable TEP patents

Using a patent value analysis, TEP[45] patents were scored based on the size of the patent family and on the number of forward patent citations. A high score is obtained if the Family Size is large, which would be an indicator of the market significance of the patent, and if the Number of Forward Citations is large, which is an indicator of the significance of the technology described. From the analysis done, the patents with a high value score as well as patents that have a large number of citations were selected and listed in Table 10 below. Figure 14 shows which recent patents are believed to have high potential, in view of the family size.

Overall TEP scores are lower than for GCT[46] patents, and in general we have less patents with a high Forward Citation Size. Yet again, recent inventions are rolled out in a high number of countries (Large Family Sizes) which means that the applicants see a lot of potential and economic interest in their developments (lower right of the figure, large circles). In general, the size of Patent Families is large.

[45] TEP: Tissue Engineered Products
[46] GCT : Gene and Cell Therapy

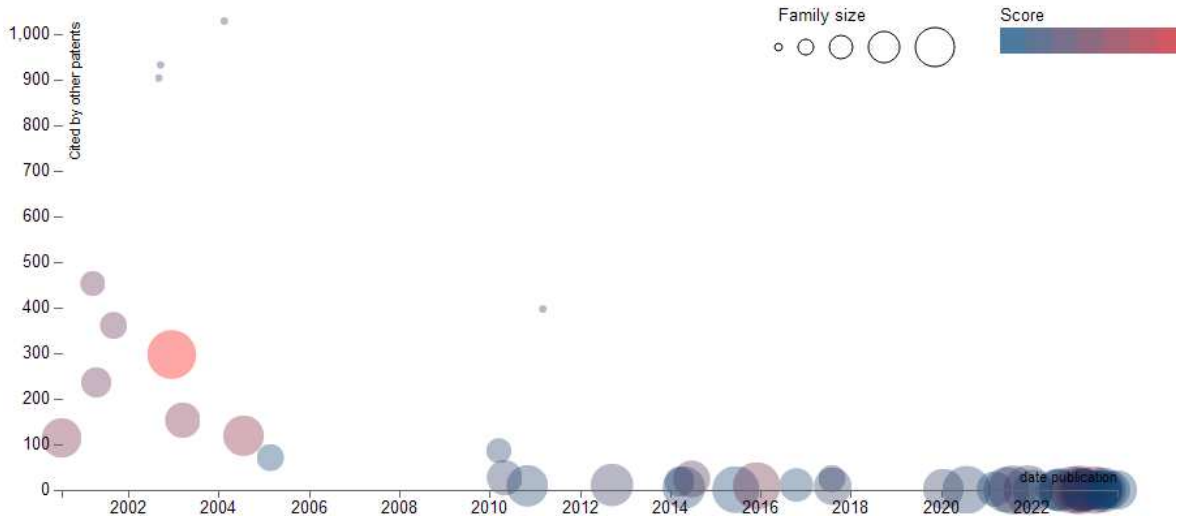

Figure 14: Importance of recently filed TEP patents based on Recency, Family Size and Forward Citations Size (period 2012-2023)

We identified the following as valuable, in the period 2002-2023:

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
WO02098443A2	68	12 Dec 2002	45	297
US2004138758A1	57	15 Jul 2004	21	119
US6530958B1	55	11 Mar 2003	13	153
US6083904A	55	04 Jul 2000	19	114
RU2015114990A	54	27 Nov 2015	39	9

Table 17: Most valuable TEP patents that published in the period 2002-2018

- **WO2007024708A2** (CUREVAC, **DE**) relates to pharmaceutical compositions comprising a modified mRNA that is stabilized by sequence modifications and that is optimized for translation. It is useful for tissue engineering
- **US2004138758A1** (KENSEY NASH, US) relates to implantable material for deployment in select locations or select tissue for tissue regeneration is disclosed. The implant comprises collagen, ceramics, and or other bio-resorbable materials or additives, where the implant may also be used for therapy delivery
- **US6530958B1** (APRECIA PHARMACEUTICS, original applicant: MASSACHUSETTS INSTITUTE OF TECHNOLOGY, US) relates to solid free-form (SSF) techniques for making medical devices for implantation using polymers or polymer/inorganic composites and using computer aided design. Examples of SFF methods include stereo-lithography (SLA), selective laser sintering (SLS), ballistic particle manufacturing (BPM), fusion deposition modeling (FDM), and three dimensional printing (3DP)
- **US6083904A** (YALE UNIVERSITY, US) relates to therapeutic and diagnostic methods and compositions based on Notch proteins and nucleic acids. The therapeutic can be administered to treat a nervous system disorder or to promote tissue regeneration and repair

