leem
les entreprises
du médicament

Horizon Scanning Report

Which medicines will be used to treat us in tomorrow's world?

January 2025

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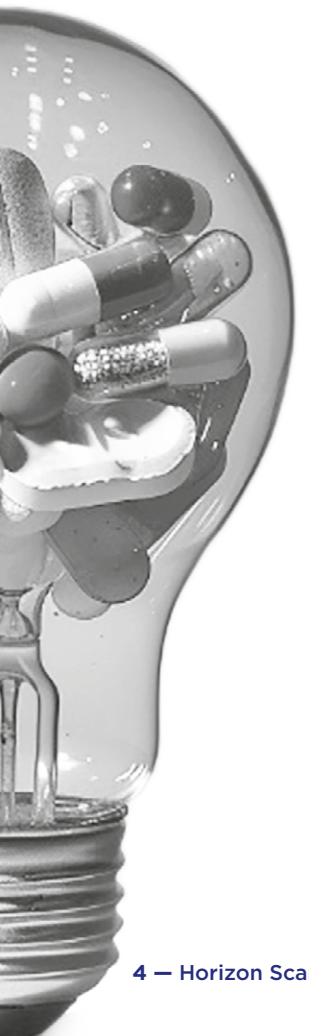
INTRODUCTION



Medicinal revolutions. From the era of antibiotics to today's new cancer treatments, **medical advances have radically reshaped the public health landscape and transformed the lives of patients**.

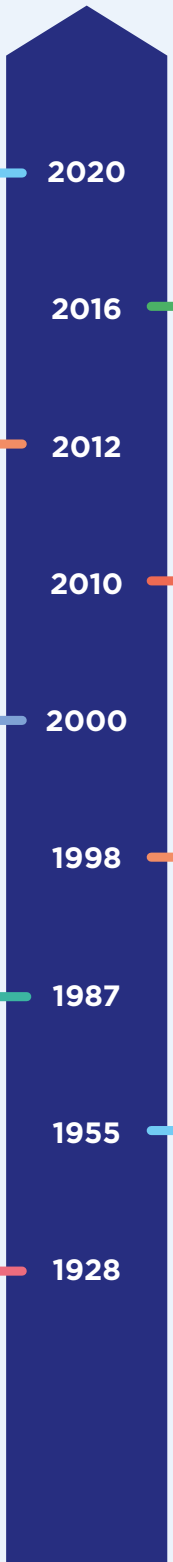
Rewind to the early 20th century. We are in the 1920s, and antibiotics are shattering certainties by making it possible to treat previously fatal bacterial infections like tuberculosis and pneumonia. Half a century later, the 1980s see the arrival of the antiretrovirals that have revolutionised the fight against HIV/AIDS.
Once considered a death sentence, this virus is now becoming a manageable chronic condition, offering patients an almost normal length of life expectancy.
Vaccines against diseases such as polio and, more recently COVID-19, are essential tools for large-scale prevention, and are profoundly changing the lives of millions of people worldwide.
We can also point to the tremendous advances made in treating cancers with targeted therapies, breakthroughs in haematology and the treatment of rare diseases...

Nevertheless, these victories should not distract attention from the many battles we have yet to wage against certain very aggressive cancers, diabetes and neurological diseases, including Alzheimer's.
To win those battles, the research arsenal is constantly being expanded with groundbreaking tools that have demonstrated their potential, including cell therapy and gene therapy.

The horizon of therapeutic progress appears boundless.
The challenge now is to ensure that everyone has the opportunity to benefit from these therapies and that our healthcare systems are capable of delivering them.
So greater visibility of future advances is essential if we are to successfully anticipate the likely costs and the conditions that will govern patient access.
Which is precisely the aim of our prospective report on innovation in medicines.

Focus on the key learnings to emerge from the study.
Medicines that have changed the lives of patients.

Medicines that have changed the lives of patients



2020 — **The first messenger RNA vaccines against COVID-19** pave the way for new applications in combatting other infectious diseases.

2016 — **Oral treatments for hepatitis C** deliver cure rates above 90%.

2012 — **The CRISPR genome-editing tool** is perfected, enabling direct modification of DNA.

2010 — The **first** therapeutic **cancer vaccine**.

2000 — Development of the **first immunotherapies**.

1998 — The **first** targeted **therapies in oncology**.

1987 — **AZT,** the **first antiretroviral** treatment for **HIV/AIDS**.

1955 — A **vaccine against poliomyelitis,** which once afflicted thousands of children worldwide.

1928 — **Alexander Fleming discovers penicillin,** opening up the **era of antibiotics** with the ability to treat fatal bacterial infections like tuberculosis, pneumonia and syphilis.

MEDICINES, A HIGHLY INNOVATIVE SECTOR

Every year, medical advances redefine the frontiers of medicine and prove themselves to be decisive turning points. Hepatitis C, once a chronic disease that was extremely challenging to cure, can now be eliminated in just a few weeks for 95% of patients, thanks to the revolutionary treatments, the first of which was approved in late 2016. More recently, there has been a giant leap forward in the treatment of cystic fibrosis. What was once a fatal disease is now, for the majority of patients, a manageable chronic condition controlled by a new therapy. And in recent months, the treatment to prevent bronchiolitis has considerably reduced the need for infant hospital admissions, providing relief for thousands of families.
Advances in gene therapy are now helping to treat rare genetic diseases such as spinal muscular atrophy by directly targeting the underlying causes at the molecular level.

