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HEALTH
2030

A prospective analysis
of health innovation

Extracted from the original French version

Edition 2020

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EDITORIAL

We are in 2030. Quentin is 18. Two years ago, he was diagnosed with Hodgkin's lymphoma. But thanks to epigenetics and immunotherapy, he's saved. Pierre is 52. He's suffered from type 1 diabetes since childhood. But thanks to cell therapy, he's cured. Marie is 79. She was recently diagnosed with heart failure, one of the world's leading causes of death. But thanks to a system of heart pumps that use undulating membrane technology to mimic natural heartbeats, she's healed. Safia is 37. The progression of her multiple sclerosis has been stopped in its tracks thanks to treatment using a combination of monoclonal antibodies....

We are in 2030. This promise isn't just medical, it's also technological and digital thanks to the contribution made by artificial intelligence algorithms, telemedicine and the ability to share health data via the health data hub introduced by the Buzyn Act... So, once again, the scope of the possible has been extended further into the future. We can now use drones to deliver treatments that cure sickle cell disease, which affects 200,000 newborns every year in Africa, and remains the world's most widespread genetic disease, affecting 50 million people. Connected contact lenses can measure glucose levels in patients' tears. A machine vision algorithm detects skin cancer by analysing more than 100,000 images tagged as benign or suspect. It outperforms 58 dermatologists!

The promise held out by innovation is also clear to see in the way healthcare is structured, where innovations are delivering a step change. Now, doctors hold consultations remotely, pharmacists give vaccinations, nurses have diagnostic duties... and patients are cared for in their own homes, where they are connected, fully informed, autonomous and compliant.

In 2030, we stopped thinking in terms of sectors like outpatient care, hospital care and medico-social care. Our health system now combines prevention, care, medico-social monitoring and even social follow-up. It delivers health value creation. Public policy has also embraced this widespread movement towards removing artificial barriers. In 2020, it focused on the reimbursement structure of a curative healthcare system. It now embraces every aspect of healthcare, from prevention to screening, individual behaviour, living environments and curative therapies.

We are in 2020. The new world of health is emerging: a world of hope, but also a more complex and more connected world in which France generally, and its pharmaceutical companies in particular, must find a way to give every patient the opportunity to access the best care for them, and enable everyone to protect themselves against illness.

But which way? Answering that question is the goal of the Health 2030 foresight approach, which seeks to identify the factors for change, understand the issues at stake and set out a clear vision encompassing potential strategic responses for tomorrow's healthcare model.

Preparing today for 2030. The more radical the innovation, the more it must be explained intelligibly. Dialogue and collaboration between all stakeholders – public authorities, doctors, pharmacists, patients and healthcare companies – are essential. We are in 2020, and we're already working towards 2030.

Frédéric Collet *is the Chairman of Leem, the French Pharmaceutical Companies Association, which conducted this Health in 2030 foresight study in collaboration with the think tank Futuribles.*

The whole French study is available on www.leem.org

HEALTH 2030
THE VECTORS OF INNOVATION

- Overview of 14 vectors of innovation that are set to shape advances in research, diagnosis, therapies and patient support. They are presented according to their position in the chain of research, diagnosis, therapies and patient support, starting with the most upstream ones.

THE TECHNOLOGICAL & THERAPEUTIC REVOLUTION

> Multidisciplinarity: combining physics - chemistry - biology - computer science - mathematics

> Integration and transdisciplinarity

1980

LIFE SCIENCES DESCRIPTIVE BIOLOGY

Explanatory barriers following the surge in molecular biology

Compartmentalisation

TECHNOLOGIES

- Tests, errors
- Extrapolation (separate approaches, virology, microbiology, etc.)

RANDOM INNOVATIONS

- Combinatorial chemistry drug discovery process, innovation schools of thought

2000

LIFE SCIENCES EMERGENCE OF SYSTEMS BIOLOGY

Barriers of complexity and processing of mass data

TECHNOLOGIES

- Experimental techniques and biological information processing techniques
- Bioinformatics and computational simulations
- Cell imaging
- Large-scale genetics (genotyping, DNA chips, etc.)
- "Omic" molecular targeting (genomic, proteomic, transcriptomic, etc.)

BIOLOGICAL INNOVATIONS

- Emergence of genetic engineering
- Biomedicines: recombinant proteins, monoclonal antibodies, etc.

2030

SYSTEMS BIOLOGY AND INTEGRATIVE APPROACH

Ethical barriers

TECHNOLOGIES

- CRISPR-Cas9
- Epigenetics
- Microbiota
- Microfluidics
- Artificial Intelligence/Data
- Nanotechnology
- Cell therapy
- Gene therapy
- Vaccines
- Immunology

BREAKTHROUGH INNOVATIONS

- Nanomedicine, smart pill
- Regenerative medicine
- Reprogramming
- Epidrugs
- Immunotherapies
- RNA interference
- Combined therapies

The vectors of innovation "on the front line"

From 1990 to 2000, significant progress was made in our understanding of genome function and in the development of innovative medicines through biotechnology. Medicines derived from living organisms (immunotherapies, CAR-T cells, gene therapies, etc.) and the use of new vectors of innovation (CRISPR-Cas9, artificial intelligence, nanotechnology, etc.) have emerged as game changers in the decade between 2010 and 2020 and are paving the way for ever greater therapeutic advances between now and 2030.

And there is no indication that the pace of the therapeutic revolution is about to slacken: since the human genome was first sequenced in 2003, which took thirteen years and cost USD 3 billion, the cost of sequencing has plummeted.

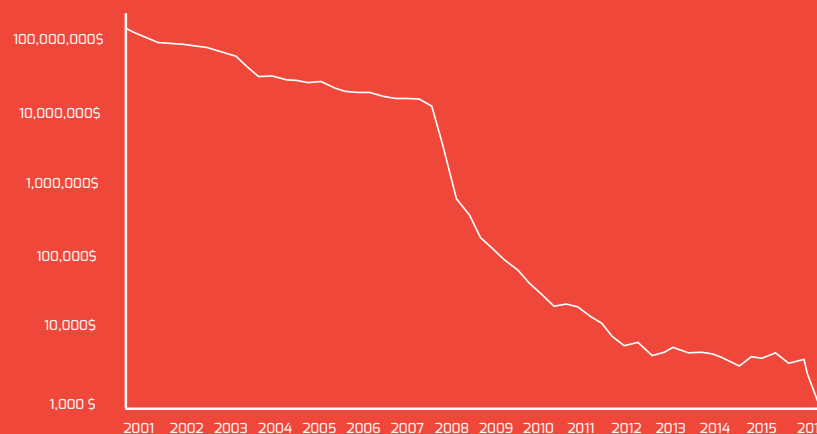Today, sequencers are able to study in real time those genes that are identified as important in a given disease. They can also detect a bacterium or a virus that has infected someone. In West Africa, this type of sequencer was used to identify the Ebola virus genomes in 148 patients. The race for miniaturisation continues unabated: a microchip inserted into a USB stick is now used to detect DNA and yield results viewable on any computer. This microchip, which was developed by Chris Toumazou of Imperial College in London, studies 1% of the 3 billion base pairs that differentiate us from one another, a little like creating our own personal biological IP address.

Other vectors are paving the way for potentially major therapeutic advances between now and 2030. Out of thirteen drivers of progress in therapeutics between now and 2030, eight have actually emerged since 2013. The ever-growing number and diversity of therapeutic solutions will result in an integrated approach to each patient's care pathway, from diagnosis to follow-up and including treatment adjustment.

At the same time, diagnostic tools will be developed that are integrated into the daily lives of patients, thereby enabling adoption of the latest biomarkers. These advances will all help to develop an understanding of the pathophysiological mechanisms of complex diseases and to identify patient groups that match a more specific profile defined by a particular metabolic or genetic makeup.

Precision medicine is on the way to becoming a major component of therapeutic strategies as a beneficiary of the large number of technological advances and general awareness of the need for a paradigm shift in the way we approach disease.

COST OF SEQUENCING THE HUMAN GENOME

Source: NIH.2017.

VECTORS OF INNOVATION
AS SEEN BY SCIENTISTS AND EXPERTS

- CRISPR-Cas9 — **CARINE GIOVANNANGELI**, Museum of Natural History, Paris

- EPIGENETICS — **JONATHAN WEITZMAN**, Paris Diderot University, Paris

- MICROBIOTA — **NADINE CERF-BENSUSSAN**, Imagine Institut, Paris

- MICROFLUIDICS — **PATRICK TABELING**, Institut Pierre-Gilles de Gennes, Paris

- NANOMEDICINE — **NATHALIE MIGNET**, Paris Descartes University, Paris

- REGENERATIVE MEDICINE — **MARC PESCHANSKI**, I-STEM Institut, Corbeil

- GENE THERAPY — **MARC PESCHANSKI**, I-STEM Institut, Corbeil

- IMMUNOTHERAPY — **MARC BONNEVILLE**, Institut Merieux, Lyon

- VACCINATION — **NICHOLAS JACKSON & JEAN LANG**, Sanofi Pasteur, Lyon

- HEALTH DATA — **ALAIN LIVARTOWSKI**, Institut Curie, Paris

- ARTIFICIAL INTELLIGENCE — **MARCO FIORINI**, Ariis*, Paris

- THE INTEGRATIVE APPROACH OF ADVANCED — **GENEVIÈVE ALMOUZNI**, Institut Curie, Paris

- INTEGRATIVE MEDICINE — **ALAIN TOLEDANO**, Institut Rafael, Levallois-Perret

- PATIENT AUTONOMY — **CHAHRA LOUAFI**, Bpifrance, Paris

CRISPR-CAS9

WHAT ARE WE TALKING ABOUT?

CRISPR-Cas9 is a tool that allows a DNA segment to be quickly and easily modified, often compared to the copy&paste feature in a word processing document. Once the gene that needs to be removed is identified, it can be cut by these "molecular scissors" and replaced with another one.
CRISPR-Cas9 technology is only 5 years old and yet is already being used by more than 3,000 laboratories worldwide.

Définition

ADN, or deoxyribonucleic acid, is a nucleic acid composed of deoxyribose, phosphate, adenine (A), cytosine (C), guanine (G) and thymine (T). DNA contains the genetic instructions used in the development and functioning of all living organisms and some viruses.

The main function of the DNA molecule is the long-term storage of information to construct other components of the cell, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but the other DNA sequences are also involved in regulating the expression of this genetic information.

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ "A revolution that will shake the planet on an unimaginable scale." **André Choulika, CEO of Cellectis**

● **The infinite opportunities that genetics offers**

CRISPR-Cas9 offers unlimited possibilities for genetics: deleting an unhealthy gene and replacing it with a healthy sequence or even investigating the exact function of a gene... No branch of biology will be left out, and new applications are being published every day, especially since CRISPR-Cas9 is an exceptionally fast technique.

Genomic engineering[1]

The TALEN, ZFN and CRISPR-Cas9 genome surgery tools can cut DNA sequences by disabling or removing any gene and replacing it with another.

Three techniques   Time needed for experiments

ZFN*   ··
TALEN   ····· Weeks   *Zinc-finger nucleases
CRISPR-Cas9 ····· Days

● **Treating genetic diseases**

The main feature of CRISPR-Cas9 is its ability to recognise and cut a particular DNA sequence. Modified by researchers to recognise the sequence of their choosing, CRISPR-Cas9 has the potential to delete mutations and become the mainstay of gene therapies in the treatment of many genetic diseases.

CURRENT DEVELOPMENTS

● **Understanding how the brain works**

Avenues of research abound and bring with them many hopes such as that of elucidating how the brain works. The scope for fundamental research in neuroscience is increased hugely by the use of CRISPR: by cutting a specific gene from an animal model, its role in brain development, for example, can be more accurately determined. Moreover, it is paving the way for a number of therapeutic applications. For example, if a gene is implicated in a mental disorder, it may eventually be possible to eliminate, correct or replace it with this genetic scalpel.

● **The genetic mapping of mental disorders**

It is also becoming possible to establish the genetic profile of a large number of brain conditions. Especially since they are often multigenic. In the case of autism, for example, more than 300 genetic variants have already been identified. However, they are not all expressed in the same way in the different neurons.

With CRISPR-Cas9, it is becoming possible to investigate these gene variations. Besides, genes that code for a protein are not the only parts of DNA involved in the development of disorders. Between these parts lie sequences of regulatory DNA, which have long been considered genetic waste. And yet these non-coding parts actually play an essential role in many pathologies. In the future, CRISPR-Cas9 may help to better characterise the role of these fragments, which is still largely unknown.

▶ **CRISPR-Cas9: une "success story" en plusieurs étapes**

1987. A researcher at Osaka University spotted some rather unusual DNA sequences in the genome of Escherichia coli bacteria. In some parts of these sequences, the four base pairs of DNA - adenine (A), guanine (G), cytosine (C) and thymine (T) - formed sequences immediately followed by the same sequences in the opposite direction: they could therefore be read in both directions, like palindromes. Not really knowing to what use they could be put, these enigmatic sequences were of no interest to anyone at first. Research continued.

2002. The naming: the DNA fragments interspersed between these palindromes were often virus DNA fragments capable of infecting bacteria.

2005. An additional discovery: les morceaux d'ADN intercalés entre ces palindromes sont souvent des morceaux d'ADN de virus capables d'infecter des bactéries.

2007. The food industry got involved: researchers from the Danish company Danisco found that among the Streptococcus thermophilus bacteria used to make yoghurts and cheeses, those with CRISPR sequences are better able survive viral infections. The bacteria seem to store in their CRISPR sequences the DNA of viruses that have previously infected them, which allows them to identify and fight these viruses.

Over the next five years, the work of various laboratories led to the understanding that viral DNA from CRISPR sequences is copied into smaller molecules called RNAs that bind to an enzyme called Cas9. In the bacteria, if a CRISPR viral RNA combined with Cas9 comes across a matching DNA virus, it pairs with that DNA. Once attached, the Cas9 protein eliminates the virus by cutting out the two strands of its DNA.

CRISPR-CAS9

2012. Eureka! American scientist Jennifer Doudna of California's Berkeley University teamed up with French microbiologist Emmanuelle Charpentier of Sweden's Umeå University and Danisco researchers to demonstrate that viral RNA can be replaced by any sequence of interest and that simply by pairing the CRISPR RNA and Cas9 protein it is possible to cut the corresponding DNA. The CRISPR-Cas9 system is therefore a powerful tool in the detection of a particular DNA sequence and functions as a formidable and precise pair of scissors. The door is now open to determining the function, removal and replacement of a selected gene.

2013. First breakthrough with human genes: teams succeed in removing genes from human cells. The technique is applied to all kinds of cells and organisms: rice, flies, zebrafish, etc..

2013-2018. All-encompassing research: the technique has even been modified so that the Cas9 protein does not cut the targeted gene but stimulates its expression.

In the summer of 2014, researchers were tackling an incurable genetic disease: Duchenne muscular dystrophy, a muscle degeneration disease caused by mutations in the gene coding for the protein essential for the proper functioning of muscle fibres. They were able to correct this mutation in mouse embryos and then re-implant them into surrogate mothers. Nine months after birth, the muscles of mice with at least 40% of corrected cells were perfectly normal!
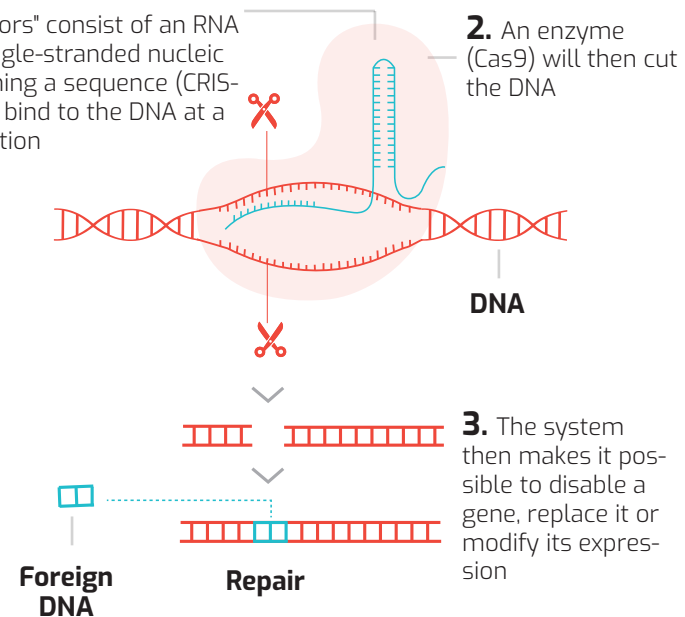
A team at the Massachusetts Institute of Technology used CRISPR-Cas9 to correct an incurable genetic disease of the liver: tyrosinemia, caused by a genetic mutation in a gene needed to break down an amino acid called tyrosine.

In mice with this condition, CRISPR-Cas9 succeeded in replacing the deficient gene with its healthy form in about 0.5% of liver cells (hepatocytes). After one month, these healthy cells had proliferated, accounting for one third of all hepatocytes.

California researchers were successful in improving vision in rats with a form of hereditary blindness. Preclinical and clinical trials are increasing in number by the day.

A technique that cuts DNA to better repair it[1]

1. The "scissors" consist of an RNA strand (a single-stranded nucleic acid) containing a sequence (CRIS-PR) that will bind to the DNA at a specific location

2. An enzyme (Cas9) will then cut the DNA

DNA

3. The system then makes it possible to disable a gene, replace it or modify its expression

Foreign DNA

Repair

BARRIERS TO BE OVERCOME

- **Overcoming the antibody barrier**

From 65 to 79% of the population reportedly have antibodies against CRISPR-Cas9 type proteins. And 46% of the population are also thought to have white blood cells directed specifically against these proteins. These are the findings of a study pre-published in January 2018 and conducted by researchers at Stanford University in California.

- **Overcoming the off-target effect**

While it is very easy to target a specific gene with CRISPR-Cas9, it can lead to other unwanted changes in other parts of the genome. Thus, in seeking to achieve a desired modification with the Cas9 enzyme, researchers may end up with dozens of "off-target" modifications. This is precisely what happened in 2015 when a team led by Junjiu Huang, a geneticist from Sun Yat-sen University in Guangdong Province, China, modified human embryos to suppress the gene responsible for beta thalassaemia, a blood disorder. Improvements in the CRISPR-Cas9 system to reduce these adverse effects have already been described and many laboratories are still working on them.

- **Assessing the ethical, genetic and environmental implications of CRISPR-Cas9**

• **A first concern.** In late March 2017, a Chinese research team managed for the first time to modify the genome of viable human embryos. Using the CRISPR-Cas9 technique, this was the first time that "normal" embryos had been modified and, in these studies, there appeared to be fewer adverse effects than previously described in equivalent studies but on non-viable embryos.

Although CRISPR technology has already proved extremely useful in the biomedical field, the problem arises when it comes to modifying germ cells (gametes for example) whose mutations are transmissible. These modifications are strictly prohibited under Article 13 of the Oviedo Convention[1] on interventions on the human genome. On the other hand, the CRISPR-Cas9 technique used to modify somatic cells[2], such as for example CAR-modified T-cells, poses no specific problems other than the usual concerns over safety and efficacy of the modified cells.