- **RU2015114990A** (SIWA, US) relates to materials and methods for removing cells which interfere with regenerative processes. The apparatuses, compositions and methods selectively kill partially functional and/or non-functional cells versus functional cells while protecting functional proliferative cells to the extent that, upon removal of the killed cells by disintegration or scavenging, functional cells replace the partially- or non-functional cells

We identified the following as valuable, in the period 2019-2023:

Publication No.	Score	Publication Date	Size Family	Size Forward Citations
CN115624569A	53	20 Jan 2023	45	0
AU2023202857A1	52	25 May 2023	40	0
JP2023106525A	50	01 Aug 2023	32	0
US2022378847A1	50	01 Dec 2022	38	0
EP3915367A1	50	01 Dec 2021	47	0

Table 18: Most valuable CRISPR patents that published in the period 2019-2023[47]

- **CN115624569A** (**ANTOINE TURZI**, PRIVATE INVENTOR, **CH**) relates to materials and methods for preparing wound repair agents, tubes and devices
- **AU2023202857A1** (POLARITY TE, US) provides for constructs of micro-aggregate multicellular, minimally polarized grafts containing Leucine-rich repeat-containing G-protein coupled Receptor (LGR) expressing cells for wound therapy applications, tissue engineering, cell therapy applications etc.
- **JP2023106525A** (OSAKA UNIVERSITY, JP) relates to implantable material for deployment in select locations or select tissue for tissue regeneration is disclosed. The implant comprises collagen, ceramics, and or other bio-resorbable materials or additives, where the implant may also be used for therapy delivery
- **US2022378847A1** (PLURI BIOTECH, IL[48]) relates to treating ischemia by providing adherent cells of a placenta or adipose tissue
- **EP3915367A1** (SAMUMED, US) relates to compounds which activate Wnt/β-catenin signaling and thus treats or prevents diseases related to signal transduction, such as osteoporosis; wound healing; traumatic brain injuries related to the differentiation and development of the central nervous system comprising Parkinson's disease, Alzheimer's disease, epilepsy, schizophrenia; eye diseases; diseases related to differentiation and growth of stem cell, comprising hair loss; hematopoiesis related diseases & tissue regeneration related diseases

5.6.4 New trends in Tissue Engineering

New trends and technologies that are positively impacting this field include smart biomaterials, new stem cell sources, advanced three-dimensional bioprinting, vascular engineering, organoids, organ-on-chip, advanced bioreactors and microfluidics-based physiological platforms[49]. All of these materials and processes are patent protected.

[47] Family member published in 2019-2023, though some are derived from earlier filed international patent applications
[48] IL : Israel
[49] Tissue engineering: current status and future perspectives - ScienceDirect, analysis of the patent dataset (period 2013-2023)

What we further see is the introduction of nanotechnology and the adaptation of scaffold surface to enhance tissue growth and cell adhesions. Computer modelling is used to make solid free-forms and bioprinting with decellularized materials is made possible.

6 Conclusion

Advanced Therapy Medicinal Products (ATMPs) are a class of innovative medical products that encompass (I) Gene Therapy, (II) Cell Therapy, and (III) Tissue Engineering. These therapies are designed to treat, intercept, prevent or diagnose diseases by intervening in the body's cellular and genetic makeup. ATMPs represent a new era in medicine, offering cutting-edge approaches to address unmet medical needs.

This report provides an analysis of the innovative activities in the field of ATMPs by a review of the patent activity and of the recent patent publications on this topic.