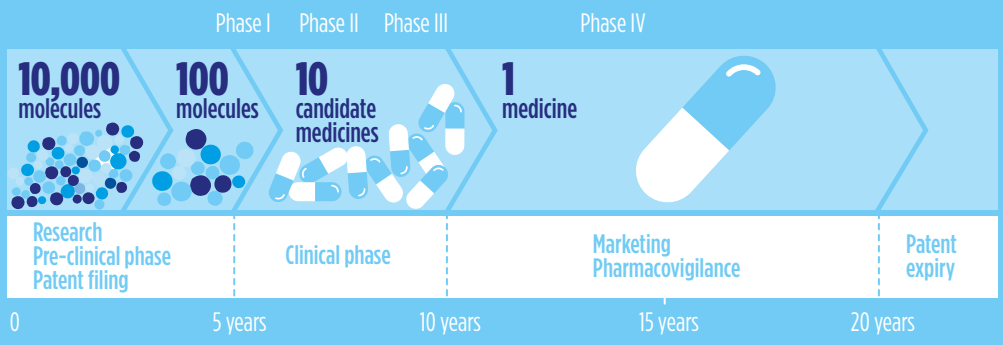
But we must never lose sight of the fact that all these innovations are the result of upstream research work on a massive scale. The new medicine development pathway is long, risky and costly, and involves three key stages:

- **Research**, during which thousands of molecules are subjected to a battery of tests to investigate their chemical and pharmacological properties and pinpoint those that could be of therapeutic value. The ultimate aim is to identify molecules which, based on discoveries resulting from fundamental research, could potentially meet a medical need, combat a disease or improve patient quality of life.

- **Pre-clinical trials** to select a molecule of potential therapeutic value that could be developed into a medicine. These tests are conducted on cells (*in vitro*) and animals (*in vivo*). They have two essential goals: to assess the safety, tolerability and efficacy of the new medicine across multiple models at different stages of development, and to determine the dosage to be administered to human patients in the first phase of clinical trials.

- **Clinical and pharmaceutical development** to test the candidate medicine on human patients in clinical trials. Phase 1 trials test tolerability/safety. Phase 2 trials assess the efficacy of the product and determine the optimum dosage.

➜ The individual phases of clinical research and the medicines life cycle



Lastly, Phase 3 – or Pivotal - trials assess the efficacy and safety of the medicine by administering it to hundreds and even thousands of patients.

Estimates suggest that an average of between 5,000 and 10,000 molecules are tested for every one that ultimately reaches the market as an approved medicine. It really is like looking for a needle in a giant haystack. The whole process can take up to a decade, on average. Such effort must be supported by massive investment, with research and development costs averaging $2.6 billion to bring a new medicine to the market[1].

And the good news is that research activity in the pharmaceutical industry shows no signs of slowing down. Of the 271 MAs approved by the European Medicines Agency between 2021 and mid-2023, 45% involved new active substances.

There are currently nearly 1,800 clinical research programmes underway worldwide, which could lead to the development of more than 600 potential new molecules by 2027.

(1) https://www.europeanpharmaceuticalreview.com/news/28197/cost-develop-win-marketing-approval-new-drug-2-6-billion-according-tufts-center-study-drug-development/

→ Clinical research and new molecules for 2027

1,787
clinical research programmes
at 28/07/23

1,127
medicines in development
(targeting around 600 different mechanisms of action)

660
potential new molecules between
now and 2027

→ Medicines, an innovation cycle that is very... long

12-18 months for a new smartphone

3-5 ans for a new car

5-10 ans for a new aircraft

10-15 ans for a new medicine

TREATING WHAT AND HOW?

Oncology (25% of molecules in development) **and neurology** (16% of molecules in development) **dominate current research projects**, closely followed by infectious diseases and metabolic disorders. Despite extremely high failure rates, diseases such as Alzheimer's remain top priorities, underlining the urgent need to address currently unmet medical needs. Despite very high attrition rates, we are also seeing the emergence of indications for medical needs that are not, or insufficiently, covered, some of which have poor prognoses.

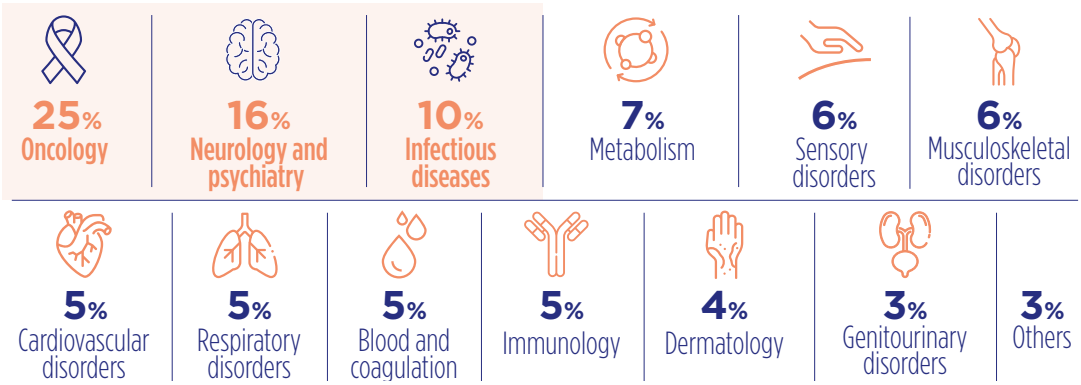
Pharmaceutical companies are focusing massive investment on challenging diseases, many of which currently offer poor prognoses. This commitment underscores the potential for significant advances in the treatment of diseases such as acute myeloid leukaemia and type 1 diabetes. **The pharmaceutical industry prioritises its research where the need is greatest, regardless of the level of difficulty involved**, which particularly benefits rare diseases, where such efforts are making their orphan status a thing of the past.