Nor will the technique give rise to greater problems in somatic cells with the development of Cas9 because it will no longer cut the genetic sequence but will act as a sort of raft anchored to an enzyme that will target and correct the mutation in situ.

• **A second concern.** Genome editing of the mosquito is a solution being investigated to eradicate diseases such as malaria. Scientists fear though that this method might run out of control and threaten biodiversity. CRISPR can be used to create a new species of mosquito that could replace mosquito species carrying the Zika virus, dengue fever or malaria.

An impact analysis needs to be performed. The eradication of mosquito populations could disrupt biodiversity and disrupt the food chain. Modified mosquito genes would be transmitted to neighbouring insects and thereby sterilise species that are vital to humans, such as bees.

The strategy is to release sterile mosquitoes into the wild to reduce the population: mating with sterile insects will thus prevent reproduction. As these insects die quickly, regular releases are required to continue to decrease the population. How to stop a chain reaction in nature if negative effects are observed?

[1]1Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. It was signed on 4 April 1997 in Oviedo, Spain. / [2]Namely, all cells not belonging to the germ line and constituting the vast majority of cells that make up an individual.

EPIGENETICS

WHAT ARE WE TALKING ABOUT?

Epigenetics is the study of the relationship between genotype (an individual's genome information) and phenotype (set of observable characteristics of an individual's organism).

DNA into the mainstream, whereupon all eyes (and research) turned to genetics and led to the development of DNA sequencing technologies in the 1980s. The twenty-first century opened with the publication of the sequence of the entire human genome. But, contrary to expectations, decoding the genome did not yield answers to all the questions that researchers were raising, particularly with regard to the treatment of many genetic diseases.

Definition

The genotype represents the entire genetic makeup of an individual. Genotyping is therefore a discipline that aims to determine the nature of a genetic variation at a specific position in the genome for a given individual. The differences between two human beings are estimated to be about 3 million nucleotides out of the 3 billion nucleotides in the human genome. The phenotype is the set of observable characteristics of an organism (anatomical, morphological, molecular or physiological). It is determined by both genes and the environment.

The term epigenetic was first coined by Conrad Hal Waddington in the 1940s as "the branch of biology which studies the causal interaction between genes and their products, which bring the phenotype into being". Today, the most common definition of epigenetics is "the study of heritable changes in gene function that do not entail a change in DNA sequence". To use a metaphor, genetics is how genes are written, epigenetics is how they are read. The accessibility of a gene within the nucleus of a cell, and thus its capacity to be transcribed and then translated into a protein, will depend on chemical modifications to DNA (for example, methylation) and on proteins that surround the DNA. The epigenome is the set of epigenetic modifications of a cell.

Epigenetic inheritance is fundamental at the cellular level because it contributes to the organism's memory of cell identity. Epigenetic modifications are influenced by intrinsic or extrinsic environmental factors. Our lifestyles could thus leave an "epigenetic trace" in our cells that can be passed from one generation to the next. The discovery in 1953 of the double helix structure of DNA by James Watson and Francis Crick brought

Epigenetic mechanisms

For each living being, genetic information is carried by DNA, whose sequence is identical in all cells of the same organism. It is coded by the specific sequence of the four nucleic bases: adenine, thymine, cytosine and guanine (A-T-C-G).

The decryption of this four-letter code does not explain how the same succession can produce so many combinations. One of the most telling examples is that a single stem cell is able to generate an entire organism that is composed of different cells, in both structure and function. Their origin being the same, these cells have exactly the same genetic code that is interpreted differently thanks to a slew of epigenetic mechanisms.

Each cell exploits several types of independent epigenetic mechanisms, whose mode of action involves DNA and proteins. In fact, in order for the nucleus of a cell measuring 5 to 6 μm in diameter to contain two metres of DNA, several layers of compaction are necessary.

Some epigenetic mechanisms affect the structure of chromatin by transitioning it from a condensed to a decondensed state, or vice versa, depending on whether a gene needs to be expressed or repressed. Others are directly involved in DNA regulatory sequences in the vicinity of genes. These particular sequences do not code for any protein, but control where and when the genes are expressed.
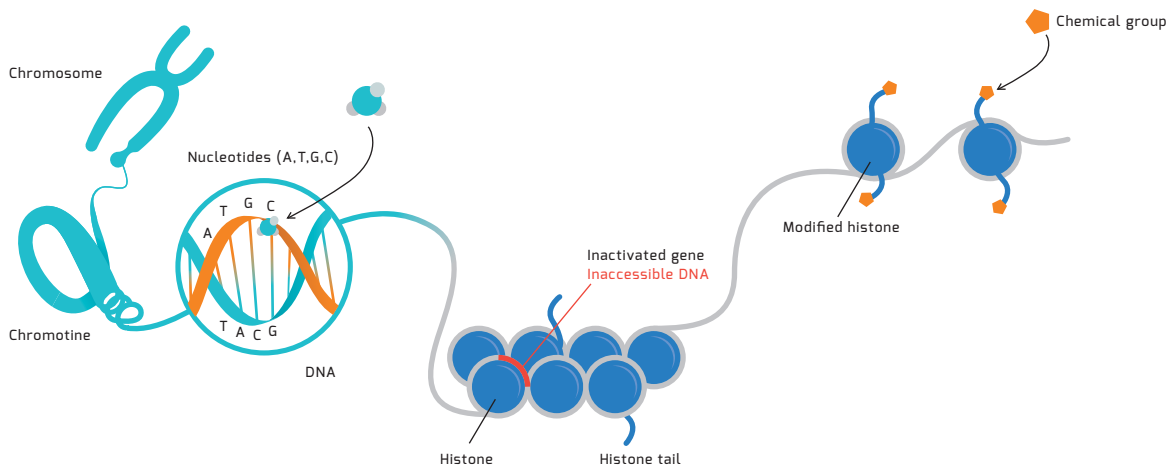
The DNA double helix winds around protein octamers called histones to form nucleosomes. These structures are then organised in space to form more or less dense chromatin fibres. The highly compact state is called heterochromatin and prevents gene transcription. Euchromatin is less condensed and comprises the active portion of the genome.

These alterations make it possible to regulate gene expression without changing the DNA sequence. Using the metaphor of a book, the genome can be compared to the sentences in a book while the epigenome corresponds to its accents: the same text can then be read in different ways depending on whether certain words have grave, acute or circumflex accents.

The activation status of our genes is therefore subject to numerous tools available in the nucleus of each cell.

Two mechanisms for modulating gene activity

Epigenetics refers to processes that regulate gene expression but do not change the DNA sequence. They use two mechanisms that modify chromatin states: wrapping of the DNA molecule around histone proteins that make up chromosomes. These chromatin states are highly sensitive to environmental factors. Their modifications could be implicated in ageing and in certain diseases.

1. DNA methylation

This is one of the main epigenetic mechanisms: it involves the addition of "methyl groups" on nucleotides (the "letters" A, T, G and C which form the DNA sequence). Low methylation promotes gene expression while high methylation inhibits it.

2. Histone modification

DNA wraps around histone proteins to form small beads. The addition of chemical groups to these histones affects the compactness of these coils and can modify the accessibility of certain genes, which are then translated into proteins, or not.

Chromosome

Nucleotides (A,T,G,C)

Chromotine

DNA

Histone

Histone tail

Inactivated gene
Inaccessible DNA

Modified histone

Chemical group

EPIGENETICS

Epigenetics acts at three levels

1. At the individual level: during development, it plays an important role in cell differentiation and maintaining their identity throughout life.
2. At the generational level: some chromatin states can be transmitted to offspring over several generations.
3. On an evolutionary time scale: experts are wondering whether it plays a role in the evolution of species.

Epigenetic mechanisms are responsible for the identity of our cells, but they can also help to determine who we are. For example, identical twins, who share exactly the same genomic sequence, are nevertheless different, due primarily to each having their own specific epigenome.

And yet, even though epigenetic phenomena are part of our daily lives and ensure that we stay healthy, their disruption can cause diseases such as cancer, Alzheimer's disease, depression or asthma.

However, unlike the genetic code, whose mutations are irreversible, modifications due to epigenetic phenomena are potentially reversible and vary according to the cell environment. They therefore offer a promising future for the development of drugs to treat the diseases mentioned.

"Epigenetic variations are fairly plastic. They can be erased by chemical treatments, which opens up enormous therapeutic opportunities. This hope has already materialised in the development of the first 'epidrugs' designed to treat certain cancers." (Edith Heard, Professor at the College de France, Chair of Epigenetics and cellular Memory).

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **Understanding the complex relationship between genotype and phenotype and exploring the links between individual genetic variations, the environment and human diseases.**
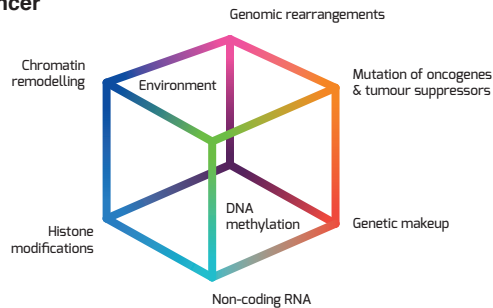
● By identifying many diseases caused by epigenetic mutations or alterations in specific genes, a thorough molecular diagnosis will be possible (pre- and post-natal).

● Greater account will be taken of epigenetics in disease occurrence. Knowledge of disease mechanisms will lead to the development of targeted and effective treatments that are tailored to specific alterations, thus reducing harmful side effects.

● Understanding the link between genotype and phenotype will herald a new era of personalised medicine and a greater appreciation of disease risks and susceptibilities: pharmacogenetics will develop in tandem with pharmacoepigenetics.

● These advances in the field of genetics and epigenetics will be accompanied by improvements in drug design, gene therapy approaches, gene surgery and stem cell therapies.

● We will continue to learn how our environment, our diet and our lifestyle interact with our genetic makeup, and how they impact our epigenomic status to determine our health and susceptibility to disease.

CURRENT DEVELOPMENTS

The advent of epigenetics has changed the way we think about inheritable diseases by including the environmental dimension, hence the proliferation of studies on the importance of epigenetic imprint modification in the development of many diseases.

Where gene therapy involves changing genes, "epigenetic therapy" may act on gene expression. It may also involve acting directly on the nature of the DNA components. This is the case with therapies to reactivate a silent gene, making it possible to prevent DNA methylation (which affects gene expression in each cell). These solutions may prove effective in the treatment of lung cancer and some leukaemias when linked to DNA hypermethylation.

**Epigenetics
to tackle cancer**

In 2016, the market for anti-cancer epidrugs was buoyant and dynamic. It accounted for USD 2.7 billion and was growing by 25% per year. Americans are the biggest players. They include pharmaceutical companies, mid-cap companies and a few start-ups, including EpiReMed (from the CNRS Pharmacochemistry - Cancer Epigenetic Regulation Unit), Storm Therapeutics (GB), Cambridge Epigenetix (GB), Epizyme (United States), Zenith Epigenetics (Canada).

Between 2000 and 2016, epigenetics was the subject of more than 30,000 publications.

BARRIERS TO BE OVERCOME

The coming decades will see the advent of promising advances in genetics, epigenetics and genomics, which will open up new avenues for the diagnosis and treatment of diseases.

Projects being developed today include epigenome sequencing or target validation and inhibitor screening. Foremost among these are epigenome mapping by the Roadmap Epigenomics Pro-gram, supported by the National Institutes of Health (NIH), and the EU-funded Blueprint pro-ject.

The ENCODE project (Encyclopedia of DNA Elements), led by a consortium funded primarily by the US National Human Genome Research Institute (NHGRI), aims to identify all functional elements of the human genome and epigenome. Research into epigenetics is being conducted in Europe and worldwide through public consortia and is structured to include private partnerships as well. The Structural Genomics Consortium (SGC), an open data partnership whose goal is to produce three-dimensional structures of epigenetic targets to develop new inhibitors, brings together big names from the private and public sector (AbbVie, Bayer, Janssen, Novartis, Pfizer, Oxford and Toronto University, Karolinska Institute, etc.).

● **Challenges to be met**

• These projects will require significant investments in new technologies, especially high-throughput sequencing and stem cell research.
• These technologies raise new challenges around storage of large data and sensitive biological materials, as well as data analysis and risk assessment. It will be equally important to incorporate the understanding gained of genetic and epigenetic characteristics into clinical trials and drug screening programmes.
• Another challenge will be finding ways to develop collaborations between, on the one hand, academic and industry researchers to promote the emergence of these new therapies and, on the other hand, the medical community to convey this information to patients.

● **Prerequisites for addressing these challenges**

• The creation of professional, shared and well-managed databases to store medical information and molecular data, the use of artificial intelligence and the development of deep learning algorithms to interpret the results.
• The development of high-performance technology platforms, staffed to maintain, manage and statistically analyse these data.
• The strengthening of professional interactions between the scientific and medical community and the general public, as well as the improvement of analytical tools.
• The establishment of interdisciplinary networks of collaborators, including scientists and philosophers, to investigate the social impact of knowledge about genetic and epigenetic information.

MICROBIOTA

WHAT ARE WE TALKING ABOUT?

The human microbiota is a set of microorganisms - bacteria, viruses, parasites, nonpathogenic fungi, known as "commensals" - hosted by the human body.

The human gut microbiota contains the largest bacterial community in the human body, made up of 10^{13} bacteria and residing mainly in the small intes-tine and the colon.

● **The gut microbiota in figures**

10^{13} bacteria

viruses, especially phages (that infect bacteria only), fungi

Between 300 and 500 species

per individual out of a total 1,500 to 2,000 species detected in human faeces

Between 500,000 and 600,000 bacterial genes

per individual in a catalogue of more than 10 million bacterial genes (compared to 22,000 genes in the human genome)

● **Symbiotic bacteria of the human body**

Mouth

Skin

Colon

10^{13} bacteria

Œsophagus

Stomach

Vagina

● Firmicutes
● Bacteroidetes
● Actinobacteria
● Proteobacteria
● Other phyla

Source diagram: Dethlefsen and al Nature 2007.

Among the many bacterial genes collectively encoded by the microbiota, an ever-present cluster of genes is considered necessary in order for the bacteria to adapt to the gut ecosystem. However, very large numbers of genes are expressed differently from one individual to another. Although their precise individual role is still something of a mystery, it is now accepted that some perform important functions for the host. Numerous experimental studies based on the eradication of the microbiota have indeed shown that it significantly influences the physiology of its host and the development of many pathologies.
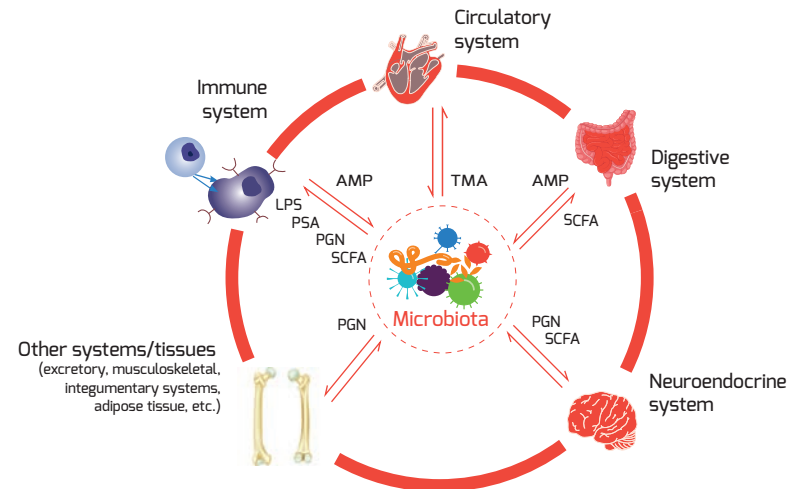
In the gut, besides acting as a barrier against path-ogenic microbes, a role recognised for the past sixty years and more, microbiota plays a key role in the digestion of non-digestible carbohydrates. In and away from the gut, the microbiota modulates the functioning of the immune system and the metabo-lism of its host, the effects of which impact multi-ple organs (gut, liver, lungs, kidneys, brain), as well as the bones and cardiovascular system, as several recent studies have shown. As a result, it has been suggested that the host and its microbiota form a superorganism.

More and more studies are showing a correlation between microbiota diversity, lifestyle and the onset of chronic inflammatory or metabolic diseases.

Species diversity, and therefore microbial gene di-versity, is thus reduced in individuals with a chronic disease compared to that of healthy subjects. A de-cline in gut microbiota diversity is also observed in humans living in industrialised countries. It is more diverse among people who have retained a tradi-tional diet and lifestyle.

Experimental work shows that it is possible for an-imals to transfer a chronic disease or a predisposi-tion to such disease. Experiments with the microbi-ota of patients suggest that microbiota changes, combined with industrialisation, could be the root cause of the epidemic of chronic diseases that come with this change in lifestyle.

● **Host & microbiota: a superorganism**

● "Quorum signals" are molecular signals sent by bacteria to their congeners.
● The acronyms AMP, LPS, PGN, SCFA, TMA all refer to metabolites, in other words intermediates that form in the body during a metabolic process.

Two questions therefore arise that guide current research on microbiota:

1. **What factors influence the composition of microbiota? Particular changes over the course of a person's life? Diet? Antibiotics?**

2. **What are the effects of microbiota on the host and what are the mechanisms involved?**

MICROBIOTA

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

● **Promising therapeutic avenues using studies on microbiota composition and its effects on its host**

• Gut microbiota, which plays a key role in metabolism and the immune system via its metabolites, can therefore influence treatment response. The metabolism of certain medicines, including digitalis, cancer drugs and statins, may be modified by the composition of the microbiota. It is conceivable therefore that therapeutic interventions could eventually be determined according to the composition of the microbiota.

• Microbiota analysis could become a patient stratification tool, used to monitor disease progression (e.g. inflammatory bowel diseases) and patient health status. Responders and non-responders to treatment could also be stratified.

● **New ways to understand and predict the role of microorganisms** in microbiota in human health and disease through artificial intelligence approaches, integrating data drawn partly from a "multi-omic" analysis of patients and partly from microbiota.

● **A fresh look at birth**, based on considerable clinical and experimental evidence, shows how crucial the way microbiota establishes itself in the first months of life for the child's development and future health. Any delay or a change in its establishment may explain the onset of chronic diseases later on, such as allergies, inflammatory bowel diseases, obesity and metabolic syndrome.

CURRENT DEVELOPMENTS

▶ **Identifying the factors influencing the composition of microbiota**

DIET
Microbiota composition evolves according to the host's diet, as shown by changes in the microbiota composition of mice after a diet rich in sugars and fats.

● **Change in microbiota composition in response to a dietary change in mice**

TRADITIONAL FIBRE RICH DIET   *DIET RICH IN SUGAR AND FAT*

CHO   **Western**

Microbiota composition

- Firmicutes (Mollicutes)
- Bacteroidetes
- Other Firmicutes
- Other divisions

ANTIBIOTIC CONSUMPTION
It also varies according to antibiotic consumption.