Technology Watch on ATMPs in a nutshell
– focus is on Advanced Therapy Medicinal Products (ATMPs)
– number of inventions in the field of ATMPs has **tripled** over the last decade
– upswing in filing numbers started in the **2000s**
– steep increase in filing numbers since **2020**
– high proportion of **international patent applications**, suggesting high economic expectations with regard to the technologies in question and multinational commercialization strategy
– most active applicants in the field of ATMPs are companies and academics from the **United States and Europe**
– key players in the field of ATMPs are **academic/research centres and some small and medium-sized enterprises**
– key companies are based **in the US and in Europe**
– not only big pharma but also **small and medium-sized enterprises have ATMPs on the market**, showing the importance of biotech start-ups and scale-ups in the ATMP ecosystem.
– **Belgium takes position 15** in the international ranking of patent filings, and continues to build and show expertise around ATMPs
– Expected, as **Belgium is widely known to have a rich and dynamic ATMP sector**

A summary for the major subclasses and some important trends is provided in the Next Page.
We see that Europe is one of the main players in this field next to the US.

What we further see is that techniques of one field are used in another field & that overall major advancements have been made. This is an area with a lot of potential and a huge unmet medical need in Europe.

GENE THERAPY

- steep increase in filing numbers since **2020**
- key players are based **in the US and in Europe**

CELL THERAPY

- steep increase in filing numbers since **2019**
- key players are primarily based **in the US, some in Europe**

TISSUE ENGINEERING

- less patent applications in this field
- key players are based **in the US, then follow Europe, China, Japan and Korea**

mRNA technologies (with focus on mRNA vaccines)

- dominated by US & European players, most patents are being filed by academics
- various European players active the past 5 years

CAR T-cell immunotherapy

- dominated by US & European players, some Chinese players too
- various European players active the past 5 years

CRISPR-Cas technologies

- China files most of the patents but the top 10 is dominated by US & European players
- no major players based in Europe the past 5 years

ANNEX I: REFERENCES

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ANNEX II: LIST OF ACRONYMS AND ABBREVIATIONS

- ARM: Advanced Regenerative Medicines
- AT: Advanced Therapies
- ATMP: Advanced Therapy Medicinal Products
- CAR-NK: Chimeric antigen receptor Natural Killer-cells
- CAR-T: Chimeric antigen receptor T-cells
- CBIO: Cell-Based Immunology Therapy
- CDMO: Contract Development and Manufacturing Organization
- CGT: Cell and Gene Therapies
- CPC: Cooperative Patent Classification
- CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
- CRDO: Contract Research and Development Organization
- CRO: Contract Research Organization
- CTMP: Cell Therapy Medicinal Products
- EMA: European Medicine Agency
- EPO: European Patent Office
- GMCT: Gene-Modified Cells Therapy
- GTMP: Gene Therapy Medicinal Products
- IPC: International Patent Classification
- iPSC: Induced pluripotent stem cell
- LNP: Lipid nanoparticle
- PDNA: Plasmid DNA
- SMA: Spinal Muscular Atrophy
- TEP: Tissue Engineered Products
- USPTO: US Patent and Trademark Office
- WIPO: World Intellectual Property Office

ANNEX III: SEARCH STRATEGY AND DATASETS

In order to explore the ATMP patent landscape, a number of different patent datasets were created using the tool "PatentInspiration".

Three different datasets were created for (I) Gene Therapy, (II) Cell Therapy and (III) Tissue Engineering looking for particular keywords in titles and abstracts (ti, ab). These datasets were then combined into one single dataset related to Advanced Therapy Medicinal Products in general (ti, ab).

This led to a large dataset of over 18,000 containing patent families from over the past 20 years. This large dataset was then further cleaned out to remove irrelevant patents. A final dataset of ~ 13,000 patent families was maintained and analysed.

Text pattern analysis in title, abstract, claims and description and claims (ti, ab, cl, d) was used to gain more in-depth insights.