Explanation...

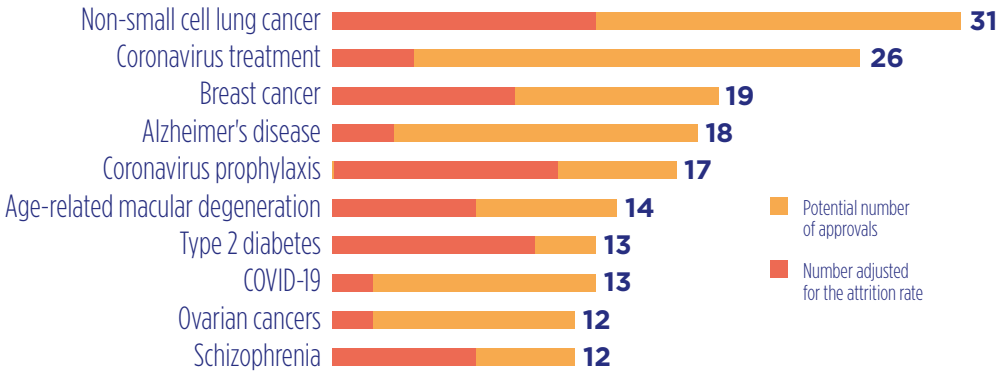
WHAT IS THE ATTRITION RATE?

In the context of new medicines research, **the attrition rate is the percentage of molecules or candidate medicines that fail to make it through every stage of development.** In other words, it refers to the number of research projects that are abandoned due to their low prospects of resulting in a marketable medicine. Imagine that a company begins with 100 molecules in the research phase. Many of these molecules will fail during pre-clinical trials (laboratory and animal testing) and clinical trials (human testing). Some will prove ineffective, while others may have excessively serious side effects. If, at the end of the process, only 1 molecule of the original 100 results in a marketable medicine, then 99 other molecules will have failed. The attrition rate is therefore 99%.

➜ The main therapeutic areas covered by clinical research



➜ The Top 10 indications targeted by phase 3 clinical research programmes

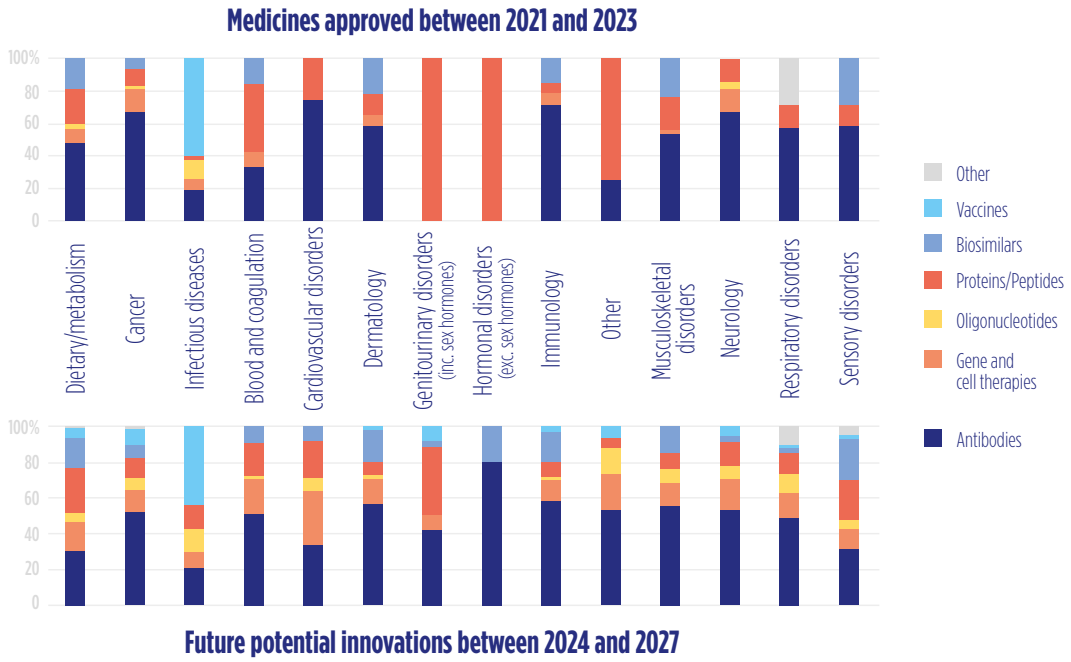


Take Alzheimer's disease, for example, which is one of the indications most frequently represented in clinical research programmes. Although failure rates are extremely high, pharmaceutical companies continue to invest in the quest to find effective treatments. Between 1998 and 2017, only 4 of the 150 medicines researched were approved[(2)]. Around 18 therapies are currently in phase 3 development.