● **Change in microbiota in response to oral antibiotic consumption in humans**

Before taking antibiotics   *During antibiotic treatment*   *After ending antibiotics*

Phylum concentration by category

- Firmicutes
- Bacteroidetes
- Proteobacteria
- Other phyla of bacteria

Microbiota composition is very dynamic and is influenced by the environment in which the host lives, soil microbiota, animal microbiota. Nevertheless, microbial niches, formed between 0 and 3 years of age, provide it with a stable core.

THE "STABLE CORE" OF MICROBIOTA

● **Development of gut microbiota after birth**

| Before birth | Birth | 4 days | 20 days | 4 to 6 months |

Aseptic

Diversified microbiota

Oral inoculation by the gut and vaginal microbiota of the mother

Influence of diet

Breast milk

Lactobacillus/Bifidus Proteobacteria

Firmicutes Bacteroidetes

▶ **Accurate understanding of microbiota functions**

• Gut microbiota helps in the digestion of our food and our metabolism. Colon bacteria in particular contain enzymes capable of breaking down complex carbohydrates from food that are not digestible by the gut enzymes.

The breakdown by gut bacteria of these molecules, commonly known as dietary fibre, leads to the formation of volatile short-chain fatty acids, the most abundant of which are acetate, propionate and butyrate. Butyrate is the energy substrate used by the epithelial cells that line the colon. Its use by colonic cells significantly increases oxygen consumption, which limits the diffusion of this gas into the lumen of the intestine, thereby maintaining conditions conducive to the growth of butyrate-producing bacteria.

• A virtuous circle is thus created: the bacteria break down the complex sugars from our food, releasing bacterial metabolites that ensure the survival of our colonic cells. In return, the metabolism of these cells creates favourable conditions for the bacteria that produce these metabolites. This is an example of the symbiosis established between gut bacteria and host.

• Gut microbiota is also capable of producing molecules essential for our survival, such as vitamins B12 or K, to modulate the absorption of sugars and lipids and to transform secondary bile acids into metabolites that influence our carbohydrate and lipid metabolism. It has been estimated that 10% of our daily energy is provided by our gut microbiota.

• The presence of the microbiota provides effective protection against colonisation by pathogenic bacteria. This barrier effect relies on a set of complex mechanisms, including competition between commensal bacteria and pathogens for the same energy substrates, the production by commensal bacteria of antibiotic substances that block the growth of other bacteria, and the stimulation by commensal bacteria of their host's immune defences.

MICROBIOTA

• Microbiota bacteria do indeed shape our immune system. They simultaneously induce signals that enhance our anti-infective defences and other signals that avoid a surge in responses, causing inflammation and tissue destruction.

These effects of microbiota take place in the gut and reinforce its function as a barrier against entry by gut bacteria. They also work on the immune system away from the gut, in the lungs, for example, by providing additional protection against bacterial and viral infections, while limiting allergic responses, the effects of which vary anyway according to microbiota composition.

• The signalling pathways activated by the microbiota are the subject of a large number of studies. In the gut, these signals may be the result of direct contact between bacteria and host cells. Nevertheless, the majority of commensal bacteria present in the intestine are wrapped in a mucus film that keeps them away from the epithelium.

By contrast, microorganisms produce an abundance of metabolites that are able to induce signals locally in the mucosa, but also remotely, after spreading through the blood and lymph systems. Some metabolites can also activate relays in the nervous system.

A major challenge today is that of establishing which of the metabolites produced by microbiota have effects on the host, determining the signals induced and their consequences for the host, and identifying the particular species involved in their production and the mechanisms regulating their production in the gut. The biological effects already observed are indeed considerable when it comes to regulation of inflammation, carbohydrate and lipid metabolism, behaviour, satiety or pain, for example.

Such studies hold out hope for the development of new biomarkers derived from bacterial metabolism or based on the quantification of specific bacteria. The microbiota accessible in faecal samples could therefore prove to be a source of new diagnostic biomarkers or bacterial species that can be used for therapeutic purposes. The Faecalibacterium prausnitzii bacterium, along with a set of Clostridium strains capable of exerting anti-inflammatory effects, are examples of these new probiotics.

Finally, stool transplantation has recently been classified as a medicine in France. The principle involves the inoculation of a patient (the recipient) with human stool from a healthy individual (the donor).

The only currently accepted indication is for antibiotic-resistant Clostridium difficile diarrhoea, the efficacy of which was initially demonstrated by a Dutch team and is now confirmed. Several clinical trials are underway to test faecal transplantation in other diseases such as Crohn's disease, irritable bowel syndrome or liver diseases.
The results of the first published studies for ulcerative colitis, an inflammatory bowel disease, are encouraging, but fall far short of the success rate seen with Clostridium difficile infection.

• Other approaches in the form of capsules are currently being developed. A number of issues concerning efficacy and safety have yet to be resolved. Although the transplanted strains will probably be able to establish themselves in the gut of patients who have developed Clostridium difficile because their own flora has been eliminated as a result of antibiotic resistance, permanently establishing new strains in an individual with a well-established microbiota is no simple operation.

In characterising microbiota as related to health or disease, and with our knowledge of the functions of microbiota, it is incumbent on us to consider the host, whether human or animal, in an integrated way and to develop an ecological approach to our health.

BARRIERS TO BE OVERCOME

Microbiota appears to be an ecosystem whose complexity far exceeds anything ever imagined. Not all the tools needed to understand this complex ecosystem are in place, and there is still much work needed to streamlin this information.

● **Methods are being developed to study microbiota**

The quality of the methods and tools used will provide insight into how microbes and human cells interact, for the discovery of new metabolites and original molecular targets, and to embark on therapeutic experiments.

● **Hypotheses: the aim is to prove a causal link between changes in microbiota and specific diseases**

The role of microbiota is thus widely alluded to in a number of neuropsychiatric diseases: autism, anxiety and depression. Other studies have suggested that microbiota may play an important role in neurodegenerative diseases: it is thought to be implicated in brain inflammation in Alzheimer's disease by contributing to the formation of amyloid plaques. Very recently published or ongoing studies suggest specific pathways involving metabolites produced by certain bacterial strains.

● **The ability of microbiota to resist changes**

Microbiota may in fact hinder any attempts at therapeutic manipulation. Thoroughgoing work is still needed to understand the mechanisms that control the composition of microbiota in order for it to be manipulated at minimal risk. An ever increasing number of researchers are turning their attention to this issue.

● **Inadequate construction of an ecosystem dedicated to researching and developing new microbiota-derived treatments**

France is well placed thanks to some specialist research laboratories that have played a decisive role in describing microbiota in normal and pathological situations and in identifying strains of interest. Nevertheless, significant efforts still need to be made to share databases and standardised procedures between research actors, to set up and streamline the tools and platforms needed for mechanistic studies, to create the bioinformatics approaches required to integrate and interpret the mass of data generated, and finally, to develop start-ups capable of qualifying biomarkers and developing advanced therapeutic solutions, based on the implantation of specific bacteria and faecal transfers.

MICROFLUIDICS

WHAT ARE WE TALKING ABOUT?

Microfluidics is the science of fluid manipulation on the micro-scale (of the order of one-thousandth of a millimetre). It is used in lab-on-a-chip devices, miniaturised laboratories measuring just 1 or 2 centimetres that are capable of very fast analysis using a minimal number of reagents. For example, it is fair to say that DNA sequencers could not perform without microfluidics.

──── **Définition** ────

Fluid is a material medium that is infinitely deformable. This term includes liquids and gases, and by extension, for the purposes of this factsheet, blood, water, oil, cell suspensions, DNA samples, etc..

This burgeoning field of research is often inspired by observations of nature, which perfectly controls fluid flows in microchannels.

A tree is an example of a microfluidic system. It evenly distributes sap to thousands of leaves by relying on a network of millions of tiny capillaries with diameters varying between hundreds of microns and about 30 nanometres. There are thousands of integrated valves in the tree that prevent the formation of systemic embolism.

● **The benefit of microfluidics**

1. It speeds up fluid-based diagnostics and analyses. From one drop of blood, for example, TSH (thyroid stimulating hormone) and different hormone levels can be obtained in a few minutes, pathogens can be identified and DNA and RNA sequencing can be performed in a matter of hours.
2. It allows multiple analyses to be carried out simultaneously on a massive scale. d'échantillon, une cellule unique "single cell" par exemple.
3. It performs analyses from very small sample quantities, a single cell for example.
4. It lowers the costs of analysis.

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

● Personalised medicine: microfluidics will identify, from a sample of hundreds of thousands of cells, those harbouring oncogenic mutations. This information can thus be used to initiate cancer treatment by significantly reducing recurrence.

● The widespread use of liquid biopsy, whereby circulating tumour cells can be retrieved and as much information on the composition of the tumour and its stage of development thus collected without the need for any surgical intervention.

● With microfluidics, millions of tests each hour could be performed using microdroplets. This method can be used to select groups of cells that produce, for example, highly effective antibodies against a bacterium.
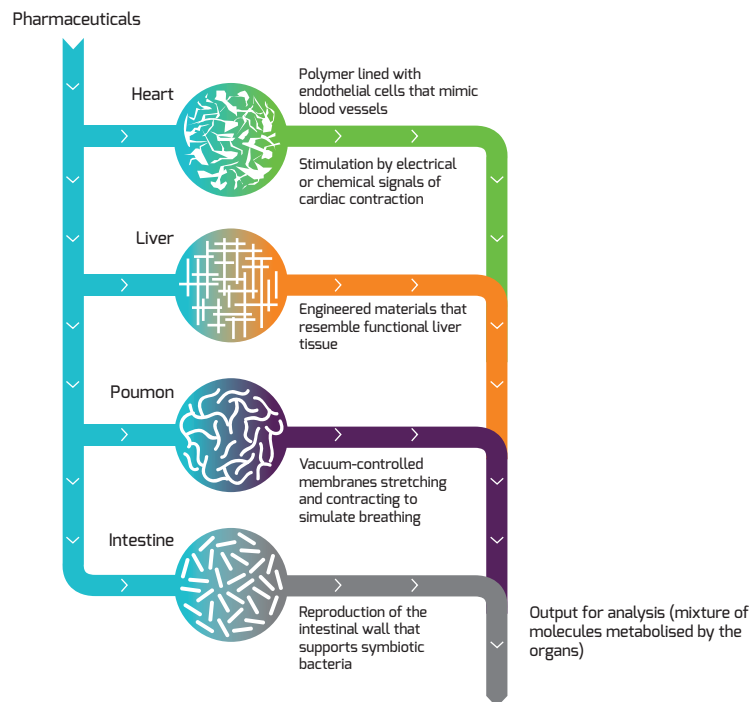
An example of researching the best antivirus weapon

Step one the virus is inoculated into an animal. The cells of the animal's immune system - the B cells - react by producing antibodies. These then combine with specific molecules present on the surface of the virus called antigens.

Step two B cells with enhanced affinity for antigens produce better antibodies. And it is precisely this "elite" that we are trying to identify. Blood is then taken from the animal to recover the B cells, which are then placed in a nutrient solution and sent to a channel in the microfluidic culture plate. This channel will cross another one in which an oil circulates with a controlled flow. As the two fluids are unable to mix, the oil will then form a small container, encapsulating a single cell, with a little of its nutrient liquid.

Step three each droplet then becomes a test medium with its B cell, which will produce its own antibodies after a few days of incubation. All that remains is for the researchers to introduce the antigens of the target virus and to use an optical system to detect which B cell produces the most

● Microfluidics could revolutionise the pharmaceutical industry and the search for new drugs by managing to test molecules 10,000 times faster and 10,000 times more cheaply. It will also be able to create new and more efficient delivery systems.

● Organ-on-a-chip technology is making headway thanks to advances in stem cells research. The next goal is to create a system in which all human organs are connected through microfluidic blood capillaries, as shown in the diagram below.

Pharmaceuticals

Heart — Polymer lined with endothelial cells that mimic blood vessels / Stimulation by electrical or chemical signals of cardiac contraction

Liver — Engineered materials that resemble functional liver tissue

Poumon — Vacuum-controlled membranes stretching and contracting to simulate breathing

Intestine — Reproduction of the intestinal wall that supports symbiotic bacteria

Output for analysis (mixture of molecules metabolised by the organs)

MICROFLUIDICS

CURRENT DEVELOPMENTS

▶ **Microfluidics is set to spark a revolution in biology and chemistry similar to that brought by microprocessors to electronics and computers.**

• **Some key figures**
- A very large number of companies are currently developing microfluidic technology. More than 250 companies and 10,000 researchers around the world are working in this field.
- The microfluidics market is valued at USD 6 billion a year[1].
- For example, the single cell market, which is heavily impacted by microfluidics, is valued at USD 1 billion.

• **Where France stands**

France is one of the world's leading nations in the field.

400
people

50
laboratories

50
start-ups

─── **A flagship institute: the Institut Pierre-Gilles de Gennes** ───

Microfluidics or the art of using new technologies to manipulate minute volumes of fluids
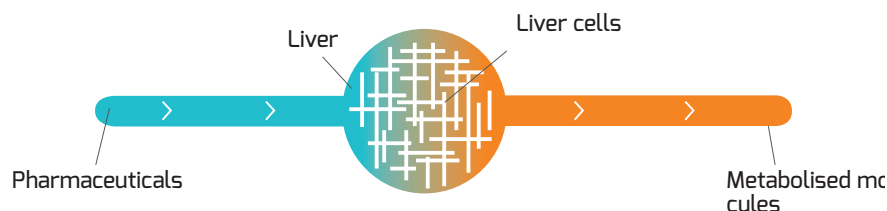Speaking of the world of industry and of scientific research, Pierre-Gilles de Gennes would say that "both have everything to gain by working together". He repeatedly spoke of the need to learn to overcome the boundaries between scientific disciplines for more fruitful rewards and for them to reach the full measure of their potential. The Institut Pierre-Gilles de Gennes (IPGG) was created in this spirit: to bring together, in a cross-disciplinary domain (microfluidics), experts from various disciplines (physics, biology, chemistry, technology) and develop fundamental and applied research in health, energy, food, cosmetics, instrumentation ... Twenty start-ups are incubated there.
www.institut-pgg.fr

▶ Microfluidics is already a reality: it allows complex analyses to be performed on single drop and products to be injected more easily into the human body.

• **Some examples**

- **The lab-on-a-chip** can diagnose an actual heart attack from a drop of blood. The diagnosis is delivered in fifteen minutes whereas the traditional systems would require more than ten hours.

- **The genotyping chip** makes it possible to identify not only an object (for example a virus) from characteristic gene sequences, but also RNA and proteins.

- **Pathogen diagnostic chips** use a body sample to determine the presence of a virus, bacteria or microorganism in minutes, and at very low cost.

- **Microchip blood testing** now take twenty minutes to detect the AIDS virus, syphilis and a dozen other infectious diseases (hepatitis B and C, herpes, etc.)

- **Micropumps** are used to inject a product into the human body. The injection pump delivers insulin to the liver in the treatment of diabetes and is more effective and comfortable for the patient.

BARRIERS TO BE OVERCOME

▶ Microfluidics is making breakthroughs in the field of cancer by modelling certain organs (liver, kidney, lung, intestine).

Liver
Liver cells
Pharmaceuticals
Metabolised molecules

The challenge for microfluidics is to reproduce the vascularisation of these organs and all transfers between the vascularisation fluid and the internal tissues of the organ; prototypes are currently being used with this in mind.

● **BioFab 4500, a 3D printer capable of printing human organs**

● **Scientific bottlenecks**

These relate to:

1. the limits of fluid handling capabilities which, although powerful, still need to make further progress;
2. the limits of building complex microfluidic systems able to mimic the complexity of living organisms, in organ-on-a-chip technology or fluid management in DNA memory.

● **Economic bottlenecks**

These require:

1. awareness and support in order for France to make leadership gains;
2. reconciliation between research and business as a boost for adventurous researchers;
3. development of the start-up base and risk-taking to allow world leaders to emerge.

NANOMEDECINE

WHAT ARE WE TALKING ABOUT?

At the beginning of the 20th century, the German scientist Paul Ehrlich came up with the theory of a "magic bullet" that would actively target infectious agents within the body. This concept is now a reality thanks to nanotechnology-enabled drug vectorisation. Nanomedicine uses nanotechnology to develop innovative applications, more precisely nano-objects in the field of health, by exploiting the physical, chemical and biological properties of materials at the nanoscale. Having materials at the nanoscale makes it possible to act within cells and to draw on entirely new skills, two factors that generate innovation.

● **The scale of nanomedicine**

A nanometre is a unit of measurement as small as one billionth of a metre, about 1/50,000th the width of a human hair!

STANDARD NANOMEDICINE SIZE

| 10^{-1} NM WATER MOLECULE | DNA | 10^0 NM PROTEIN | 10^1 NM RIBOSOME | 10^2 NM NUCLEAR PORE | 10^3 NM MITOCHONDRION | 10^4 NM CELL |

Tunnelling microscopy

Atomic force microscopy

Electron beam lithography

Photolithography

Virus-like particles

Dendrimers

Liposomes /micelles

Nanoparticles (nanotubes, quantum dots)

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **The applications of nanomedicine will lead to more accurate and appropriate treatment of diseases.**

They are very precise in their ability to interact in a targeted way with tissues, cells, and even molecules. At the nanoscale, some substances or materials can change properties and become more resistant, more reactive ... Others, like nanocrystals, cause faster dissolution of the active principle than the active principle alone.

• Nanovectors specifically targeting certain cell types to release an active substance without inducing toxicity in other cell types.

• Nano-objects bearing a fluorescent or radioactive label: able to detect functional impairments at an early stage; helpful in image-guided surgery.

Nanotechnologies will also make it possible to design nanocomposites that bypass rejection phenomena following grafts or in regenerative medicine ...
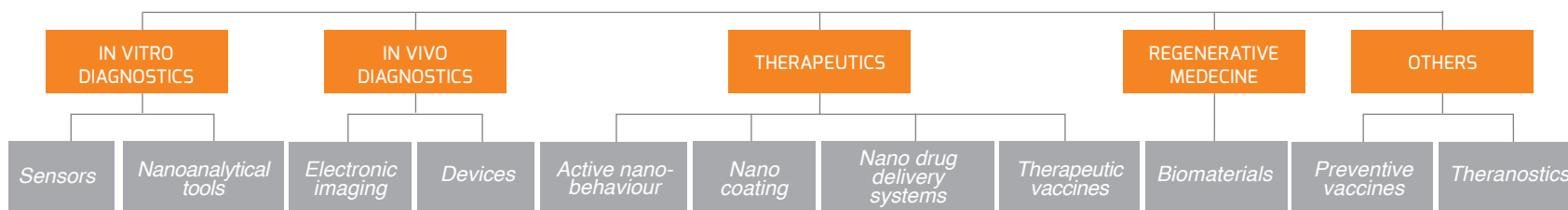
Nanomedicine

IN VITRO DIAGNOSTICS		IN VIVO DIAGNOSTICS		THERAPEUTICS				REGENERATIVE MEDECINE	OTHERS	
Sensors	Nanoanalytical tools	Electronic imaging	Devices	Active nano-behaviour	Nano coating	Nano drug delivery systems	Therapeutic vaccines	Biomaterials	Preventive vaccines	Theranostics

Globally, nanotechnologies are contributing to the development of new medical techniques for diagnosis, therapy and patient follow-up. Today's scientific developments in nanomedicine will deliver new technological responses and significantly improve treatments by 2030.