Set 1: Gene therapy (~3,500 patents)

- Patents with ("Gene* therap* medicin*" OR "gene* therap*" OR "therapeutic transgene*" OR "therapeutic nucleic acid*" OR "gene* vaccination" OR "therapeutic gene*" OR "gene* treatment" OR "anti?sense therapy" OR "anti?sense gene therapy" OR "gene* vaccinat*" OR "somatic gene therap*" OR "cellular transfect*" OR "treating genetic disease*" OR "intracellular immunization*" OR "protein therap*" OR "transfecting tumor cell*" OR "therap* nucleot* sequence*" OR "somatic gene transfer*" OR "gene replac* therap*" OR "anti?sense oligonucleot* therap*" OR "gene* vaccinat*" OR "therap* sequence*")
- In combination with the following CPC classes (top20): C12N15/00, A61K48/00, A61K38/00, A61P35/00, C12N5/00, A61K39/00, C12N2750/00, C07K2319/00, A61P43/00, A61K31/00, A61K9/00, C12N9/00, C12N2830/00, C12N2710/00, C07K16/00, C12N2740/00
- Excluded: plant, dental and veterinary applications
- Settings: 1 patent per family, those with empty title or abstract are hidden, period covered: 2000-2023

Set 2: Cell therapy (~3,000 patents)

- Patents with ("somatic?cell therap* medic*" OR "cell* therap*" OR "cell?based therap*" OR "cell replac* therap*" OR "cell* transplant*" OR "cell immunotherap*" OR "stem cell graft*" OR "growth factor* therap*" OR "genetically?altered cell*" OR "regenerat* medic*" OR "hematopoietic reconstitution" OR "regenerat* therap*" OR "cell replac*" OR "therap* cell*" OR "dc therap*" OR "cellul* immunotherap*" OR "transplant* medic*" OR "hsc transplant*")
- In combination with the following CPC classes (top20): A61K35/00, C12N5/00, A61P35/00, A61K39/00, C07K14/00, C07K16/00, A61K38/00, A61K31/00, C07K2317/00, A61K45/00, A61P37/00, C12N2501/00, C07K2319/00, C12N15/00, A61K2300/00, G01N33/00, C12N2510/00, A61P43/00, A61K9/00
- Excluded: plant, dental and veterinary applications
- Settings: 1 patent per family, those with empty title or abstract are hidden, period covered: 2000-2023

Set 3: Tissue engineering (~2,300 patents)

- Patents with ("Tissue?engineer* medic*" OR "tissue?engineer*" OR "tissue reconstruct*" OR "tissue regenerat*" OR "regenerat* medic*" OR "artificial tissue*" OR "tissue replac*" OR "tissue generat*" OR "tissue regen*" OR "tissue substit*" OR "engineer* tissue*" OR "tissue repair*" OR "bone repair" OR "skin replacem*" OR "artificial organ*" OR "cartilage repair*" OR "bioartificial organ*" OR "organ regener*" OR "artificial articular cartilage" OR "cartilage substit*" OR "artificial cartilage" OR "repair* tissue*" OR " tissue repair*" OR "cartilage replac*")
- In combination with the following CPC classes (top20): A61L27/00, C12N5/00, A61F2/00, A61K35/00, A61L2431/00, A61K38/00, A61B17/00, A61K31/00, A61L2300/00, A61K9/00, A61P19/00, A61P17/00, C07K14/00, C12N2533/00, A61P43/00, A61L31/00, A61K47/00, A61P9/00, C12N2501/00
- Excluded: plant, dental and veterinary applications
- Settings: 1 patent per family, those with empty title or abstract are hidden, period covered: 2000-2023

Set 4: mRNA technologies (~3,000 patents)

- Subset of the ATMP full patent set of 13,000 Patents
- Limitation: Patents with ("mRNA technol" or "mRNA vaccin*")
- In combination with the following CPC classes (top20): C12N15/00, A61K48/00, A61K2300/00, A61K45/00, A61P43, A61K38/00, A61K35/00, C12N2510/00, C12N2750/00, A61P29/00, A61P25/00
- Excluded: plant, dental and veterinary applications
- Settings: 1 patent per family, those with empty title or abstract are hidden, period covered: 2000-2023

Set 5: CAR T-Cell immunotherapy (~2,000 patents)

- Subset of the ATMP full patent set of 13,000 Patents
- Limitation: Patents with ("car?t" or "chimeric antigen receptor*")
- In combination with the following CPC classes (top20): C12N15/00, C12N2310/00, C12N9/00
- Excluded: plant, dental and veterinary applications
- Settings: 1 patent per family, those with empty title or abstract are hidden, period covered: 2000-2023

Set 6: CRISPR-Cas technologies (~1,500 patents)