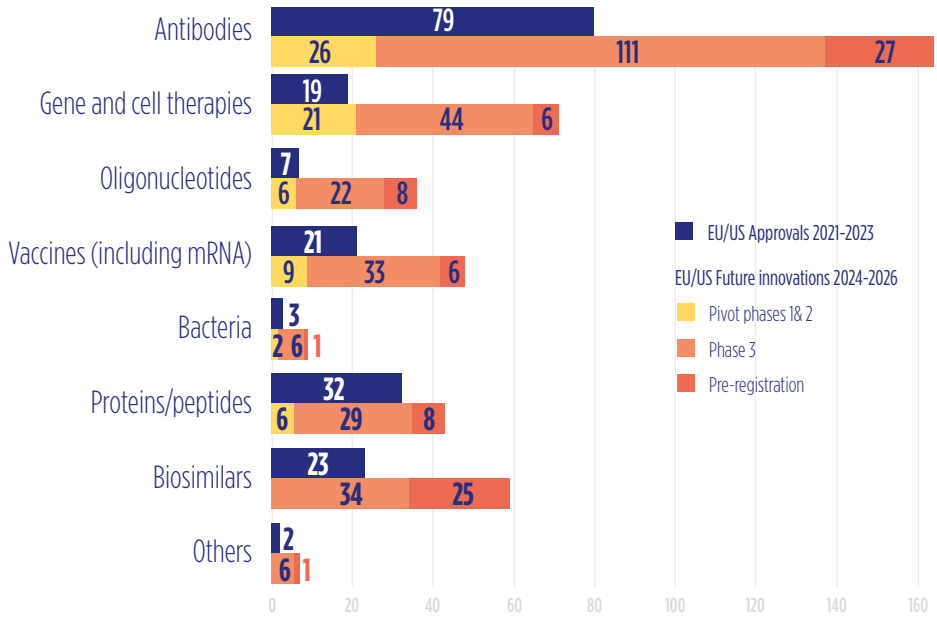
The 40/60 split between biological and chemical medicines remains stable, but biological medicines are expanding into increasingly diverse therapeutic areas. Although the majority are antibodies (43% of all biotherapies under development), other types are also emerging, including therapeutic vaccines, gene and cell therapies and oligonucleotides. This diversification could really change the treatment of certain diseases. This is particularly true of gene and cell therapies.

(2) PhRMA. Researching Alzheimer's Medicines: Setbacks and Stepping Stones, 2018.

➜ The therapeutic areas targeted by biomedicines are increasing in their diversity



➜ Number of biological therapies recently approved or under development



THE MAIN TYPES OF BIOLOGICAL MEDICINES CURRENTLY IN DEVELOPMENT

ANTIBODIES

Antibodies are proteins that bind to their target and neutralise it, enabling it then to be eliminated. They are destroyed in the stomach and would therefore be ineffective if administered orally. This is why **all antibodies are injected**. Monoclonal antibodies are created by cloning a unique white blood cell in culture and are engineered to bind to a single specific target.
85 different monoclonal antibody INNs are currently available in the French market for the treatment of chronic inflammatory diseases (Crohn's disease, rheumatoid arthritis, psoriasis, etc.), cancers and transplant rejection. They have revolutionised many types of treatment.

GENE THERAPY

Gene therapy is a therapeutic strategy that involves **introducing genes into the cells or tissues of a person to treat a disease**.
There are two methods: **either direct injection of the functional genetic material** (naked DNA solution, liposomes or viral vector) **prior multiplication in the laboratory** using mutated cells from the body.

CELL THERAPY

Cell therapy involves **transplanting cells to restore tissue or organ function** For example, stem cell therapy leverages the ability of these cells to differentiate into many other types of cells to reconstitute cellular and tissue structures that have been destroyed or are missing as a result of certain diseases.

OLIGONUCLEOTIDES

Oligonucleotides are **short segments of nucleic acid chains** (DNA or RNA), **that bind to a target RNA and modify its expression** in order to treat diseases.