● **The contributions of nanomedicine by 2030**

• Nano-objects capable of deceiving the immune system to better treat certain diseases.

• Nano-objects capable of activating the immune system to restore an organism's response to disease.

Therapeutic applications

DELIVERY SYSTEM	ACTIVE IMPLANTS	NANOMEDICINES
• *Nano-needles (administration and monitoring of nanoparticles crossing the blood-brain barrier)*	• *Restoration of vision, pacemakers*	• *Nanoparticle heating*
• *Nanotubes*	• *Hearing aids*	• *Photodynamics*
• *Nanovectors for gene therapy*	• *Knee prostheses*	• *Chemotherapy*
	• *Device for control of motor function*	• *Radiotherapy*

NANOMEDECINE

Nanomedicines will also be very useful in imaging by acting to "switch on" a tumour and make it more easily visible on MRI. This gives rise to a particularly innovative technique, one that is still at the experimental research stage, namely "nanotheranostics", in which a drug and an imaging agent are combined in the same administered nanoparticle. This allows it to cure while visually recording the path of particles, thereby ensuring that they reach the areas targeted in the body. Theranostics also makes it possible to visualise nanoparticle accumulation and then trigger the local release of the active principle with, for example, ultrasound-activated microbubbles.

Trials are also being conducted to vectorise microRNA, i.e. small nucleotide sequences. Another challenge is to succeed in targeting the brain tissue by crossing the blood-brain barrier. Although essential for the protection of the central nervous system, it does however act as a brake to the treatment of localised pathologies inside the skull. With the evolving capabilities of neurosurgical tools, the application of new nanomedicines in the treatment of brain cancers is emerging as a promising area of research.

CURRENT DEVELOPMENTS

▶ The use of nanovectors, which are capable of transporting and releasing the active substance of a medicine into the target cells, especially in the case of cancer or inflammatory diseases, and of nano-objects, which are able to amplify the efficacy of radiotherapy while preserving healthy tissue and improving diagnosis.

● **The use of nanovectors**

Nanomedicine is today offering answers to the difficulties encountered by conventional therapeutics. It involves integrating an active principle into a vector (micelle, liposome, polymer shell), or the use of mineral nanomaterials (gold nanoparticles, porous silicon, etc.) to specifically direct the drug to a target tissue, without it being distributed elsewhere in the body.

Vectorisation can also involve an active principle, the physicochemical properties of which hitherto prevented it from being administered as such. Carried by the nanovector, the active principle is further protected by biological degradation before reaching its target tissue.

It can finally be "triggered" or released gradually over time, using its combination with a nanocomposite that can be activated through a signal (laser, X-rays, ultrasound, etc.).

Nanomedicines therefore improve the benefit/risk ratio of medicines by increasing their efficacy and bioavailability in the target tissue or organ, while reducing dosage and toxicity risk.

This type of nanomedicine could potentially play a role in many diseases. However, it is in cancer where most advances have been made: Nine nanomedicines are already being marketed worldwide. Clinical trials are currently being conducted for 15 other products, 5 of which have reached phase III. This type of treatment provides two major advantages in the fight against cancer. Since it is more targeted, healthy tissues are less damaged than with chemotherapy and radiation. And by penetrating into the heart of tumour cells, the active ingredient is more effective. It still has its limits though: nanovectors can only be distributed in tumours if they are vascularised, which means determining treatment in advance in order to offer personalised medicine. Moreover, the necrotic core of tumours does not always allow for delivery of an active principle and requires a combination of therapies to prevent tumour recurrence.

These nanoparticles are injected into the patient's bloodstream via an infusion, for example. The nanoparticles transport their cargo to the cancer cells, thereby preventing most of the harmful effects that the drug might have on healthy tissues. In addition, when an active substance is delivered in the form of a nanomedicine, it is encapsulated and therefore protected from degradation throughout its journey in the body.

The most commonly reported route of administration at present is the systemic route. However, as nanoparticles are recognised as non-self particles, they will be dealt with by the immune system's cells to be degraded and eliminated by the liver.

To solve this problem, researchers make a simple modification to the surface of the nanoparticles to sneak past our immune system's defences. Many strategies aim to increase the circulation time of systemically injected particles. Indeed, if vascularised tumours are to be attained, by increasing the lifetime of the particles in the blood, the number of particles accumulated in the tumours will increase.

A maximum quantity still needs to be conveyed to the cancer cells, however. Researchers must once again apply their innovative talents to this area because, at present, the accumulated amount rarely exceeds 5% of the injected dose. Most of the dose is deposited in the liver, which limits the use of repeat injections (risk of toxicity).

● **Ongoing improvement of nanovectors**

Discovery by a French team led by Professor Patrick Couvreur

Instead of encapsulating the drug molecule, the team imagined linking it by a chemical bond to the carrier squalene, a natural lipid found in human skin, olive oil or whale fat. When coupled with a drug molecule and placed in water, this lipid spontaneously forms nanoparticles. Once "squalenized", the vector can carry up to 50% of drug to the cell or tissue to be treated, compared to 1 to 5% with a conventional capsule. Tests carried out with an anticancer agent in animal tumour models (pancreatic/colon cancers, leukaemia) showed much greater efficacy than with the conventional drug. Similarly successful tests have been performed with another molecule used in the treatment of stroke. In both cases, the level of drug found in the circulation is much higher..

● **Other avenues of research**

Adding molecules to the nanoparticle surface that recognise only cancer cells. Researchers are exploring the prospect of third-generation nanoparticles with a view to targeting cancer stem cells that are highly resistant to conventional chemotherapy.

Combining nanomedicines with physical methods to increase the speed and quantity of drugs released into the tumour. The administration of a drug can therefore be triggered remotely by ultrasound emission.

● **Nano-objects to amplify the efficacy of radiotherapy**

Nanomedicines are also used as a heat source to increase the efficacy of conventional radiotherapy or chemotherapy treatments. When cells in the body are exposed to higher-than-normal temperatures, changes take place that make cells more sensitive to the effects of radiation or the administration of chemotherapy.

The French company Nanobiotix has designed a nanoparticle called NanoXray, composed of hafnium oxide. This compound is capable of emitting many electrons when activated by X-rays.
This causes heating and thus significantly enhances the efficacy of radiation therapy on a tumour, with a view to reducing the radiation dose needed.

The French company NH TherAguiX also developed nanoparticles, gadolinium-based this time, to potentiate the effect of radiotherapy. These intravenously injected nanoparticles (< 5 nm and visible on MRI) are extremely promising. Dr Nathalie Mignet's team has also demonstrated the potential of these nanoparticles for renal function imaging.

NANOMEDECINE

● Improving current diagnostic tools

Many imaging techniques (radiography, MRI, scintigraphy, etc.) are based on monitoring what happens to contrast products when injected into the body. Nanoparticles offer an interesting alternative to the agents currently used (organic fluorides or radioactive isotopes), by potentially improving the resolution and features of the images obtained, while being better tolerated by the body.

▶ Today, properties of nanoparticles are already being exploited in magnetic resonance imaging (MRI), which uses iron oxide nanoparticles for certain applications. Research is ongoing to expand the range of available agents and the imaging techniques suitable for these agents.

● Nanomedicines bring multiple benefits

Nanomedicines are subject to the same regulatory constraints as conventional medicines before marketing authorisation (MA) is granted, especially when it comes to assessing actual medical benefit and possible adverse reactions.

Diagnostic benefits

- *Improved specificity targeting*
- *Improved performance: sensitivity, detection threshold, speed*
- *Early disease detection*
- *Reliability and accuracy of results*
- *Device miniaturisation*
- *Stabilisation of biocomponents*
- *Lower consumption of reagents for analyses (lower costs)*
- *New and better imaging technologies*

Therapeutic benefits

- *Improved drug efficacy*
- *Fewer side effects and less toxicity*
- *Reduction in the amount of active molecule each time*
- *Targeting of therapies*
- *New therapeutic approaches and new mechanisms of action*
- *Improved biocompatibility for tissue engineering*

BARRIERS TO BE OVERCOMER

● **Speeding up the medical applications of nanotechnology**

The number of patents filed in France is by no means insignificant. Yet we must not fail to recognise that the medical applications of nanotechnologies are generally still poorly developed. Although still unforthcoming, companies are in fact working on nano systems without saying so, the major difficulty being production and characterisation to enable them to meet the regulations of the National Agency for Safety for Medicines and Health Products (ANSM).

France must structure itself in this area by setting up a dedicated laboratory, similar to the American NCL[1], with recognised laboratories for nanotechnology validation. We are forced to rely on existing groups such as the French Society of Nanomedicine, which brings industry and researchers into contact with one another and draws on its existing web of collaborations.

In other words, an active French network needs to be built. These researchers can then contact the National Research Agency (ANR), which has funded many nanotechnology projects, or Europe, under its dedicated Nanomed programme. Finally, most nanomedicines are listed as "medical devices" to facilitate their marketing, making it difficult to find them.

● **Going forward in the field of nanotoxicology**

The recent development of nanomaterials outside the field of medicine (cosmetics, food, etc.) has led to applications which, for want of objectivity and toxicological and epidemiological studies, have left the public somewhat wary of all nanotechnologies. Advances in nanotoxicology will be essential not only to answer questions relating specifically to the field of nanomedicine, but above all to understand the non-medical risks of dermal, digestive or respiratory exposure to nanoparticles. Unfortunately, the studies are difficult to compare and rarely usable: a network with qualified methods would be necessary.

● **Responding to the philosophical and ethical questions raised by the use of nanotechnologies**

The handling and use of nanomaterials have an impact on living systems and the environment. As this field expands and applications increase exponentially, civil society and researchers are questioning the risks inherent in this new field: do we control them, can we contain them sufficiently? First of all, there are safety and toxicity risks for living beings and the environment.

Societal upheaval is yet another consideration: is the use of nanomedicines and nanotechnologies likely to lead us towards an era of human enhancement and profoundly transform the very notion of humanity as a consequence? This is why some national or international public institutions are advocating not only for an assessment of the safety of nanomedical products but for an ethics and strict regulations around these products, on a global scale if possible.

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[1]*US Nanomedicine Characterization Laboratory, founded by the National Cancer Institute (NCI) to speed up the development of promising nanoprocessing and nano diagnostic techniques.*

REGENERATIVE MEDICINE

WHAT ARE WE TALKING ABOUT ?

Cell therapy involves transplanting cells to restore tissue or organ function. The objective is to provide long-term patient care through a single injection of therapeutic cells.

● **The principle behind cell therapy: the example of autologous iPS cell transplantation**

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **Cell therapy offers a real opportunity to meet the challenges of regenerative medicine.**

In March 2018, two patients with AMD (macular degeneration of the retina) recovered their sight after a cell graft onto their retinal fundus. They were able to read a text at a rate of 80 letters per minute, the standard being 200 letters per minute.

This is a major groundbreaking success, a proof of concept that opens the door to treatments with cell therapies for different degenerative diseases such as degeneration of the cartilage (osteoarthritis), muscle (myopathy), skin and bones (diabetic ulcers), brain (neurodegenerative diseases) that affect millions of people around the world.

Removal of a skin fragment

Culturing of the sampled skin cells

Sox2   Klf4

Oct4

C-myc

Addition of 4 genes to these cells by viral infection

Graft onto the person in whom the skin biopsy was performed

iPS cell differentiation into desired tissue (neurons, muscle cells, retinas, etc.)

After several days, pluripotent cells are obtained[1]

[1]*Pluripotency: ability of a cell to be able to generate all the tissues of an adult body*

CURRENT DEVELOPMENTS

Two problems need addressing before allowing patients access to cell therapy.

- **A quantitative issue: the example of myocardial infarction**

2 to 5 billion (10^9)

heart cells (cardiomyocytes) are destroyed by myocardial infarction heart cells (cardiomyocytes) are destroyed by myocardial infarction

2×10^{14} cells

or 2 x 109 x 100,000 cells must be produced to treat these 100,000 patients and transplant them with new heart cells

100,000 heart attacks

are treated each year in France

10 millions

Petri dishes are needed to meet this demand for heart cells (not to mention the use of skin, bone, muscle cells etc. for other diseases)

▶ There is therefore a need to move to an industrial phase of cell production, whether they be heart, retina, muscle or other cells.

- **A qualitative issue**

These cells, whether bone, heart or retina cells, face being rejected as foreign bodies by the immune system. A way has to be found, therefore, to deceive the immune system. Two main lines of action are identified:

1. Deceive CD8 and natural killer (NK) cells, the immune system's two lines of attack, by producing phantom lines for CD8 and neutral lines for NK.

2. Pursuing another line of reasoning: understand why the immune system allows a woman to carry a baby - who may be regarded as a foreign body - inside her. Placenta cells carry proteins that prevent the immune system from attacking because they come from the insertion of retroviral sequences, retrotransposons, into the genome of one of our ancestors. A retroviral sequence can therefore be introduced into cell lines (iPS or ES) before transforming them into skin cells, bone cells, etc.

BARRIERS TO BE OVERCOME

Industrial, economic and technological issues

We must embark on an industrial phase of stem cell production for therapeutic use. The global market is growing every year.
The market value is estimated to be worth USD 12 billion in 2020 and USD 31 billion in 2026. It is worth USD 4.5 billion at present. Ten stem cell products are on the market and none have been produced in France.

- **A strategic choice to be made**

▶ "Moving from academic studies to industrial stem cell production is a paradigm shift that involves a significant change in the scale of cell preparation and production processes to translate into marketable drugs[1]."

- **A scientific issue**

How do we prevent stem cell cells from proliferating uncontrollably in the body? How can we destroy them? Researchers are proposing to introduce a suicide system into the cell that can be activated at will. It is based on the mechanism of Aciclovir ®/Acycl
Aciclovir ®/Acyclovir is converted into a nucleotide by an enzyme, viral thymidine kinase, which is 3000 times more effective than cellular thymidine kinase. Once introduced into viral DNA, this nucleotide blocks its replication and destroys the cells carrying the herpes virus.

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[1]Recommendations of the Academies of Medicine and Technology published in April 2018.

GENE THERAPY

WHAT ARE WE TALKING ABOUT?

Gene therapy is a therapeutic strategy that involves the penetration of genes into an individual's cells or tissues to treat a disease.

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**

Modification of
IN VIVO
cells

Modification of
EX VIVO
cells

Naked DNA
solution

Sampling
of diseased
cells

Retrovirus containing
the gene to be
transferred

Liposomes

Target organ

Intravenous,
intramuscular,
intraperitoneal,
aerosol injection

Ex vivo
culture

Infection
of cells
in culture

Therapeutic
gene

Viral vector

Reintroduction
of modified
cells into
the patient

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030 ························

▶ **Gene therapies are booming through massive industry investment in this field**

It is now possible to develop viral vectors capable of transferring genes efficiently and sustainably, both in vivo and ex vivo. Progress has made it possible to fundamentally change the genetic makeup of these viruses: they can thus be made as harmless as possible and quieter for the host's immune system.

The range of vectors is broad: there are non-replicating, integrative or non-integrative, viral or non-viral vectors suited to different indications.

• Integrative vectors, such as retroviruses and lentiviruses, allow a therapeutic gene to be inserted into the host's DNA, thus ensuring its retention in daughter cells after division.

• Non-integrative vectors (adenoviruses, AAV), on the other hand, prevent the random integration of the gene into the host's DNA

• Other tests are even being attempted with naked DNA directly injected into the body.

▶ AAV viral vectors, derived from the human adeno-associated parvovirus, have emerged over the past three decades as extremely powerful tools because of their simplicity and ability to infect a wide variety of tissues in vivo.

CURRENT DEVELOPMENTS ························

The first ever gene therapy trial in humans dates back to 1995 with the treatment of a patient with severe immunodeficiency (ADA SCID) by injection of stem cells and genetically modified lymphocytes. This first step led to a breakthrough in the 2000s following the successful treatment by Alain Fischer and his team of children with another form of immune deficiency (SCID X-1).

Gene therapy is often portrayed as a means of combating monogenic diseases, i.e. diseases associated with the dysfunction of a single gene, by injecting a healthy gene to replace a diseased gene.

The reality is quite different: many gene therapy trials have been carried out in the field of rare diseases. In 2016, a 13-year-old boy with sickle cell disease was successfully treated with gene therapy. A world first achieved by doctors at Necker Hospital. The teenager, who suffered from a particularly severe form of sickle cell disease, saw the disappearance of symptoms such as painful episodes, chronic anaemia, fatigue and joint disorders that sometimes even prevented him from walking. This success offers hope of a treatment to the millions of people living with sickle cell disease worldwide. Each year, 480 babies are born with the disease in France, two-thirds of whom in the Ile-de-France Region.

Many oncology trials are currently underway. This is because gene therapy appears to be a formidable vector of innovation by giving the immune system the ability to destroy cancer cells.

This mechanism has already been used in marrow transplants performed to treat leukaemia: the effectiveness of the transplant relies on the action of donor lymphocytes present in the graft, which will attack the leukaemic cells. The use of a compatible donor (often from the same family) nevertheless requires the prior destruction of the transplanted patient's immune system to avoid rejection. Hence the idea of using the patient's lymphocytes as a medicine to best avoid the phenomena of rejection.

GENE THERAPY

CAR-T cells are the "industrial" products developed from this idea: they are made from the patient's T cells and then genetically modified to express on their surface an artificial receptor called a Chimeric Antigen Receptor (CAR), capable of specifically recognising cancer cells.

These synthetic T cells can thus recognise not only HLA[1] complexes and peptides, but also structures such as sugars, carbohydrates or glycolipids, which can be interesting targets on cancer cells. Indeed, CARs have alternative receptors that function independently of the system for detecting and recognising foreign cells in the body.

The enthusiasm for CAR therapy stems from the potential that this technique holds, namely to make an absolutely specific drug that is capable of distinguishing tumour cells from normal ones and of reconciling the sometimes contradictory imperatives of efficacy and absence of toxicity.

● **Challenges to be met**

• **The challenge of vector quantity**
Several types of vectors can be used but lentiviruses appear to be the most effective so far.

• **The challenge of quality**
CAR therapy is the result of an assembly of processes and techniques to produce "designated" lymphocytes for the target antigen. One way to further improve the effectiveness of gene therapy is to use the CRISPR-Cas9 technique to avoid introducing the gene randomly into the T-cell.

● **Number of clinical trials worldwide investigating CAR therapies**

● **Nombre total d'essais cliniques dans le monde par grande zone géographique**

● **Gene therapies in development**

BARRIERS TO BE OVERCOME

These new drugs from living organisms require mastery of gene transfer technologies to collect, modify and re-inject lymphocytes, and eventually cure many forms of cancer.