- Subset of the ATMP full patent set of 13,000 Patents
- Limitation: Patents with ("CRISPR" or "CRISPR?Cas")
- In combination with the following CPC classes (top20): C07K2319/03, C07K2317/622, C07K2317/55, C07K14
- Excluded: plant, dental and veterinary applications
- Settings: 1 patent per family, those with empty title or abstract are hidden, period covered: 2000-2023

ANNEX IV: BELGIAN COMPANIES ACTIVE IN THE ATMP FIELD

Belgium has an extended list of companies that are active in the field of Advanced Therapy Medicinal Products (ATMPs). Ecosystems have developed and competitiveness clusters are being formed to consolidate and maintain a leading position in Europe, that requires strategic efforts, adequate means and collaborative decision-making (biowin.org, 2024)[50]. The ATMP PIT[51] in Walloon receives 81 million in funding the coming years, of which 60% comes from the government and 40% from private funds of companies.

Biotech & Biopharma companies involved:

Company	Location	Activities
Allegro	Antwerp, Flanders	Tissue Engineering, biocompatible nanotechnology for the regeneration of human cells and tissue
AnaBioTec	Evergem, Flanders	Cell & Gene therapy, analytical service provider for amongst others cell & gene therapy solutions
Artialis Group	Liege, Flanders	General, testing services for ATMPs
Beta Cell	Asse, Flanders	Cell therapy, treating diabetes with encapsulated pancreatic cells
BioInx	Ghent, Flanders	General, 3D bioprinting inks for instance for organ-on-chip
Biosenic (ex-Bone Therapeutics)	Gosselies, Wallonia	Cell therapy, orthopaedics and bone diseases
Catalent	Gosselies, Wallonia	Cell & Gene therapy, commercial scale production
Cellistic	Gosselies, Wallonia	Cell therapy, iPSC[52]-based platforms that accelerate the development and manufacture of your cell therapies
Cell-Matters[53]	Liège, Wallonia	Cell therapy, End-to-end cryo services
Celyad (Cardio3 Biosciences)	Gosselies, Wallonia	Revolutionary technologies for chimeric antigen receptor (CAR) T-cells
Curevac	Ottignies, Wallonia	Cell & Gene therapy, mRNA therapeutic solutions
eTheRNA Immunotherapies	Niel, Flanders	Cell & Gene therapy, Lipid nanoparticle (LNP) formulation and RNA chemistry
Eurofins BioPharma Product Testing	Nazareth, Flanders	General, platform methods to test ATMPs
Eurogentec/Kaneka	Liège, Wallonia	Cell & Gene therapy, GMP biomanufacturing of mRNA based medicines (mRNA vaccines)
Exo Biologics	Liège, Wallonia	Cell therapy, next generation of nanomedicine therapy using Exosomes Extracellular Vesicles (EVs)
Exothera (Univercells Group)	Jumet, Wallonia	Gene therapy, viral vector and nucleic acid development and manufacturing
Galapagos (acquired CellPoint & AboundBio)	Mechelen, Flanders	Cell therapy, CAR-T manufacturing
Genflow Biosciences Belgium	Charleroi, Wallonia	Cell & Gene therapy, anti-aging and mitochondrial dysfunctions
GSK Biologics	Wavre-Rixensart, Wallonia	Cell & Gene therapy, mRNA vaccines (with Curevac)

[50] The ATMP-PIT portfolio, biowin.org, 2024
[51] PIT: Partnership in Technology
[52] iPSC: Induced pluripotent stem cells
[53] Ex-Vitricell, now part of Cryoport. Originally a spin-off of the University of Liège

Henogen (now Thermo Fischer)	Charleroi, Wallonia	Tissue Engineering, tissue growth scaffolds