PROTEINS/PEPTIDES

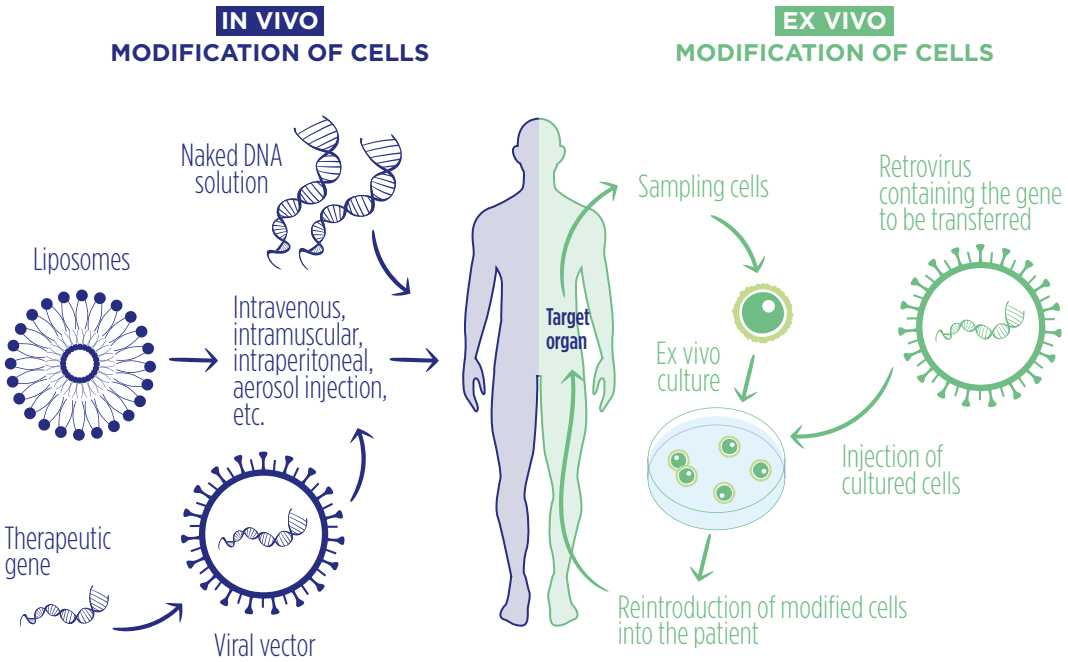
A therapeutic peptide is a **small chain of amino acids** (protein fragment) **that mimics natural molecules** present in the body **and interacts with specific receptors**, thereby regulating precise biological processes.

THE PROMISE OF GENE THERAPIES

Gene therapies are **innovative medical approaches** developed to treat or cure diseases by modifying a person's genes or cells. They represent a major hope for medicine, and account for 16% of biotherapies currently under development (advanced phases of clinical trials).

Gene therapy treats disease by introducing, suppressing or modifying genes in a patient's cells.
There are two approaches: either inject the functional genetic material directly (naked DNA solution, liposomes or viral vector) or multiply it first in the laboratory in mutated cells of the body.

➜ The two gene therapy pathways



The first ever gene therapy trial in human dates back to 1995 when a patient with severe immunodeficiency was treated via injection of stem cells and genetically modified lymphocytes. This first step led to a breakthrough in the 2000s following the successful treatment of children with another form of immunodeficiency. In 2016, a 13 year-old boy with sickle cell disease was successfully treated in France using gene therapy; a world first. The teenager, who suffered from a particularly severe form of sickle cell disease, experienced the disappearance of symptoms such as painful episodes, chronic anaemia, fatigue and joint disorders that sometimes even prevented him from walking. Many trials are now underway for other rare diseases and in oncology. Gene therapy has emerged as a formidable vector for innovation, by enabling the immune system to destroy cancer cells.

Some gene therapies use living or modified cells.
These cells may be harvested from t he patient themselves (autologous) or from a donor (allogeneic). Some of these CAR-T (Chimeric Antigen Receptor) therapies use immune system cells (more specifically T lymphocytes) that have been genetically modified to produce an antigenic receptor on their surface, enabling them to recognise and destroy cancer cells.

These therapies hold out great promise for the treatment of incurable or serious diseases.
These therapies hold out great promise for the treatment of incurable or serious diseases, such as cancers, rare genetic diseases, immunological diseases and certain degenerative diseases.

More than 350 gene therapies are at various stages of development. Oncology accounts for one in three in vivo gene therapies, and 86% of ex vivo gene therapies. 60% of gene therapies (ex vivo and in vivo) target rare diseases. Among those gene therapies that could potentially be introduced over the next few years, there is a first wave of in vivo therapies that use a wide variety of injection techniques. Previously confined to cancer, CAR-T cell treatments are also being investigated in other therapeutic areas. These therapies impose a lengthy pathway on both manufacturers and hospitals.
The technique begins with cells being harvested from the cancer patient; these are then genetically modified, multiplied in the laboratory and then reintroduced into the patient's body intravenously.
If the clinical trials now underway prove conclusive, it will require the near-term restructuring of the health-care system.

Unfortunately, far fewer of the small and medium-sized companies involved in gene and cell therapy development for 88% of all programmes have their head office operations in Europe than in the USA.

This is one of the major learnings from this first Horizon Scanning: Europe is lagging behind in terms of the number of therapies approved and the speed of regulatory approval.
Re-energising European competitiveness is crucial!

Key dates for CAR-T cells

2020

Ongoing developments and new indications — CAR-T therapies continue to evolve and are being tested for use with other types of cancer, including multiple myeloma and other solid tumours, although these remain more difficult to target.

2018

Commercial supply of Yescarta — The FDA approves another CAR-T treatment for adult patients with diffuse large B-cell lymphoma, a type of blood cancer.

2017

First FDA approval — The US Food and Drug Administration (FDA) approves the first CAR-T cell-based treatment to treat acute lymphoblastic leukaemia in children and young adults.

2012

First major clinical successes — Patients with leukaemia resistant to other treatments show complete remission after receiving CAR-T cell-based therapies. This marks a major advance in cancer treatment.

2002

Second-generation CAR-T — Enhanced CAR receptors with modifications to include co-stimulatory signals, increasing the efficacy of CAR-T cells and their lifespan in the body.