There are now several indications for which gene therapy works: SCID-X1 immunodeficiency or bubble baby disease, adrenoleukodystrophy (neurodegenerative disease), beta-thalassaemia (hereditary disease affecting haemoglobin).

It is the result of an effort to mobilise this research, partly through support from the European Commission with investments of hundreds of millions of euros (Horizon 2020 Health programme). Gene therapy has thus reached a level of maturity to be rolled out industrially.

Gene therapy has yet to overcome regulatory and industrial hurdles to successfully deliver innovative new medicines. Standardising viral gene therapy drugs remains a real challenge given the paucity of registered innovative therapies and hence only a handful of examples that can shed light on the pharmaceutical development path of drugs of this kind.

▶ The priority today is to make CAR-T cells accessible to lymphoma and leukaemia sufferers, but also, more broadly, to patients with solid cancers. Solid tumours are particularly good at hiding from and inhibiting the immune system. Work is underway to develop a CAR-T cell capable of recognising two targets instead of one.

	AUTHORISATION	PENDING MARKETING	PHASE III	PHASE I / II
● DERMATOLOGY			1	2
● HAEMATOLOGY			3	16
● METABOLIC DISEASES	Tirpavovec 2012		5	23
● NEUROLOGY			1	4
● ONCOLOGY (rare cancers)			1	2
● OPHTHALMOLOGY	Voretigene Neparvovec		3	24
● OTHERS	Strimvelis 2016	1	2	13
TOTAL	**3**	**1**	**16**	**84**

Diagrams adapted from a Wells Fargo presentation - April 2018.

IMMUNOTHERAPY

WHAT ARE WE TALKING ABOUT?

The immune system defends the body against infections and diseases. It is composed of cells (lymphocytes, phagocytes, etc.) and organs (bone marrow, thymus, lymphatic system, etc.) that work together to protect the body and allow it to defend itself against all external pathogens.

IMMUNE REACTIONS

(IMMEDIATE) PHAGOCYTOSIS	
PHAGOCYTE	
infection of the internal environment	*Antigen e.g. bacteria*
Triggering of the immediate, non-specific immune response: phagocytosis	
INGESTION	
DIGESTION	
INFECTION REGRESSES	
DEATH AND DIGESTION OF	

SPECIFIC BACTERIA

LYMPHOCYTES

B LYMPHOCYTES (OR CELLS)

SPECIFIC ANTIGEN RECOGNITION

MULTIPLICATION

T LYMPHOCYTES (OR CELLS)

ANTIBODY SECRETING LYMPHOCYTES

KILLER LYMPHOCYTES (OR CELLS)

ANTIBODIES →

"MEMORY" LYMPHOCYTES

NEUTRALISATION OF ANTIGENS →

DESTRUCTION BY CONTACT OF VIRUS-INFECTED CELLS

PHAGOCYTOSIS OF ANTIGEN-ANTIBODY COMPLEXES

PHAGOCYTE

INFECTED CELLS DESTROYED

Transformed diagram taken from an earth and life science manual (Year 10) publishe

▶ Lymphocytes play a key role in immune response: they are white blood cells found in the blood and lymphatic system.
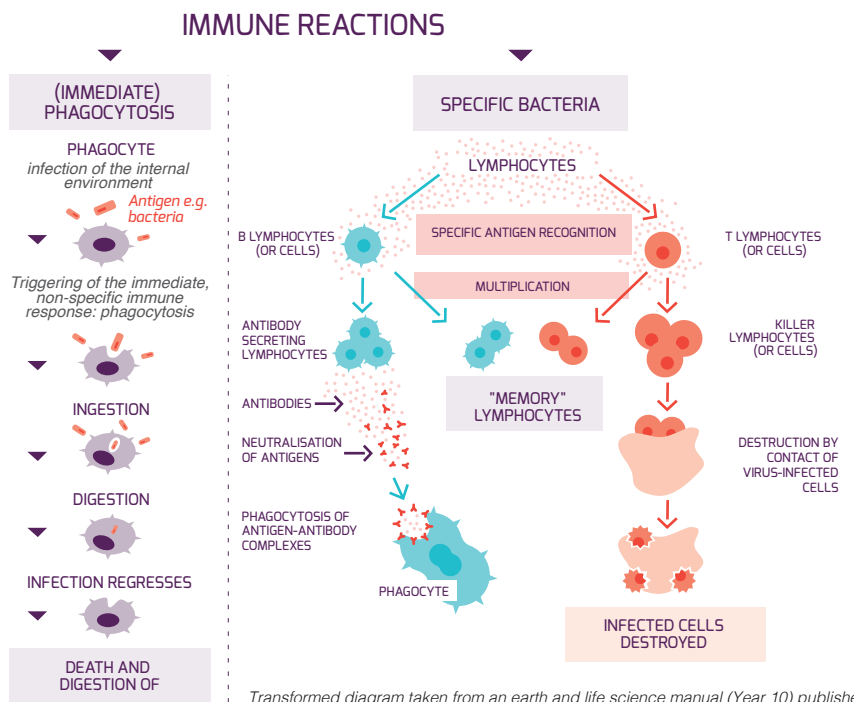
T cells destroy damaged and infected cells in the body and provide B cells with factors that allow them to proliferate and make antibodies. These cells recognise and destroy cancer cells or cells infected with intracellular pathogens (viruses, bacteria, etc.). They develop a more intense response against tumour cells or infected cells that they have already encountered (immune "memory").

B cells can be converted into plasma cells to make antibodies that help fight infections and diseases. Like T cells, B cells can also remember the types of infections and diseases the body has already fought against. If the same germ enters the body, the B cells can quickly produce more antibodies to help fight it.

Antibodies are proteins made by B cells that circulate in the blood. They fight infections and tumours by binding to antigens expressed by infectious agents and then activating mechanisms leading to their elimination. Each antibody is made to recognise a specific antigen.

▶ Cancer and the immune system

The approximately 100,000 billion cells that make up our body are constantly replicating. Some, by replicating, undergo mutations of parts of their DNA. Some of these mutations modify the natural "mortality" of the cells concerned, thereby resulting in uncontrolled proliferation of these non-functioning cells which are detached from the function of the organ they compose, thus forming a cancer. Canceration can lead to the expression of antigens detected by the immune system, T cells in particular.

▶ Immunotherapy is a treatment which stimulates a immune response against cancer. It can be used at each step of the cycle of cancer's immunity, which consists of seven.

When each step is proceeding normally, the patient's immune system can effectively fight cancer. But if one step dysfunctions, cancer can thus proliferate regardless of any immune system's reaction.

The immune system is responsible for fighting cancer and can be very effective in systematically destroying cancer cells, but also less effective while still preventing cancer from taking hold or being overrun by cancerous cells.

Immunotherapies are designed to correct defects in the immune system and restore it to a level of immune equilibrium, a sort of non-aggression pact with cancer that researchers hope to extend for as long as possible.

● **The 7 key steps of immunotherapy**

Step one: antigen release. The cancer cell releases its foreign proteins, tumour antigens, into the tumour environment.

Step two: antigen presentation. Inside the lymph nodes, the T cells recognise the tumour antigens.

Step three: lymphocyte activation. The antigens activate the T cells in the lymph nodes.

Step four: cell trafficking. The T cells migrate in the blood vessels to the periphery of the tumour.

Step five: infiltration of lymphocytes into the tumour.

Step six: binding to the tumour cells. Once in the tumour, the lymphocytes bind to the cancer cells

Step seven: destruction of the cancer cells.

The cycle then starts again: the dying cancer cells release antigens, which activate lymphocytes... Each completed cycle strengthens the immune response. Cancer immunotherapy research targets these different steps in order to wake up the immune system.

IMMUNOTHERAPY

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **By designing drugs or combinations of drugs capable of treating many cancers, even metastases, immunotherapy widens the field in the fight against this disease.**

Recent research shows that the same immunotherapy can lead to a decrease in the size of a tumour, or to its disappearance even, in many cancers. The biological processes of immunotherapy are therefore not specific to one or two types of cancer, but are true of all cancers. This does not mean though that long-lasting tumour immunity can be successfully restored in all patients.

But whatever the type of cancer, there is the chance of a response. The challenge is to increase that chance.

Certain antibodies that are able to reactivate the anti-tumour activity of T cells have been shown to be effective against metastatic melanoma and certain types of cancer (lung, prostate, kidney or bladder). Studies show that the activity of these drugs could prove effective in the treatment of other types of cancer: mesothelioma (known as asbestos lung cancer) ENT, skin, ovarian, thyroid and other cancers.

Several avenues of immunotherapy are being studied in the field of gastrointestinal cancers (stomach cancer, colorectal cancer, etc.) whose tumours have a large number of mutations that could elicit an immune reaction.

Immunotherapy is not just for cancer treatment. It is used to stimulate the immune system against various infectious agents, especially in patients with weakened immunity (HIV patients, patients after chemotherapy or radiotherapy).

It can also be used to treat immune system imbalances in diseases such as lupus, rheumatoid arthritis, multiple sclerosis, etc.. The goal is to block immune responses in addition to conventional immunosuppressive therapies.

CURRENT DEVELOPMENTS

Many approaches are being developed: There are 1,375 cancer immunotherapy clinical trials listed on www.clinicaltrials.gov. The objective of such clinical research is to obtain an immune response that targets cancer cells.

In step 5, for example, the infiltration step, the tumour cells are able to create a physical and/or chemical barrier that prevents their infiltration by the immune cells. One drug that is already approved for use in oncology has succeeded in breaking through this barrier. The immune cells can then enter the tumour and fight the cancer cells.

In the last step of the cycle, step 7, where the immune cells destroy the cancer cells, the proteins PD-L1 and CTLA-4, expressed on the surface of cancer cells like immune system disabling keys, protect cancer cells from immune cell attack. When their action is thwarted by monoclonal antibodies (called "anti-PD-L1" or "anti-CTLA4"), which bind to these disabling keys to reduce their effect, the immune cells can once again kill the cancer cells. The response can be swift and long-lasting.

Yet another peculiarity of immunotherapy is its ability to provoke responses that are not only effective but also long-lasting: many patients, even those with metastatic cancers, are now in remission. They may not be cured, but it is rare to see a response to treatment with such lasting effects at the late stages of cancer progression.

● **Research is thriving**

A recent approach has shifted from selecting immune cells to genetically modifying them. In this type of treatment, immune cells, known as T cells, are collected from the patient's blood and then genetically modified in the laboratory to express specific receptors on their surface. The receptor in question is called the chimeric antigen receptor (CAR). These receptors will allow the modified cells, called CAR-T cells, to detect antigens present on tumour cells.
Combinations of different immunotherapy agents are also being studied, as well as combinations of immunotherapies and chemotherapies. Chemotherapy engages in a very complex interaction with the immune system. And in some cases it can even boost the action of the immune system. Immunotherapy combinations that match specific patient profiles and target specific tumours are a very promising area of contemporary research.

Factsheet produced with the help of **Marc Bonneville**,

President of Ariis (Alliance for Research and Innovation in the Healthcare Industries) and Director of Medical and Scientific Affairs at Institut Mérieux

Many therapeutic trials are attempting to combine an anti-PD-1 antibody with another immunotherapy directed at other targets, chemotherapy or targeted radiotherapy. These combinations can be effective, as is the case with the combined anti-CTLA-4/anti-PD-1 treatment for melanoma, which doubles response rates ... but shows significantly higher rates of severe toxicities. There are many possible combinations and it is absolutely necessary to further rationalise the selection process.

BARRIERS TO BE OVERCOME

The response to a single immunotherapy treatment (monotherapy) varies widely and is not always tangible when measured against the usual criteria for evaluating treatment response.

• Even if there is no response, the treatment may still be beneficial to the patient.

• The response may also be delayed and the tumour may regress long after the start of treatment.

• In some cases, the response may even occur after treatment has stopped.

• In other cases, there appears to be no response, but on receiving another treatment - chemotherapy for example - the patient's response is greatly increased.

Immunotherapy is new and innovative, and is sure be one of the most widely used therapies in the coming years.

We have yet to determine what causes a response to a particular immunotherapy treatment in a given patient and, more generally, have yet to gain a better understanding of the immune mechanisms induced by these immunotherapies and related to hugely diverse tumour microenvironments. With precision medicine, the expression by the patient's tumour cells of the therapeutic target (e.g. EGFR) is a key predictor of treatment response.

With immunotherapy, if PD-1 receptor expression increases the chances of a treatment response, the patient may have chances of a response even in the absence of expression of this receptor, which suggests that PD-1 expression is transient. The impressive efficacy of anti-PD-1 antibodies in Hodgkin's lymphoma also leads us to suspect other mechanisms of action.

Apart from melanoma or Hodgkin's lymphoma, for which the response rates are high (40% and 60% respectively), the percentage of patients responding to these immunotherapies as monotherapy is generally about 15%. One of the current challenges therefore is to improve our knowledge of what targets to aim at (besides PD-1, CTLA-4, etc.), particularly in the wake of advances in computer-assisted imaging, to identify the patient stratification biomarkers associated with response - and avoid unnecessary patient exposure - but above all to gain a better understanding of the resistance mechanisms so as to adapt the therapeutic strategy accordingly.

The therapeutic revolution is already here, the revolution in thinking is in progress: cancer is no longer simply uncontrolled cell development, it is also a failure of immune surveillance mechanisms. Medicine is becoming increasingly personalised, because it is now concerned with the host's immune system rather than with the the characteristics of the tumour.

VACCINATION

WHAT ARE WE TALKING ABOUT?

Between 2 to 3 million lives are saved worldwide each year thanks to vaccines A World Health Organization (WHO) finding that an additional 1.5 million lives could be saved by improving access to vaccination.

The principle behind vaccination is to expose individuals to an attenuated form of the disease to protect them from a much more virulent form. Several so-called live attenuated vaccines have been developed against measles, rubella, mumps, yellow fever or tuberculosis. Virulence attenuation is not always possible. Other methods are then used: some infectious agents can be killed by chemical treatment or heat, but are still able to provoke an immune system response. These are inactivated vaccines. In other cases, only a small portion of the infectious agent is used. These are subunit vaccines, containing a sufficient amount of purified microbial fragments for the immune system to learn to recognise the entire germ.

Regardless of vaccine type, vaccination (as a prevention measure) involves the use of the attenuated or inactivated infectious agent, or components of this agent, to trigger an immune response, which protects against subsequent infection. The immune system is able to recognise the pathogen months and years after vaccination and activate memory cells to produce specific antibodies, killer cells and a set of chemical mediators that block infection.

More than 50 vaccines or vaccine combinations are now available to the French population, the result of 200 years of research. They prevent 29 infectious diseases[1]. Vaccination is one of the most cost-effective investments in the field of public health.

[1] Vaccines Committee Platform, Leem 2018.

Disease or infection	Number of cases BEFORE vaccination	Number of cases AFTER vaccination	Estimated reduction (%)
Diphtheria	45,000	0	> 99%
Tetanus	1,000	17	> 99%
Whooping cough	500,000 to 600,000	1,000	> 99%
Paralytic polio	4,000	0	> 99%
Measles	500,000 to 600,000	< 50,000	> 87%
Hepatitis B, chronic infection	300,000	28,000	> 87%
Rubella, during pregnancy	200	40	> 55%
Mumps	500,000 to 600,000	< 30,000	> 90%
Haemophilus influenzae type B	1,000	< 50	> 90%

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **Improving existing vaccines. A lot of research is underway to improve the influenza vaccine in order to better manage the variability of the virus. Indeed, the influenza virus has the ability to mutate easily.**

Seasonal influenza is an acute viral infection caused by an influenza virus. There are three types of seasonal influenza - A, B and C. Type A influenza viruses are further typed into subtypes according to different kinds and combinations of virus surface proteins. Among the many subtypes of influenza A viruses, currently influenza A(H1N1) and A(H3N2) subtypes are circulating among humans. While B and C are relatively stable, the A virus evolves constantly according to two main mechanisms: antigenic drift and shift.

• **Antigenic drift:** Mutations within genes that code for surface proteins cause minor changes in the virus. The new variant remains so close to the previous one that the immunity conferred by a previously contracted influenza will protect against the new variant. However, the accumulation of these changes leads to an antigenic difference, which results in lower recognition of the new virus by immune systems that have encountered these viruses in the past. This phenomenon requires vaccine strains to change on a regular basis.
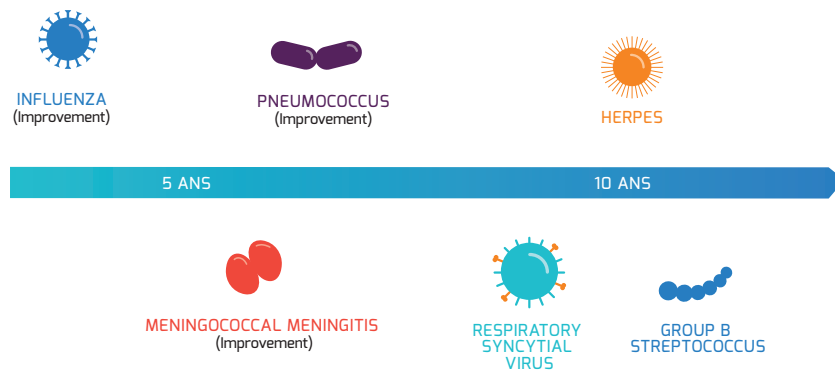
• **Antigenic shift:** radical changes in the antigenic proteins of the virus, with the replacement of one protein by another, give rise to a new virus that differs totally from the one that had been circulating until then. Pre-existing immunity confers no protection and a vaccine prepared with the previous strains is ineffective.

Source diagram: Leem 2018.

VACCINATION

▶ The new influenza vaccines will offer longer protection against the virus (two or three years) and will be better adapted to continuous virus variability.

● **New preventive vaccines**

In addition to a more effective vaccine against influenza, pneumococcus and meningococcal meningitis, five new preventive vaccines are due to be rolled out in a period of five to ten years.

INFLUENZA
(Improvement)

PNEUMOCOCCUS
(Improvement)

HERPES

5 ANS   10 ANS

MENINGOCOCCAL MENINGITIS
(Improvement)

RESPIRATORY
SYNCYTIAL
VIRUS

GROUP B
STREPTOCOCCUS

● **Therapeutic vaccines against cancer or Alzheimer's disease**

These vaccines are in the early stages of research. They are not intended to prevent an infection from developing, but to treat someone who is already sick by stimulating the immune system. Such vaccines are being studied to treat chronic infections such as AIDS or hepatitis B, but also autoimmune diseases, dementia or cancer. Indeed, "tumour antigens" that are present on the surface of cancer cells but absent from healthy cells can be used to direct the immune system against the tumour in order to destroy it.

● **Better use of vaccines and extension of immunisation coverage**

Vaccination prevents morbidity, disability and mortality caused by vaccine-preventable diseases, such as diphtheria, measles, whooping cough, pneumonia, polio, cervical cancer, hepatitis B, rotavirus diarrhoea, rubella and tetanus. However, according to WHO, global immunisation coverage (proportion of children worldwide receiving the recommended vaccines) remained at 86 percent in 2016, with no significant improvement over the past year.
Vaccines are not used enough: again according to WHO, in 2016, 19.5 million infants worldwide were not reached by routine immunisation services such as three doses of DTP vaccine (DTP3). Around 60% of these children live in ten countries: Angola, Ethiopia, India, Indonesia, Iraq, Nigeria, Pakistan, Philippines, Democratic Republic of Congo and Ukraine.