Company	Location	Activities
Janssen Pharmaceutica, part of J&J (with Legend Biotech)[54]	Ghent, Flanders	Cell therapy, CAR-T manufacturing
Legend Biotech (with J&J)[49]	Ghent, Flanders	Cell therapy, CAR-T manufacturing
MyCellHub	Liege, Wallonia	General, support platforms for cell & gene therapy (automation)
Ncardia (now Cellistic)	Gosselies, Wallonia	Cell & Gene therapy, integrated iPSC[52]-based drug discovery platform
Neurodip Biosciences	Gosselies, Wallonia	Tissue engineering, bone and tissue regenerative medicine
OncoDNA	Gosselies	Cell & Gene therapy, mRNA vaccines (with Myneo)
Orgenesis Belgium	Aye, Wallonia	Cell & Gene therapy, personalized cell & gene therapy
PDC*line Pharma	Liège, Wallonia	Cell therapy, off-the-shelf cancer immunotherapies based on a proprietary Plasmacytoid Dendritic Cell line (PDC*line) pre-loaded with peptides that are derived from target tumor antigens
Pfizer	Puurs, Flanders	Cell therapy, mRNA vaccines
Precigen Actobio	Ghent, Flanders	Cell & Gene therapy, multifunctional gene and cell therapy candidates for combination strategies
Promethera biosciences (now Cellaïon)	Gosselies, Flanders	Tissue engineering, repair of tissues and regeneration of organs using cell signaling technology
Quality Assistance	Thuin, Wallonia	Cell & Gene therapy, QC testing for RNA
Quantoom Biosciences	Nivelles, Wallonia	Cell & Gene therapy, DNA and RNA production (incl. mRNA)
Regenesys	Heverlee, Flanders	Cell therapy, "off-the-shelf" stem cell products
RevaTis	Liège, Wallonia	Regenerative Medicine and Cell therapy, multipotent adult mesenchymal stem cells from muscle biopsy, GMP production
Rheavita	Ghent, Flanders	Cell & Gene therapy, manufacturing technology for amongst others mRNA, continuous freeze drying technology allowing GMP production
THERAtRAME	Liège, Wallonia	Cell & Gene therapy, first-in-class inhibitors of the tRNA epitranscriptomics to bring new perspectives to patients with untreatable cancer
Thermo Fischer	Seneffe, Wallonia	Cell & Gene therapy, adenovirus services
Tigenix (part of Takeda)	Leuven, Flanders	Cell therapy, uses allogeneic expanded adipose-derived stem cells (eASC) to treat bowel diseases
UCB Biopharma	Braine L'alleud, Wallonia	Cell & Gene therapy, focus on allergies and neurological disorders
Univercells	Wallonia	Cell & Gene therapy, biologics for cell and gene therapy
XomeXBio	Charleroi, Belgium	Cell therapy, unique microfluidic-chip-based solution of exosomes
Xpress Biologics	Herstal, Wallonia	Cell & Gene therapy, plasmid DNA for vaccines
Ziphius Vaccines	Merelbeke, Flanders	Cell & Gene therapy, self amplifying RNA (saRNA) vaccines and therapeutics

[54] first European state-of-the-art facilities for the production of CAR-T therapy (being built)

Services providers for ATMP, basically CDMO & CRO companies

- CDMO[55]: Catalent, Cell Matters, eTheRNA, Eurofins BioPharma Product Testing, Eurogentec/Kaneka, Exothera (Univercells Group), Thermo Fisher, Xpress Biologics
- CRDO[56]: Artialis Group
- CRO[57]: Quality Assistance

ATMP production investments by big (bio)pharma

- Catalent: Opens one of the World's Largest Commercial-Scale Cell Therapy Manufacturing Facilities at its European Center of Excellence for Cell Therapies in Gosselies, Belgium (2022)
- UCB biopharma: Is scaling up facility for Gene Therapies in Braine L'Alleud (2019)
- Other large biopharma companies with ATMP manufacturing activities:
    - J&J (Janssen) and Legend Biotech collaborate and build state-of-the art production facilities in Ghent for the production of CAR-T cells used in the fight against cancer (2021).
    - Pfizer invests 1,2 billion in the expansion of production capacity, the increase of cold storage possibilities and the expansion of packaging processes in Puurs (2022).

ATMP investments by the Belgian government

- RegMed XB: Flemish government invests €15M in RegMed XB for regenerative therapies (2024). RegMed XB brings together some 500 leading scientists at Dutch and Belgian universities and institutes and a range of companies in so-called "Moonshots".
- PDC*line Pharma and partners receive a €8.1M from Walloon region and Wallonia health cluster BioWin for personalized therapeutic vaccine project

[55] CDMO: Contract Development and Manufacturing Organization
[56] CRDO: Contract Research and Development Organization
[57] CRO: Contract Research Organization