1993

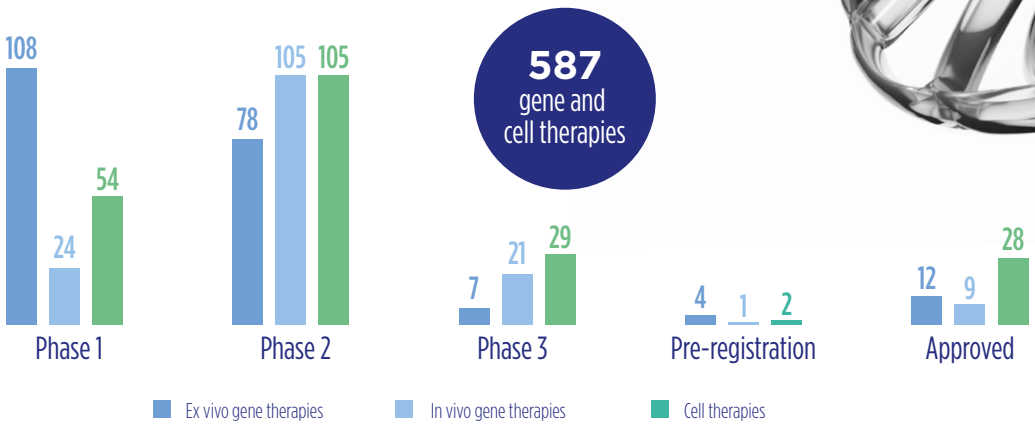
First-generation CAR-T cells — The first functional model of a CAR-T cell is developed in the laboratory. The first versions show limited effectiveness, but they lay the foundations future improvements.

1989

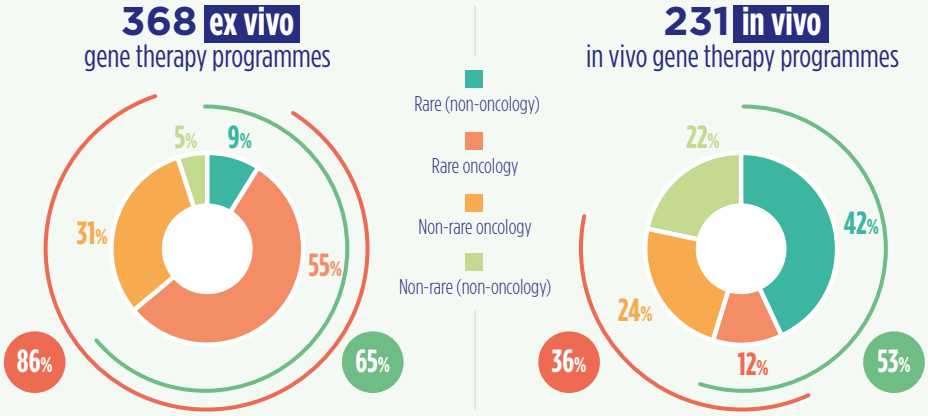
The initial concept of CAR receptors — Researchers begin to explore the idea of chimeric receptors (CAR – Chimeric Antigen Receptors) and their potential for enabling immune system T cells to recognise and attack cancer cells.

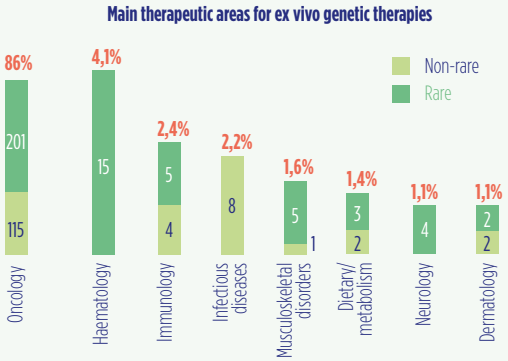
→ Gene and cell therapies in development

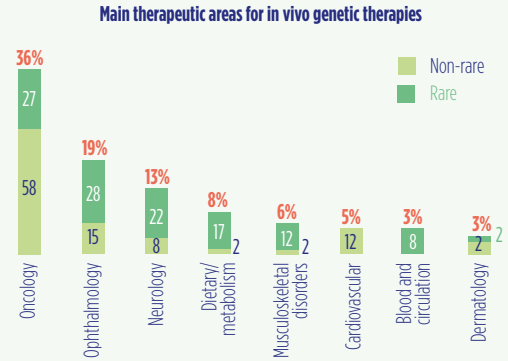
Breakdown by clinical research phase and type of therapy