CURRENT DEVELOPMENTS

● **Concentration in the vaccines industry**

In 1960, some twenty companies were operating in the vaccines industry. Today, it is concentrated in a small number of multinational companies that alone are able to research, develop and distribute vaccines.

● **Demonstration of the importance of vaccines in disease prevention**

When a vaccine against an infectious disease is released and immunisation coverage rates increase, the number of people affected by the disease drops significantly. Conversely, when immunisation coverage decreases, the disease reappears. If immunisation is not given priority, Europe may see the resurgence and spread of highly contagious diseases such as polio, measles or diphtheria. Immunisation also protects those who are not vaccinated by preventing the spread of certain infectious diseases. When enough people are vaccinated in a given population, diseases cannot spread.
In the case of measles, which is a highly contagious disease, this can only be achieved if a large percentage of the population (> 95%) is vaccinated The number of lives saved is proportional to the number of people vaccinated. According to WHO, vaccination prevents death and disability

while costing much less than treatment, for the benefit of the individual and society as a whole. Delivering and financing effective health policies must be viewed as an investment and not an expense. Health strengthens the economy, while disease weakens it.

A project that helps to demonstrate this: the European ADVANCE project, brainchild of the Innovative Medicines Initiative (IMI), brings together public partners (European Centre for Disease Prevention, European Medicines Agency, national agencies) and private partners (vaccine companies, academic researchers) to develop the methods and tests needed to build a structure capable of rapidly delivering reliable data on the benefits and risks of available vaccines. This structure should enable regulatory and supervisory authorities for public health to make the right decisions and implement strategies to restore the European public's trust in immunisation, and to use vaccines as safe and effective tools against infectious diseases.

● **Recognition of the role of vaccines in the fight against antimicrobial resistance**

The global upsurge in diseases caused by resistant bacteria, due to overuse or misuse of antibiotics, is a major public health issue. Resistant infections are actually more difficult and costly to treat and are sometimes incurable.

Human and animal immunisation is a very effective way to prevent infections and therefore resort to antibiotics. Vaccines can thus help to limit the spread of antibiotic resistance. By expanding the use of existing vaccines, antibiotic consumption and resistance development can be reduced.

Example

If every child in the world were protected against Streptococcus pneumoniae infection (a bacterium that can cause pneumonia, meningitis and middle ear infections), an estimated 11 million days of antibiotic treatment would be avoided each year. Virus vaccines such as the influenza virus, also have a role to play as patients often take antibiotics unnecessarily when they have flu-like symptoms, such as fever, that may be due to a virus.

The development and use of new vaccines to prevent bacterial diseases could further reduce the development of resistance. We also need vaccines to avoid contracting diseases caused by bacteria, which are now frequently resistant to antibiotics.

There is an alarming spread of multidrug-resistant tuberculosis (MDR-TB). In 2015, an estimated 480,000 people were affected by it. Similarly, new vaccines targeting Staphylococcus aureus (which causes skin and soft tissue infections), Klebsiella pneumoniae (which causes pneumonia, blood and urinary tract infections), Clostridium difficile (responsible for diarrhoeal diseases) and many other pathogens could provide protection against diseases that are becoming increasingly difficult to treat.

VACCINATION

BARRIERS TO BE OVERCOME

- **Meeting the challenge of complexity**

The development of new vaccines and their appropriate use involves a long and complex process. For example, it took nearly 25 years to develop a vaccine against dengue fever. Indeed, the first major step in vaccine research - pure research, which means starting from scratch and developing a vaccine candidate - takes a widely varying length of time. It can be fast - a year or two - or very long, depending on the disease being worked on. For AIDS, the search for a vaccine has been going on for thirty years, for malaria forty years. The reasons for failure are many. They have to do with the variability of the pathogen, difficulty in its handling, evasion of immune responses, etc. Where vaccines are concerned, all the easy things have been done already while all the hard things have yielded nothing thus far. And R&D costs are skyrocketing: vaccine development is now between EUR 1 billion and EUR 4 billion. The scientific community must therefore set priorities for introducing new vaccines that would have the greatest impact on public health, including antibiotic resistance, and promote investment in these products.

- **Integrating the exponential growth in technologies**

from artificial intelligence to new platforms for machine learning, immune system analysis and tissue culture.

- **Accessing the best expertise,**

and do so by being able to rely on the best talents in a highly competitive market.

- **Breaking down silos and public-private barriers**

Global demand for quality and safety is increasing, and it is hard to expect industry to engage in the research and development of new vaccines on its own. Sharing risks and benefits with other actors must be considered.

Two flagship initiatives are being built on this model:

1 The Global R&D Blueprint Initiative

Set up under the aegis of WHO and adopted in May 2016, this global initiative is a concerted strategy to prepare for the rapid activation of R&D activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crisis. It builds on the extensive mobilisation that occurred during the West Africa Ebola outbreak to find ways to contain the disease and protect the population as quickly as possible.

It has led to the development of an effective vaccine against Ebola, but it has also highlighted shortcomings in the overall organisation of the R&D scientific community. These are the lessons that the Blueprint coalition intends to learn from this experience so that the next epidemic can be dealt with effectively.

The R&D Blueprint initiative works on the basis of a list of identified priority diseases.

List of priority diseases identified by the Blueprint coalition (May 2016)

Crimean-Congo Hemorrhagic Fever

Filoviral diseases (including Ebola and Marburg)

Emerging Coronaviral Diseases (MERS-CoV and SARS)

Lassa fever

Nipah Fever

Rift Valley Fever

New infectious agent

Maladies graves nécessitant des actions complémentaires aussi vite que possible (mai 2016)

Chikungunya

Fever with Thrombocytopenia Syndrome

Zika Neurological complications and related congenital abnormalities

Source diagram: Blueprint

For each disease an R&D roadmap has been created, followed by target product profiles.

| Prioritization process | Priority list of pathogens | R&D roadmaps | Target product profiles |

DEVELOPMENT OF PRODUCTS

| Clinical trials and design | Regulatory process |

| Scientific Advisory Group | Global Coordination Mechanism | Monitoring and Evaluation |

This initiative resulted in the launch of the Coalition for Epidemic Preparedness Innovations (CEPI) at the 2017 Davos World Economic Forum, which focuses on three zoonoses:

- Lassa fever transmitted by rats;
- Nipah fever transmitted by bats;
- Middle East Respiratory Syndrome (MERS) fever, transmitted by camelids.

These new models of public-private partnerships are among the most interesting approaches to improve preparedness for emerging infectious diseases. They are based on upstream commitments concerning R&D programmes designed around benefit and risk sharing.

2 The European Innovative Medicines Initiative (IMI)
It is the largest upstream public-private partnership. It has a budget of EUR 3.3 billion over ten years, from 2014 to 2024, with the pharmaceutical industry contributing EUR 1.4 billion.

- antibiotics resistance;
- viral infections;
- fungal infections;
- zoonosis;
- respiratory infections;
- diagnosis;
- epidemic preparedness.

HEALTH DATA

WHAT ARE WE TALKING ABOUT?

"Data is the core of medical practice and its relationship with the patient. Not surprisingly, therefore, the worldwide digitisation of medical practice and the use of ever more numerous and varied sensors have led to an exponential increase in the diversity of available data".[1]

In France, health data are sourced from many places: medico-administrative databases such as Sniiram[2] and its 8.9 billion treatment forms, images of the 80 million imaging procedures performed each year, cohorts and registries, medical records, clinical trials, patient data collected via smartphones, social networks and websites, and so on.

They are therefore disparate and come in highly diverse formats, because all these data have been collected for a very specific purpose: to diagnose a disease, detect a particular mutation in the genome, reimburse treatment, measure physical activity, etc..

Artificial intelligence (AI) is emerging as a game changer by seeking to use all these data to advance research, care and innovation in health.

How? By annotating and matching the data to obtain more reliable and better quality results, but also to generate hypotheses and connections that had not been considered before. On one condition: that a sufficient amount of usable data is gathered to run the AI algorithms.

Knowing that AI algorithms require almost 100,000 images to learn how to detect melanoma and make a reliable diagnosis, it is clear that a hospital alone cannot collect the necessary amount of data; data producers must therefore work together to collect, exchange and share their data. It is also necessary to ensure that "clean", organised and properly labelled data are available.

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

● Systems with artificial intelligence, machine learning technologies and high computing power will make it possible to synthesise and model complex data to refine a diagnosis, identify the genetic mutations involved, monitor tumour growth, assist doctors in their decision-making, etc.

● In the field of oncology, the use of smart data will advance our understanding of cancer by integrating genome mutations, host/environment relationships and adaptability of living organisms, thus breaking cancer down into disease subsets and making it almost an orphan disease group.

● The move is towards a redivision of disease classification and the emergence of new research hypotheses.

● By using data well, even further advances in patient care will be possible. Because *"if treatments are well codified at the beginning of the disease, the further the disease progresses using the different available treatment lines, the fewer evidence-based medical recommendations are available and the fewer identical experience-based cases are available".[3]*

● AI will introduce a new multi-scale modelling element into the field of health that *"will involve integrating highly heterogeneous data that will open the way to revolutionary approaches".[4]*

[1]Extract from "Health and Artificial Intelligence" co-edited by Bernard Nordlinger and Cédric Villani, Paris, CNRS Editions, 2018, p.19.
[2] National Health Insurance Cross-Scheme Information System / [3] Ibid., cited p. 147. / [4] Ibid., cited p. 207..

CURRENT DEVELOPMENTS

● **Creation of the Health Data Hub in early 2019, a system for sharing health data between producers and users**

Genetic data
Molecular data
Clinical data
Real life data etc.

HEALTH DATA HUB

SNDS data
(National Health Data System)
(Système national des données de santé)

Data collected by the Internet of Things

1. Le Health Data Hub est un guichet d'accès unique à l'intégralité des données de santé soutenues par la solidarité nationale.

2. Le Health Data Hub collecte les données de santé. Il consolide le patrimoine des données de santé déjà disponibles.

3. Le Health Data Hub propose des outils pour créer des algorithmes d'analyse:
• des outils en open source (R. Milk. Python…)
• des outils en accès privé
• des outils de R&D

4. Le Health Data Hub permet d'apparier et d'analyser des données. Il met à disposition des jeux de données appariées et documentées.

S1 2019 → **S2 2019** → **2020 - 2022**

• Hub creation
• Implementation of governance
• Launch of pilot projects

• First version of the data catalogue
• First version of the technology platform with test users
• Initial results of the pilot projects

• Progressive enrichment of the data catalogue
• Continuous improvement of the technology platform
• Identification and deployment of local hubs
• Selection and support of priority projects on a recurrent basis

HEALTH DATA

● **Creation of a value chain around data and their interpretation**

RESEARCH

- Optimisation of lead generation (research leads)
- Collaborative platforms (innovation, financing)
- Digital twins of the human body

DEVELOPMENT

- Digitisation of clinical trial management processes
- Adaptive and scalable clinical trials

MARKET ACCESS

- Adaptive and scalable clinical trials
- Demonstration of medical value in real life

PRODUCTION

- Automation of production lines
- Predictive maintenance
- Automation of quality control

DISTRIBUTION

- Inventory management by augmented reality
- New models of medical transportation technologies
- Datamatrix system to combat drug counterfeiting

USES

- Transformation of the offer
- Business model transformation

VERTICAL INTEGRATION

Diagram extracted from a study by the Directorate-General for Enterprise and Industry, pending publication/February 2019.

BARRIERS TO BE OVERCOME

● **Shake-up of the medical imaging model**
"The algorithms already widely used in the creation of medical images are now powerful enough to guide the analysis of medical images as well as or better than human experts." [1]
Therapixel, for example, has successfully trained algorithms to "learn" the 640,000 mammograms collected for a global competition to distinguish suspicious mammograms from normal ones. It is also possible to build digital models (digital twins) to synthesise medical images and be able to transfer them to a real-life environment.

● **The impending shake-up of the clinical research model**
AI will significantly speed up clinical development by allowing new drugs to be tested on selected populations.

It is conceivable that phase III will eventually give way to real-life studies on selected patients according to their genetics, their phenotype, their genomic profile ... The costs of clinical research should therefore decrease. The R&D economic model will therefore change accordingly.

● Solve value sharing problems. Although patients legally own the data, in practice, however, they do not. Anonymised, secure, and undisclosed, the data are serving the patient community and advances in research. Not being able to use them would mean a lost opportunity for other patients.

● Do not adopt too rigid an interpretation of the General Data Protection Regulation (GDPR), which generates huge volumes of letters and of reports to patients while slowing down the process of collecting intelligent data.

● Tackle organisational challenges to think ahead about data collection and capitalisation.

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[1] *Ibid.cited. p.151.*

ARTIFICIAL INTELLIGENCE

WHAT ARE WE TALKING ABOUT?

Defining artificial intelligence (AI) is not easy. Its boundaries have been expanding ever since its origins as a specific field of research in the mid-20th century. Artificial intelligence refers less to a well-defined field of research than to a programme based on an ambitious goal: to understand how human cognition works and to reproduce it; to create cognitive processes comparable to those of human beings. The field is therefore naturally extremely wide, in terms of both the technical procedures used and the disciplines involved: mathematics, algorithmic, cognitive sciences, and so forth.

AI methods are very numerous and diverse (reinforcement learning, adversarial learning, neural networks, etc.), and are not new: many of the algorithms used today were designed decades ago.

All of these methods have developed rapidly as a result of spectacular performance gains in terms of computing and storage capacity, combined with

the growth in information technology over the last four decades.

Applications are proliferating: translation, driverless car, cancer diagnosis, etc. AI is developing against a technological background of global "datification" that affects each and every area and sector, from robotics to blockchain, through high-performance computing and massive storage. It is in contact with these different technological realities that the future of artificial intelligence will surely play out.[1]

● **Two ways AI can be applied to health**

Understanding the working of our organs, tissues and cells is a challenge; the complexity of these mechanisms defies human understanding ... but the power of computer analysis now gives us the tools to speed up research and deliver medically viable results.

Increased collection and storage capacity has made it possible to accumulate digitised data. Artificial intelligence algorithms are used as a new tool on these data sources, a "macroscope" capable of giving meaning, a medical value on a scale commensurate with these masses of data.

Two approaches to the analysis and use of AI in health care are now complementary. The first is somewhat "agnostic" and tends to apply algorithms to reveal inferences between the data, focusing on the effectiveness of the results obtained and the medical value of biomarkers for prevention, stratification, monitoring, etc..

The other approach is guided more by a modelling at cell, tissue or even organ scale, in an effort to guide or "supervise" algorithmic learning to increase efficiency, reduce the amount of data required for learning and further the adaptability of the solutions deployed.

● **Some key figures**

France is among the top 4 countries in the world for the global production of articles on artificial intelligence, along with China, the United States and the United Kingdom, on account of its excellence in mathematics, STIC (Science and Technology of Information and Communication) and cognitive science.

268
research teams

5,300
researchers

138 AI-related courses
AI-related courses are delivered by 81 engineering schools and 38 universities

18 master's
specialist AI master's degrees

80
mid-cap companies and SMEs

270
start-ups

specialising in AI and growing in number at a steady pace: more than 30% per year since 2010

€400 M
The amount of public funding for AI research through public-private partnerships over the five-year period, with a total budget of EUR 1.5 billion

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **Research is gathering pace Image processing (teaching machines to see), language processing (teaching machines to read), connections between health actors, real-time patient follow-up.... By 2030, artificial intelligence should be present on all health fronts, based on the continuous output of new data.**

● **There are many potential opportunities**

In terms of prevention: analyses of long-term, multidimensional data collected over large population cohorts will identify risk factors for specific diseases such as cancer, diabetes or neurodegenerative diseases. They will also make it possible to characterise rare diseases more quickly, through faster and more efficient image analysis (scanners, ultrasounds) and to build high-performance diagnostic support systems.

In terms of care: artificial intelligence will contribute to the personalisation of treatments, particularly in the case of certain cancers, which are characterised more and more according to genetic data, the challenge being to provide increasingly individualised treatment choices.

In terms of pharmacovigilance and pharmacological efficacy: increasing the basis for analysis of data from cohorts, medico-economic databases and real-life data over the long term will prompt rapid reactions in the event of an adverse drug reaction, to the point of thinking about new economic and societal care pathway models, where payment is based on effectiveness.

In terms of clinical research: the use of data will create an environment for unified access to cohorts in an effort to speed up patient selection based on more precise criteria for better testing of medical hypotheses.

ARTIFICIAL INTELLIGENCE

CURRENT DEVELOPMENTS

The applications of artificial intelligence in the health sector are very real and give great hope. With AI, it is possible for example to develop medical devices with embedded software that sets a virtuous cycle in motion: simultaneous data transmission, their remote analysis, software updates, and new functionalities resulting from these analyses, and so on.

However, although the potential of AI in health may seem considerable, and although projects are being undertaken and the results look promising, it is no revolution. Technological obstacles do not seem to be the issue, but difficulties arise around legacy data and their cleaning and curation prior to analysis or work on the interoperability of databases that are to be matched. All these obstacles bear the hallmarks of a period of transition from a legacy data system to an awareness, coupled with improved analytical capabilities, of the future value resulting from these data.
For now, the obstacles therefore lie in the data, the fuel on which AI runs, whose quality is of paramount importance.

The machine and its algorithms may be "supersonic" but they are inoperable on poor quality data: "garbage in, garbage out". Indeed, learning algorithms must be based on homogeneous and qualified data. Data are therefore essential assets for the development of AI. *"The value created by artificial intelligence comes from data needed for learning much more than from the algorithm, which is developed openly (in open source)"*, according to the National Digital Council.

Access to data is also an obstacle in itself at present, especially in the case of large clinical data warehouses, and for good reason: what will be the return on investment for institutions that allow algorithms to refine biomarkers whose analytical foundation is based on their data?

▶ A number of cultural obstacles are yet to be overcome such as the time it takes to adapt to these new technologies, while the legislative obstacles in the way of these new possibilities include a preliminary debate on the political, legal and ethical aspects of AI.

● **Who owns the data?**

Today, when a hospital holds a patient's data with his or her consent, the data are used in this treatment or diagnostic context. Legislation requires that the patient's permission be sought again if the doctor wishes to use the data for another project. This approach appears to act as a brake on big data, which requires having at its disposal as large and complete a mass of data as possible. Releasing the data is not permitted by law, or only after anonymisation and aggregation processes take place. These necessary processes, introduced by the CNIL (French Data Protection Authority), still result in the loss of aggregation options at the individual data level.

Ideally, all citizens should be empowered as a decision-maker on the issue of sharing their data, whether medical or otherwise. Extensive work should be undertaken to educate the public so that each patient is aware of the potential use to which the data may be put and is equipped to make an informed decision as to whether or not to offer them for research.