→ Diseases targeted by gene therapies

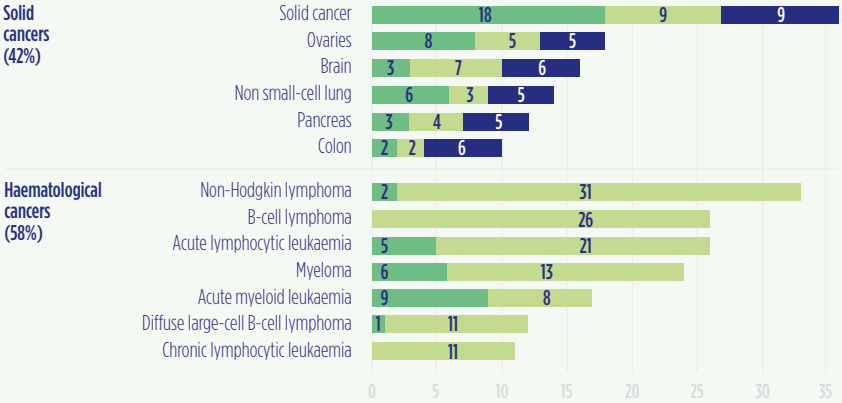






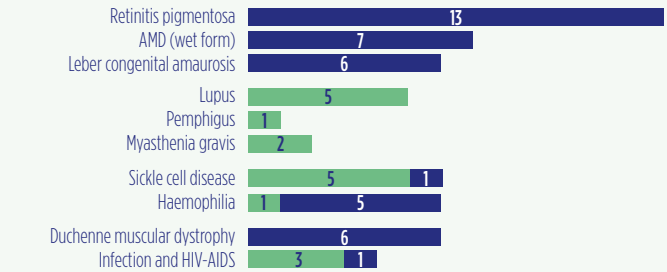
➜ Main indications targeted by gene therapies in oncology and outside oncology

Indications with more than 10 therapies in development (phase 1 to Approved)



➜ Structure care pathways to deliver equitable care

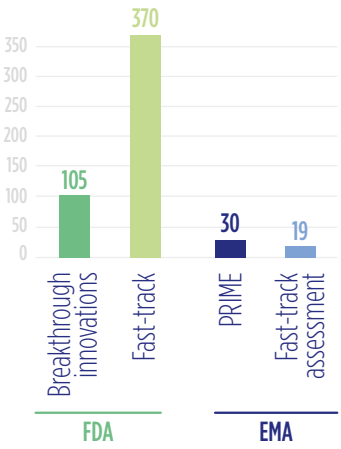
Main non-cancer indications in development (any stage)



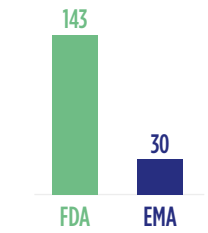
42% of the main R&D programmes focus on solid cancers, and the first applications of ex vivo gene therapies outside oncology are emerging

➜ Europe is playing catch-up

Number of programmes benefitting from fast-track procedures (2021- 2023)



Number of first approvals (2021-2023)

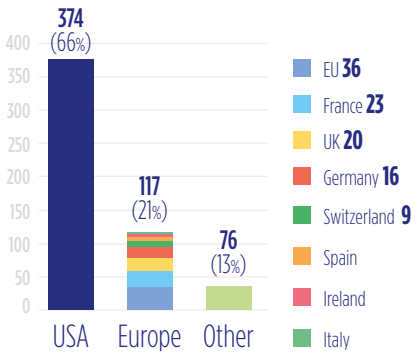


➜ Re-energising European competitiveness is crucial!

Gene and cell therapies

66% of companies outside the Top 40 have their head office in the USA (37% EU vs USA among the Top 40)

Head offices of non-Top 40 companies sponsoring programmes (phase 1 to Approved)



Interview

Marina Cavazzana,

Director of the Biotherapy and Advanced Therapies Department at the Necker Hospital AP-HP, Université Paris Cité and Director of the Biotherapy Clinical Investigation Centre, INSERM, AP-HP, Institut Imagine

We are witnessing the massive emergence of gene therapies across an increasingly wide range of therapeutic areas? What are your thoughts on this trend?

The first thing to say is that this is very good news, because these therapies will cure or – at the very least – deliver transformative clinical benefit to patients with diseases that are currently untreatable. But this brings with it two major challenges. The first is the cost to our healthcare system. How will we be able to fund these therapies and at what cost? Then there's the impact on hospitals, which is going to be very significant.

How will gene therapies impact hospitals?

In many different ways. The specialist centres for the diseases concerned are ill-prepared to prevent the toxicity of these medicines and monitor their efficacy. These therapies sometimes have unexpected clinical effects that require personalised monitoring at the patient's bedside, which a conventional hospital department is unable to provide. The pathways are not always clearly defined, and there are many carers involved, none of whom have much training in the delivery of these products. One way of improving and streamlining this pathway would be to establish the earliest-possible collaboration between manufacturers and centres, particularly at the stage of clinical research preparation. This would prevent hospitals from being overwhelmed when finding themselves faced with a phase 3 trial with no prior training in the protocol.

You raise the important issue of training healthcare professionals...

Exactly, you have to train the whole ecosystem, and it's a massive undertaking. Increasingly, we need to design virtual control arms, consider real-life data, set up efficacy studies, etc., and we need staff trained to do these things. As you said, there are many manufacturer-sponsored clinical trials underway for gene therapies. But we can also expect a substantial influx of academic clinical trials.

Interview

Sylvain Auvity,

Pharmacist (MCU-PH) at the Necker Children's Hospital in Paris

We are seeing a rapid expansion in Advanced Therapy Medicinal Products (ATMPs) across an increasingly wide range of therapeutic areas. Could this trend have knock-on effects for hospitals and the way medicines are delivered?

Of course! We work mainly on rare diseases, so we already have a fairly wide range of ATMPs, and we use the vast majority of those available at the AP-HP, in addition to clinical trials. And their use is growing. In 2023, we undertook 41 preparations of advanced therapies; in December 2024, the number was more than 360.

But that's not all. We also need to be aware that the 'one advanced therapy medicinal product = one single administration' paradigm no longer works.