An innovation such as blockchain will provide very timely solutions at a time when patient consent is quite rightly at the heart of data access and use. Blockchain is a robust technology that, by distributing information over a very large number of machines, makes it possible to track decisions or uses around the data. In other words, blockchain is a technology that will allow this consent (or changes to this consent) to be securely logged. Similarly, this technology provides a specific directory of dataset usage: who uses which dataset? This question is important in the context of the emergence of AI learning based on separate datasets.

BARRIERS TO BE OVERCOME

Until these obstacles are overcome, technical and legal solutions need to be found quickly to enable hospitals and research institutes to use the data. This new direction presupposes two conditions.

- **The appropriation of AI by the medical profession**

The time needed for the medical profession to adapt and integrate these technologies is a key point. While some doctors are enthusiastic about being supported by technology, others are more sceptical or critical even. The promises of AI are therefore very real, but the huge challenge remains of striking a new balance between the machine, the patient and the medical teams.

What if some machines compete with tasks performed by doctors? How are medical skills to be redistributed? Will AI lead to the Uberisation of medicine?

These legitimate questions and fears reflect a misunderstanding of the true limitations of AI, which will accelerate treatment suggestions based on data analysis but will give free rein to all interactions that are not currently based on data analysis, either because they are not available or because the mechanisms are of a complexity that goes beyond the very nature of "data": all interpersonal relations, all complex human choices and emotions remain the exclusive domain of the human relationship between patients, caregivers and doctors.

The intelligence known today as "artificial" is intelligent in name only. These are algorithms based on inferences between data. The nature and typology of these data are themselves reductive of reality.

- **Addressing data protection issues**

Accountability issues: if a machine misdiagnoses, if a robot malfunctions, who will be responsible? Accountability issues are highly complex and require reflection and an appropriate ethical-legal framework adapted to innovation in a competitive landscape.

Access issues: France's Medical Association, l'Ordre des Médecins, states in its January 2018 report[1] that it is, rappelle qu'il est *"imperative that the anticipated improvements in artificial intelligence, big data and robotics technologies benefit everyone and do not heighten social or socio-cultural divisions. As a democratic and republican organisation, our society must take particular care to ensure that the progress stemming potentially from these technologies in screening, in-depth knowledge of diseases and the risks of their occurrence, do not alter our solidarity model of social welfare but instead help to reduce inequalities and the risks of exclusion."*

AN INTEGRATIVE APPROACH
OF ADVANCED TECHNOLOGIES: LIFETIME

WHAT ARE WE TALKING ABOUT?

LifeTime is proposing the development and application of cutting-edge technologies in an approach in which combined and dynamic analyses are performed on an individual cell, in molecular and Omics biology and in imaging, at levels ranging from the organ to the entire body. It also involves the development of relevant experimental models, with, for example, organoid ("mini-tissue") technology, and an ability to analyse all data, including contextualisation data, via artificial intelligence or machine learning.

The ten-year programme sets out to provide innovative solutions for the early diagnosis and interception of a wide range of diseases, including cancer, neurological diseases, cardiometabolic diseases, infectious diseases and chronic diseases.

This interdisciplinary and pan-European scientific and technological project aims to quantify, model and predict the trajectories of cells in space and time within tissues and organisms in order to capture the molecular and cellular transitions that lead from healthy to diseased subjects.

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

● Over the last ten years, the evolution in patient care has benefited from the enormous progress made in our access to the sequence of genomes, carriers of genetic information. Nevertheless, it is our cells that read this information.

The current challenge is to understand how genomes work within cells, how tissues are developed from them, and the dynamics that lead a healthy cell and tissue to a diseased state. We need to go beyond the genome sequence and decipher "the book of life" by questioning its only interpreters, our cells. In this way, we will be able to make progress in the detection and methods of treating diseases.

● Through the new technologies, or more precisely their combination, these questions can be approached differently. Indeed, they offer the possibility of linking knowledge on the genome with that of the phenotype, and also of analysing the behaviour of each cell on model systems such as the mouse, but also on patient tissues.

● To better address diseases, we need to develop innovative systems that are representative of each disease and each affected tissue, such as organoid technology (which consists of creating a model of the organ, a sort of "mini-organ"). Consideration will also need to be given to each individual's diversity and gender.

● **A real paradigm shift in medical research is emerging.** Basically, we had until now broad approaches to diseases such as cancer, for example, by which we were able to obtain an average tumour profile, corresponding to an average of the observed cell characteristics. We know that tumours are often heterogeneous and some cell groups can be masked when we focus on the average characteristics of a tumour tissue. However, these cell groups can sometimes prove to be decisive for prognosis, and hence for treatment strategy.

Factsheet produced with the help of **Geneviève Almouzni,**
Director of Research at the CNRS, Honorary Director of the Research Centre of the Institut Curie, Joint Coordinator of LifeTime
Raymond Pamphile, *Scientific Advisor for Partnerships, Director of the Research Centre of the Institut Curie, and* **Marie Vidal,**
European Project Manager at the Berlin Institute for Medical Systems Biology, Max Delbrück Center for Molecular Medicine

The information collected on the individual properties of the cells represents an important mass of data that will also need to be processed, analysed and modelled. To achieve this requires the development of the necessary infrastructures and capacities in bioinformatics, artificial intelligence and data sciences. This approach can only benefit from the policies adopted for the France AI strategy and the creation of the Health Data Hub.

▶ **Some examples of the challenges facing 21st century researchers and physicians who, by 2030, want to:**

● detect at-risk patients earlier;

● offer an earlier diagnosis, if possible before the onset of disease symptoms, in order to best preserve normal function;

● have the most appropriate treatment strategies for each patient;

● better predict the clinical response to a given intervention;

● anticipate the benefit/risk ratio of each treatment for each patient.

CURRENT DEVELOPMENTS

The transnational and interdisciplinary LifeTime initiative has just reached an important milestone: in 2019, the consortium will receive EUR 1 million from the European Union, and will have one year to develop a plan to integrate its vision into the European research and innovation landscape. After this first year of funding, LifeTime is looking to develop its research and innovation programme on a large scale until 2030.

Some key figures

● LifeTime represents the vision shared by more than 120 internationally renowned European scientists.

● More than 50 prestigious research institutions in 18 countries in Europe are involved in LifeTime.

● More than 60 major industrial partners (large companies, SMEs, start-ups) from different sectors (pharmaceuticals, biotechnology and IT) support the LifeTime consortium.

In France, Institut Curie is coordinating the LifeTime initiative with the Max Delbrück Center for Molecular Medicine in Germany. The French National Centre for Scientific Research (CNRS) is playing a major role in the project, working in synergy with the Helmholtz Association in Germany.
The National Institute of Health and Medical Research (Inserm) is an associate partner, as is the Max Planck Society in Germany and the Francis Crick Institute in the United Kingdom.

AN INTEGRATIVE APPROACH
OF ADVANCED TECHNOLOGIES: LIFETIME

● **Revolutionising health**

Credit: © Spencer Phillips, EMBL-EBI

Some examples of the progress made

● The discoveries of researchers involved in LifeTime appear in the scientific magazine Science as "Breakthrough of the year 2018". Nikolaus Rajewsky, Director of the Berlin Institute for Medical Systems Biology at the Max Delbrück Center for Molecular Medicine and Joint Coordinator of LifeTime, states in it that the integrative approach to certain technologies *"will transform the next decade of research".*

● Using high-resolution live cell imaging techniques, it is possible to generate a dynamic protein atlas of human cell division (Cai Y. and Ellenberg J., *Nature*, 2018).

● Data obtained by single-cell technology allow a new interpretation of the chromosome conformation during the cell cycle (Nagano T. and Tinay A., *Nature*, 2017).

● Single-cell technologies have led to the discovery of a new type of immune cell, which may have important implications for future treatment of Alzheimer's disease (Keren-Shaul H. and Amit., Cell. 2017).

● Using model systems, the study of cell regulatory pathways has established a link between melanoma and a gene called SAMMSON. The latter plays a crucial role in the development of aggressive skin cancer. This work bodes well for better diagnosis and treatment of melanoma (Leucci E. and Marine JC., *Nature*, 2016).

BARRIERS TO BE OVERCOME

Scientific and technological bottlenecks

These relate to:

1. current methods, which do not routinely allow the characteristics of each cell to be fully determined because of their heterogeneity within organs and tissues;

2. our difficulties in grasping changes over time in cell trajectories, in reconstructing the history of cell evolution and predicting their future;

3. the limits of current computer models of diseases that prevent us from understanding the causes and biological mechanisms of diseases;

4. the lack of suitable experimental models capable of reproducing the pathological tissue. These would allow researchers to develop methods of intervention on genomes and tissue cells as close as possible to those of patients, from a precision medicine perspective.

Factsheet produced with the help of **Geneviève Almouzni,**
Director of Research at the CNRS, Honorary Director of the Research Centre of the Institut Curie, Joint Coordinator of LifeTime
Raymond Pamphile, *Scientific Advisor for Partnerships, Director of the Research Centre of the Institut Curie, and* **Marie Vidal,**
European Project Manager at the Berlin Institute for Medical Systems Biology, Max Delbrück Center for Molecular Medicine
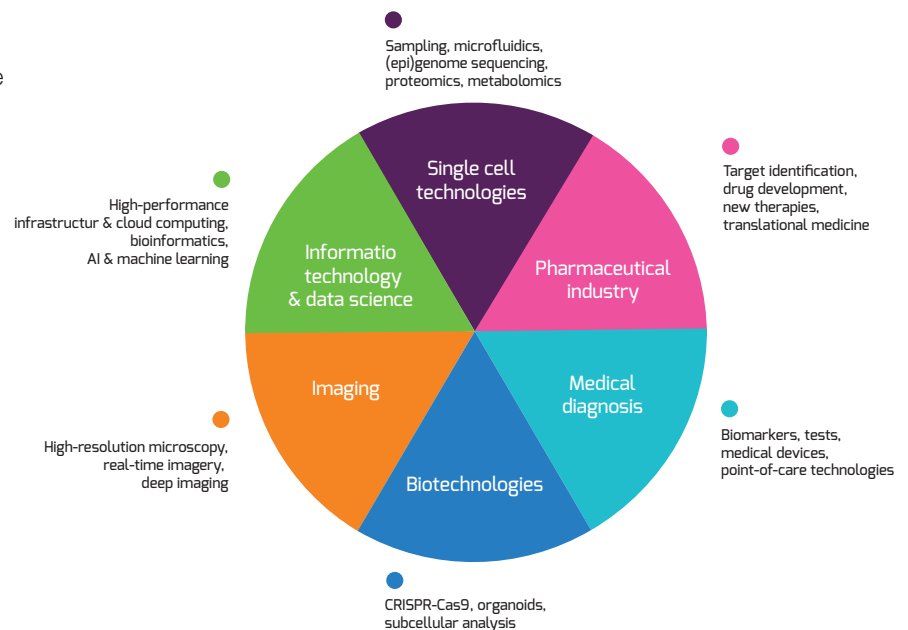
Economic bottlenecks

These require:

1. a proactive and concerted policy at the European level, with the involvement of national and regional funding agencies, so as to make better use of expertise and coordinate initiatives to promote potentially disruptive technologies;

2. the maintenance in Horizon Europe of a mechanism equivalent to that of the FET-Flagships under the Horizon 2020 programme, in terms of interdisciplinary ambition, synergies, duration and coherence;

3. the establishment of an ecosystem conducive to potentially disruptive innovations and their combined approach, in which the various actors (academic research centres, hospitals, universities, biotechnology companies, businesses, funding and assessment agencies, insurers, patients and citizens) will interact continuously to facilitate their rapid transfer into medical practice, and the establishment of high-level scientific validation criteria for the selection of new treatment strategies;

4. more investment in high-risk projects to guarantee Europe's performance and independence in a globalised and highly competitive sector;

5. greater attractiveness of careers in science and technology, with the aim of overcoming gender and ethnicity barriers.

● **Overall impact of the LifeTime initiative**

▶ Increased European competitiveness

▶ Growth of the SME, tech and service sectors

▶ Strengthened pharmaceutical and IT companies in the EU

▶ Stimulation of innovation ecosystems

▶ Reduction in health costs

▶ Single cell breakthrough tools and technologies

▶ Innovative machine learning for massive data processing

▶ New experimental and personalised disease models

▶ Transformation of medical systems

▶ Early disease detection and interception

▶ Extension of healthy lives

▶ Public awareness and citizen engagement

▶ New recommendations for the use of Big Data in clinics

▶ Maximising the use and reuse of knowledge through open access

▶ Consolidated and synergistic research programmes in Europe

▶ Research excellence through the development of talent

ECO-NOMIC | SOCIETAL
IMPACT
SCIENTIFIC

Sustained leadership of the European Union in major research areas

Sampling, microfluidics, (epi)genome sequencing, proteomics, metabolomics

High-performance infrastructur & cloud computing, bioinformatics, AI & machine learning

Single cell technologies | Pharmaceutical industry | Informatio technology & data science | Imaging | Biotechnologies | Medical diagnosis

Target identification, drug development, new therapies, translational medicine

High-resolution microscopy, real-time imagery, deep imaging

Biomarkers, tests, medical devices, point-of-care technologies

CRISPR-Cas9, organoids, subcellular analysis

INTEGRATIVE MEDICINE

WHAT ARE WE TALKING ABOUT?

In the face of multiple strategies deployed by cancer cells to circumvent, resist and evade treatments, researchers and doctors are turning increasingly to an integrated approach for better disease intelligence. It encompasses everything that is known about the biology of the tumour and its environment, along with all the available disciplines (artificial intelligence, medical imaging, virtual reality) to better determine the appropriate treatment strategy.

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **With integrative medicine, it is possible to construct a new cancer atlas that condenses all knowledge from a therapeutic and integrative perspective.**

This construction aims, one stone at a time, to overlay the old statistical approach to cancer treatment with a personalised approach, mindful both of specific experiences and the patient as a whole.

Today, 97% of the cancer population is given treatments demonstrated in 3% of patients. All the unknowns due to patient heterogeneity have been confined behind the statistical data so that all patients can be treated. Gradually, the statistical data will be supplemented by biological data (analysis of the tumour's biology: research into mutations, translocations, amplifications, characterisation of invasive immune cells), relationships between the tumour and its environment, in order to better select patients eligible for certain treatments, determine which dosage to administer, and assess the risks of relapse.

A change of perspective is taking place in cancer care in the direction of writing equations that incorporate new unknowns and producing à la carte medicines.

CURRENT DEVELOPMENTS

● **Shake-up in clinical trial conduct**

The conventional drug development paradigm, which was centred around the phase I, II, and III trial sequence, is increasingly focusing on early drug development and phase I-II. Phase I-II goes beyond the traditional drug safety/toxicity assessment, characterises the activity and biomarkers of response, and can include up to 1,000 selected patients. Phases I-II now have registration value and can secure conditional approval from the health authorities.

● **Shake-up in treatment strategy**

Tumour sequencing and its epigenetic analysis are increasingly being used to determine a treatment strategy that takes into account the host, the tumour and their interrelationships.

● **Mastery of new tools**

We are gradually shifting towards more efficient medicine, and the medical world is learning to master new tools. Data and their circulation (radio, analysis, genetic results, etc.) are key elements of this transformation, as will be our capacity in the longer term to collect, store and analyse this information for better statistical knowledge and a large margin for progress. This will result in better anticipation of any changes in the disease, early identification of warning messages and timely intervention.

BARRIERS TO BE OVERCOME

Don't set the old world at odds with the new world: Don't set the old world at odds with the new world: we must move together towards a more efficient medicine based on a global approach. In this way, relapse can be detected earlier or predicted and money saved on costly care, thereby reducing spending. Being efficient is the best way to be economical. Large-scale customisation allows resources to be allocated carefully to limit additional costs. Whatever the treatment strategy selected, and however careful and precise the upstream analysis of the tumour and its environment may be, the remission or cure of a cancer also depends on each patient's ability to cope with the news of their cancer and the plethora of tests and treatments that they will have to undergo, their reliance on their close environment and ability to return to an active social and working life after cancer.

It is necessary not only to consider the tumour in its environment, but also patients in their environment, with all the parameters that make them unique: their rationality, imagination, intuition, family roots, capacity for resilience and perspective on their disease.

The major American cancer centres turned the corner on integrative therapy in the late 1990s with the creation of integrative therapy units at the Dana-Farber Cancer Institute (Boston), the MD Anderson Cancer Center (Houston), the Memorial Sloan Kettering Center (New York) and the UCSF Osher Center for Integrative Medicine (San Francisco). Three European centres were forerunners, the Karolinska Institutet (Sweden), the English centres at University College (London) and at the Christie Hospital (Manchester).

The French centres (Léon Bérard, Bergonié, Claudius Regaud, Curie, Gustave Roussy, AP-HP) have all launched integrative therapy programmes encompassing art therapy, gardening and sports workshops as well as osteopathy, acupuncture, nutrition consultations ... The US-wide Osher Centers are the only ones to have set up a programme to evaluate these integrative therapies.

The Institut Rafaël, which opened in 2018, has the pioneering goal of uniting post-cancer care under the one roof:
• integrative therapies provided by a team of 70 caregivers;
• research and evaluation, as well as training to structure an ecosystem of humanistic innovation designed to better care for each individual in a holistic way and to promote the sharing of each individual's skills.

• **Integrative therapy**

Intuition, creativity, imagination

Scientific rationality

INTEGRATIVE THERAPY

Mindfulness, ability to take a step back

Capacity for resilience, mobilisation

Family roots, social dynamics

PATIENT AUTONOMY

WHAT ARE WE TALKING ABOUT?

A digitalized care is a global and efficient care associating both teleconsultation and patients's care between two consultations through digital use.
To treat diabetes, for example, between consultations, patients will have an electronic medical record that will allow them to arrange their follow-up.

WHAT'S ON THE HORIZON BETWEEN NOW AND 2030

▶ **Digitised care will help us to rethink and reimagine the patient's place in the care pathway.**

Health care is often akin to compartmentalised practices, with outdated ways of thinking and old-fashioned attitudes. We have the chance and the opportunity to change this way of seeing things, to recognise that we are now in an age of connected medicine, of understanding genome function, of digital technology. We have the opportunity to rethink and reimagine health care more effectively and to simultaneously redefine the patient's place within his or her care pathway.

● **Patients and e-health[1]**

Treatment procedures and prescribing at any time and remotely

Easier access to healthcare services

Prevention and well-being are boosted by the Internet of Things
> Self-tracking (apps for smartphones, bracelets, watches ...)
> Remote monitoring by dedicated centres

Medical information sharing is encouraged

[1]*Table adapted from Intériale Mutuelle.*

CURRENT DEVELOPMENTS

Current medicine is not sufficiently evidence-based, i.e. reliant on real-life data. The use of some new technologies, many of which are now successful, will provide a continuous data flow and lead to greater proactivity in preventing disease, making better diagnoses, and better managing drug prescribing, clinical trials, and so forth.