What we are seeing now is the emergence of more and more in vivo gene therapy drugs (*see infographic on page 13*) or cell therapy drugs with repeat administrations, sometimes spread over a long period, at varying intervals depending on the regimen. The impact will be massive, because the volumes generated per patient are likely to become considerable.

Are hospitals ready for that?

With difficulty. The current regulatory framework makes no distinction between ATMP sub-types. But they can have very different impacts. For example, CAR-T cells are fairly simple to manage (despite their short stability), generally requiring just one bag to be defrosted (although this is becoming less and less true!), since the main constraints are around the logistical concerns of receiving and storing them in liquid nitrogen.

In contrast, other gene therapies require up to 13 hours per patient (including 10 hours of pharmaceutical time), compared with 20 minutes for a conventional chemotherapy preparation.

And with the advent of repeated or sequential administration of these therapies, this length of time will have to be repeated several times for each patient. And that's impossible!

There are also issues with equipment and premises, the majority of which do not meet the best

practice requirements set in 2023. Given these conditions, it will be very challenging to treat all the patients who need it, and equal access to care cannot be guaranteed. In epidermolysis bullosa, we have a paediatric active file of 30 patients in France, but our initial resources allow us to carry out only four treatments per week…

Loss of opportunity for patients is a genuine concern. So what should be done to mitigate that?

The first thing is major investment in human resources and equipment. After that, there are also opportunities for increased efficiency to be explored. Today, a messenger RNA vaccine can be prepared on a lab bench in just a few minutes. But a messenger RNA gene therapy requires a specific protocol - with dedicated rooms and staff, and special equipment – which results in the 10-hour preparation time I referred to earlier. What's the difference? Quite simply, the regulatory framework! Introducing greater clarity about what needs to be covered/supervised would be a first, effective and inexpensive step towards relieving the bottleneck and treating more patients.

Then there is also the issue of regional inequality to resolve. Where gene therapies are administered repeatedly (which is the majority of cases in current clinical trials), the patient needs to visit the hospital, sometimes several times a week, which means they must live reasonably nearby. Unfortunately, this problem is already a reality, with patients being excluded from clinical research for certain therapies. This is something that needs to be planned for today and translated into the post-clinical trial period, since a whole network should be created, and multiple technical issues be addressed.

4 proposals from Leem

As this prospective study clearly shows, the prospects for breakthrough therapeutic advances are unprecedented, and in some cases offer the hope of cures in therapeutic areas that currently lack satisfactory alternatives. Gene and cell therapies will encompass virtually all therapeutic areas. So how do we prepare to welcome them? Implementing them will be very demanding and have a major impact on the healthcare system. What's more, these advances are greater and more rapidly available in the USA than in Europe. The reason for that is our less attractive and less efficient regulatory procedures. So how can we remedy this situation and reclaim leadership?

Leem has brought forward 4 proposals to ensure rapid and equitable access to advanced therapy medicinal products for all those patients who need them.

1. **Co-develop a forward-facing approach to innovation at national level to anticipate the advent of advanced therapy medicinal products.**
2. **Support, facilitate and unify centre accreditation procedures and ARS (Regional Health Agency) authorisation pathways at national level, and make it possible to extend certifications to cover different indications.**
3. **Define a strategy for organising hospital systems to absorb the increase in patient flows.**
4. **Implement the tools needed to support the performance-based agreement.**

Interview

3 questions for Thibaut Victor-Michel,

Chairman of the Leem Research & Innovation Committee

Why have you produced this Horizon Scanning Report?

Because anticipating innovations is becoming essential for all healthcare system stakeholders (regulators, funding bodies and the medical community as a whole). Most importantly, the ultimate aim is to ensure that all patients who need these advanced therapies have access to them. An analysis conducted two to three years ahead of the market availability of new medicines gives us the opportunity to quantify the scale of these advanced therapies we can expect to see, prepare for the new approaches to medicine assessment, and anticipate the organisational and even budgetary impact on existing healthcare systems.

How did you conduct this study?

We conducted an analysis of the advanced therapies likely to be granted marketing authorisation by the EMA or FDA between now and 2027 (data extraction at 30 June 2023). The prospective analysis was conducted on the basis of manufacturer-sponsored clinical trials with investigation sites in Europe and the USA (*source: Citeline*). In addition to this work, we have focused specifically on gene and cell therapies (data extraction at 18 December 2023), from the early stages of clinical research through to those products already available.

What is the outlook?

This study reveals that there is a significant volume of advanced therapies now on the way. If we want patients in France and Europe to have early and equitable access to these treatments, we need to ensure that they are properly funded and that care pathways are planned in advance so that we can make the necessary changes at regional level.

GLOSSARY

MA

Marketing Authorisation (official approval for a medicine to be marketed granted by the health authorities).

ARS

French Regional Health Agency.

INN

International Non-proprietary Name (unique generic name assigned to a pharmaceutical substance that is standardised worldwide to identify medicines independently of their brand name).

CAR-T

Chimeric Antigen Receptor T-cells (T lymphocytes genetically modified to target cancer cells).

CRISPR

Clustered Regularly Interspaced Short Palindromic Repeats (a technology that enables DNA to be edited by cutting and modifying specific sequences).

AMD

Age-related Macular Degeneration.

EMA

European Medicines Agency.

FDA

Food and Drug administration.

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