The awareness is there: given the explosion of health costs, a transition is occurring from a logic of volume to a logic of value in an attempt to change the focus and place emphasis on prevention, the best suited treatments, and the efficiency of the healthcare system. This is a challenge for the health system, a challenge to be met with the help of new technologies and of patients who are willing to take part in this revolution.

Because, this revolution will change the practice of medicine.
Is it really necessary to spend an hour in a waiting room for a ten-minute consultation? Telemedicine will transform where healthcare is delivered, and other technological changes are taking place in the meantime - a smart ring to measure sleep, implantable devices to measure blood alcohol content, blood sugar levels, to make real-time recordings inside patients' bodies, to measure behaviour and its impact on many diseases, and to assess the efficacy of a medicine. All these evolutionary changes turn patients into active participants and not victims of this revolution and prompt them to view their care pathway from a different perspective: they have the power and the opportunity to do so.

They will be in possession of their own health information, and will no longer be passively waiting to visit the doctor before being treated. They will now be able to play an active role in their care, decide to participate in a trial, learn about new protocols, advances in research, be given coaching, receive results on their smartphones ... Some smartphones are literally becoming healthcare devices and their capabilities are growing year after year. Today's smartphone is about a billion times faster and more powerful than a 1970s supercomputer. The information channels are there and the patient/individual has already switched to digital (77% of French people[1] own a smartphone). The conditions are in place to make the patient more empowered and engaged.

BARRIERS TO BE OVERCOME

Thinking that this revolution will be reserved for a small number of patients.

On the contrary, the exchange of information with patients will help answer their questions and needs, streamline their care pathway, facilitate relations with their doctor and thus optimise healthcare costs.

On the contrary, the exchange of information with patients will help answer their questions and needs, streamline their care pathway, facilitate relations with their doctor and thus optimise healthcare costs.

Just one example: in 2015, of the EUR 133.6 billion spent on social security, mental health expenditure was estimated to be EUR 19.3 billion. This is more than the EUR 14.1 billion dedicated to cancer care. And yet costs are skyrocketing in psychiatry because of compliance problems. Patients stop and then resume their treatment. To remedy this, remote consultations combined with digital therapy may be a solution. With them, contact can be maintained with the patient between two face-to-face consultations.

A patient autonomy fund (Bpifrance) was set up in January 2018. The fund is interested in exploring new uses with high medical value that will revolutionise medicine through digital technology: diagnosis (artificial intelligence, deep/machine learning), real-time disease monitoring, patient management (remote consultation and monitoring) and the efficacy of their care pathway. Its mission is to identify them, having previously recognised the needs they meet as innovative solutions, to support their rapid and sustainable launch on the market, following effective structuring work.

Innovation in the efficacy of healthcare will also lie in the convergence and aggregation of solutions so that the best possible offer of care is delivered to most closely meet the expressed need. France is particularly well placed to implement these "human" innovations at the crossroads of health and digital technology. Its medicine and doctors have an excellent reputation and its mathematicians produce powerful algorithms that are envied all over the world. France is therefore the obvious testing ground for this change and French patients are active participants in a care pathway that is effective, modellable and exportable, probably before 2030.

[1] *Deloitte study, 2017.*

HEALTH 2030
WHAT THERAPEUTIC ADVANCES WILL THERE BE IN 2030?

- Advances in diagnostics, in the understanding of diseases, in treatments and in patient support. They are presented in summarised form for 12 diseases or disease groups.

MAJOR MILESTONES
IN TREATMENT ADVANCES

2030 ?

2018 New drugs for ovarian cancer and haemophilia

2017 First anti-leukaemia CAR therapies

2016 First anti-PD-1 therapies for kidney cancer and Hodgkin's lymphoma

2015 New drug for Parkinson's disease. First anti-PD-1 therapies for metastatic melanoma

2014 First immunotherapies. First treatment able to cure hepatitis C

2011 Targeted treatments for hepatitis C and metastatic melanoma

2010 First anti-CTLA-4 therapy for metastatic melanoma

2009 Specific treatments for rare diseases: factor XIII deficiency, fibrinogen deficiency, Fabry disease, etc.

2008 Targeted therapy for follicular lymphoma (form of leukaemia)

2007 Protein kinase inhibitors (advanced kidney cancer)

2006 Anti-cancer vaccine (for papillomavirus causing cervical cancer)

2005 First anti-angiogenic monoclonal antibody (colorectal cancer)

2004 Aromatase inhibitors (hormone-dependent breast cancers)

2003 HIV fusion inhibitors

2001 First targeted cancer drug for chronic myeloid leukaemia

2000 TNFα First treatment for a form of AMD (macular degeneration of the retina)

1998 Anti-TNFα agents

1989 Proton pump inhibitors (PPI)

1988 Statins

1987 First antiretrovirals

1986 First monoclonal antibody

1980 Production of interferon by genetic recombination

1967 Beta-blockers

1964 First polio vaccine

1941 First antibiotic. Penicillin

1922 Discovery of insulin

1902 Rabies vaccine

1899 Aspirin

The march of therapeutic progress!

After a lull in the 2000s, the last decade has seen an almost incessant stream of innovations that have turned the prognoses of hepatitis C, metastatic melanoma, Hodgkin's lymphoma and some lung cancers on their head ...

The horizon of therapeutic progress appears limitless.

By 2030, we will have witnessed an unprecedented surge in therapeutic innovations: more than 4,000 clinical trials[1] are currently underway in the field of cancer. Even assuming that only one-tenth of these developments actually culminates in a new medicinal product available to patients, innovations are set to increase in number and pace at an exceptional rate.

And this explosion will not only affect cancer: 445 clinical trials are ongoing in the field of cardiovascular diseases and 640 in the field of infectious diseases. Treatment will be combined with medical devices and smart applications.

This concept of a comprehensive and integrated therapeutic solution already exists. In diabetes, different insulins can be combined and administered by a pump implanted in the body which is controlled by a smart device for measuring blood sugar level. The device is remotely monitored by an expert system connected to the patient's telephone and the patient self-administers the treatment via an application. The range of possibilities between now and 2030 appears vast and is increasing by the day.

The rich therapeutic arsenal, the ability to better identify genes, or indeed the power of artificial intelligence algorithms are bound to yield even more personalised and better suited medicines. By 2030, there may be as many treatment protocols as there are sick people. And medicine will treat not diseases but people, who will be able to print their drug prescriptions at home, be operated on by robot surgeons, self-care using virtual reality games and devices, and acquire superhero powers as some American futurists promise.

Investing in innovation

If France does not want to miss out on the health innovations in the pipeline, it must adopt a long-term strategic vision that cannot be confined to regulatory and financial issues regarding the creation and spread of innovation. Indeed, it is crucial that creators have a major say in research into new drugs as well as in other areas of research. As Bernard Meunier, holder of the Liliane Bettencourt Chair in Technological Innovation at the Collège de France, said in his inaugural lecture in November 2014, *"the creation of medicines is rarely the result of large networks; it very often takes place within a team. The networks come into play later, during a drug candidate's clinical development phases, by bringing together teams from different hospitals in different countries once the actual creation phase is already complete".*

At a time when China is positioning itself as a major player in innovation - publishing 426,000 studies in 2016 compared with 409,000 in the United States - France and Europe must continue to invest in research and promote creativity and inventiveness.

ANTICIPATING THERAPEUTIC ADVANCES: FOLLOW-UP OF PHASE I, II, III CLINICAL TRIALS

Leem's Innovation Database, April 2018

The aim of Leem's clinical trial database, the Innovation Database, is to anticipate innovations in therapeutics.

THERAPEUTIC AREA	CLINICAL TRIALS PHASE I, II, III
CANCER	3,463
CARDIOVASCULAR DISEASES	234
DIABETES	170
HIV-AIDS	42
PARKINSON'S DISEASE	47
ALZHEIMER'S DISEASE	82
VISION DISORDERS	163

CALCULATION METHODOLOGY

Leem's Innovation Database lists all Phase I, II and III clinical trials for chemical-based and biological drugs in which at least one industrial sponsor is taking part. All trials starting after January 2013 are taken into account. Trials conducted in Asia and Africa are alone excluded from the database. The figures were extracted in April 2018.

Evaluate Database, July 2017

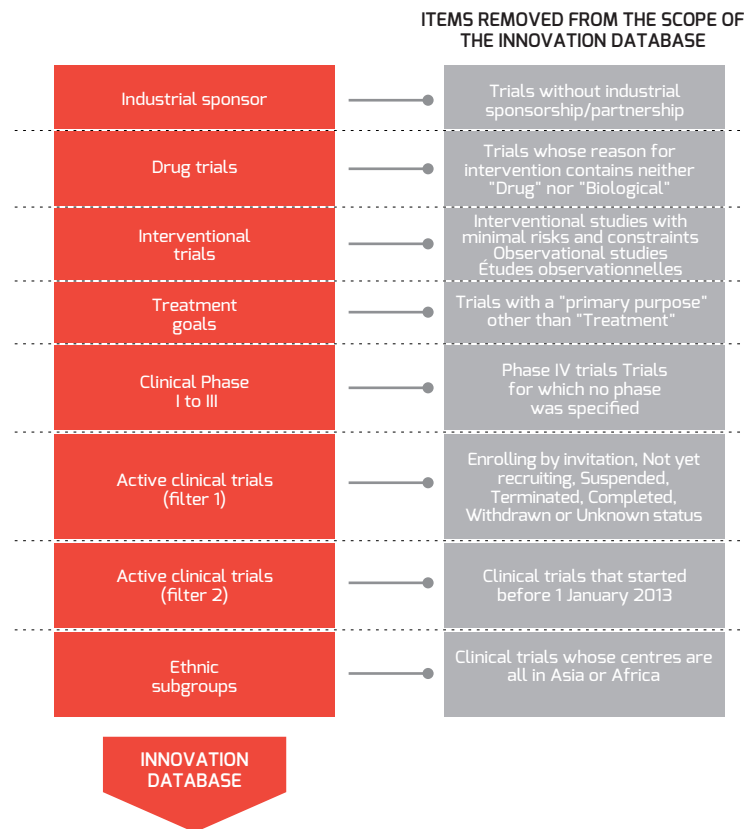| THERAPEUTIC AREA	CLINICAL TRIALS PHASE I, II, III
CANCER	4,006
CARDIOVASCULAR DISEASES	445
DIABETES	264
HIV-AIDS	82
PARKINSON'S DISEASE	65
ALZHEIMER'S DISEASE	143
MULTIPLE SCLEROSIS	32
LIVER DISEASES	132
VISION DISORDERS	288 according to Pharm Project figures of September 2018
RARE DISEASES	1,362 according to Cortellis Database figures of May 2018

CALCULATION METHODOLOGY

The Evaluate Database lists all Phase I, II and III interventional clinical trials involving medicines and biological medicines resulting from academic, collective or industrial research throughout the world.

INNOVATION DATABASE: CALCULATION METHODOLOGY

Leem's Innovation Database relies on the extraction of data from the website clinicaltrials.org, a clinical trial registry that centralises information on clinical trials conducted in nearly 200 countries. This registry, managed by the U.S. National Institutes of Health (NIH), is the most comprehensive clinical trial database to date. During the construction of this database, management rules were introduced to select ongoing clinical drug trials conducted directly or indirectly by pharmaceutical companies. The filters used are:

- Selection of clinical trials sponsored by industry or in partnership with a pharmaceutical company: clinical trials not conducted by a pharmaceutical manufacturer were excluded.

- Selection of clinical drug trials only: trials whose reason for intervention does not contain "Drug" or "Biological" were excluded. With this filter, it is possible to eliminate trials involving only surgery or radiotherapy.

- Selection of interventional trials only: interventional studies with minimal risks and constraints were removed, along with observational studies, from the scope of the Innovation Database.

- Selection of clinical trials whose purpose is treatment: clinical trials with a "primary purpose" other than "Treatment" were not included in the scope of the Innovation Database. This filter makes it possible to rule out clinical trials for diagnostics in particular. .

- Selection of clinical phases I to III: only phase I, phase I/II, phase II, phase II/III and phase III clinical trials were included in the database scope. Phase IV trials or studies for which no phase was specified were excluded.

- Selection of active clinical trials (filter 1): only active clinical trials ("Active, not recruiting" and "Recruiting") were retained. Trials listed as Enrolling by Invitation, Not Yet Recruiting, Suspended, Terminated, Completed, Withdrawn, or whose status is unknown were removed from the scope.

- Selection of active clinical trials (filter 2): clinical trials that started before[1] January 2013 were removed from the scope of the Innovation Database.

- Selection of trials not involving ethnic subgroups: certain ethnic differences (including genetic differences) may cause variations in safety, efficacy or dosage1. This is particularly the case in trials involving certain Asian or African populations. Clinical trials whose centres are all present in Asia or Africa were thus removed from the scope of the Innovation Database.

ITEMS REMOVED FROM THE SCOPE OF THE INNOVATION DATABASE

Filter	Items removed
Industrial sponsor	Trials without industrial sponsorship/partnership
Drug trials	Trials whose reason for intervention contains neither "Drug" nor "Biological"
Interventional trials	Interventional studies with minimal risks and constraints Observational studies Études observationnelles
Treatment goals	Trials with a "primary purpose" other than "Treatment"
Clinical Phase I to III	Phase IV trials Trials for which no phase was specified
Active clinical trials (filter 1)	Enrolling by invitation, Not yet recruiting, Suspended, Terminated, Completed, Withdrawn or Unknown status
Active clinical trials (filter 2)	Clinical trials that started before 1 January 2013
Ethnic subgroups	Clinical trials whose centres are all in Asia or Africa

INNOVATION DATABASE

Subsequently, items from clinicaltrials.gov were supplemented with information extracted from several databases:

- **Drugbank:** a dual purpose bioinformatics–cheminformatics database. It is hosted by the University of Alberta in Canada. Drugbank has made it possible to identify molecule synonyms.

- **FDA:** United States Food and Drug Agency. It lists all U.S. marketing authorisations as well as fast-track drugs.

- **ATIH:** Technical Agency for Information on Hospital Care. It lists information on all Temporary Authorisations for Use (ATU) granted in France.

- **ANSM and EMA:** National Agency for Medicines and Health Products Safety and the European Medicines Agency They list information on all French and European marketing authorisations.

[1]https://www.eupati.eu/fr/developpement-et-essais-cliniques/populations-particulieres-dans-les-etudes-cliniques/

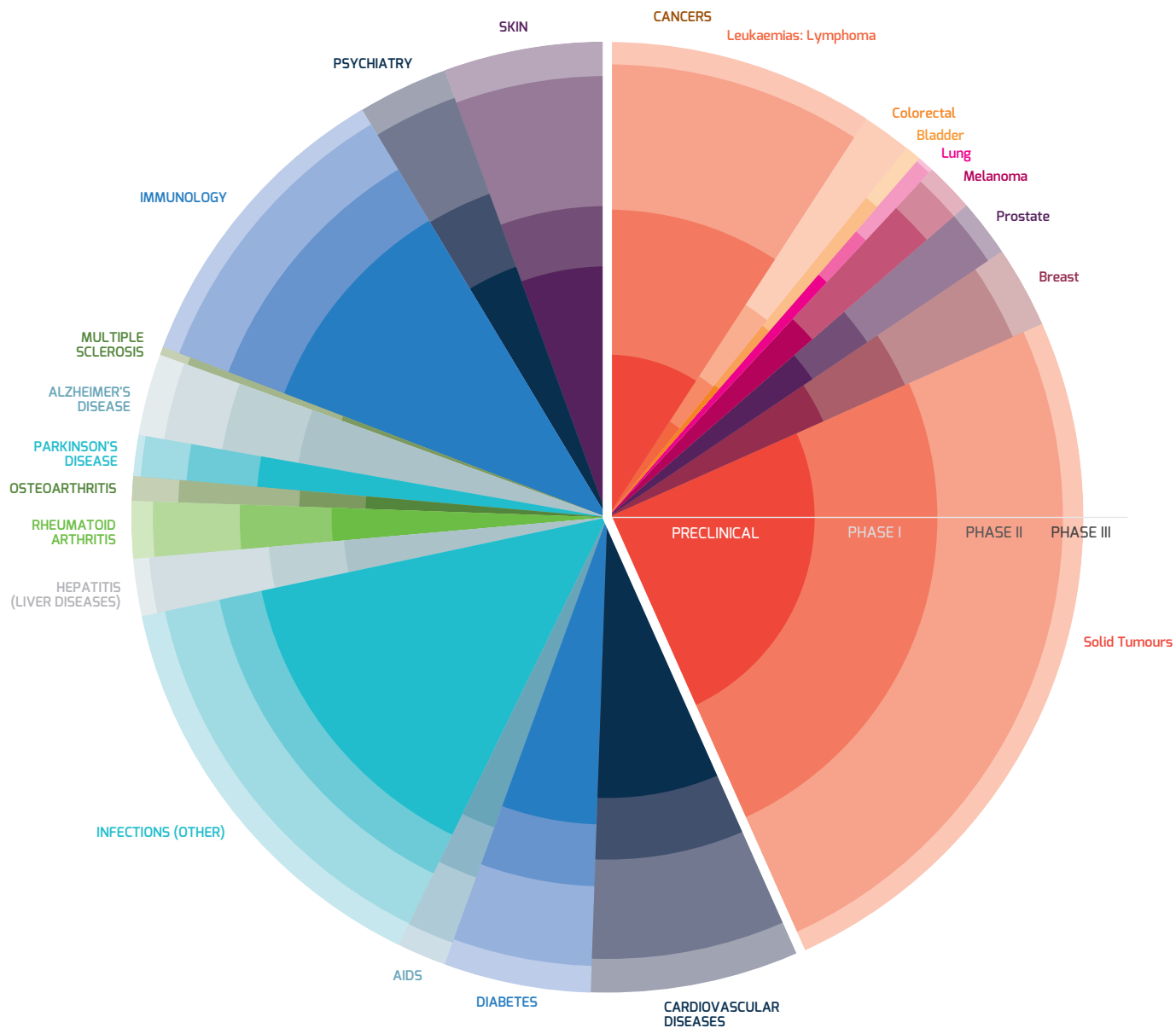# PRECLINICAL DEVELOPMENT AND PHASE I, II, III CLINICAL TRIALS

	PRECLINICAL DEVELOPMENT	CLINICAL TRIALS			TOTAL
		PHASE I	PHASE II	PHASE III	
CANCERS (TOTAL)	4,621	1,757	1,920	329	4,006
Leukaemia, lymphomas	487	433	434	67	934
Colorectal	98	46	73	19	138
Bladder	29	13	28	11	52
Lung	73	13	21	1	35
Melanoma	102	57	87	9	153
Prostate	146	39	86	10	135
Breast	212	80	108	27	215
Solid tumours	1,648	976	998	164	2,138
CARDIOVASCULAR DISEASES	642	141	227	77	445
DIABETES	482	97	125	42	264
AIDS	186	30	39	13	82
INFECTIONS (other)	1,603	195	252	109	556
HEPATITIS (liver diseases)	165	47	75	10	132
RHEUMATOID ARTHRITIS	165	55	52	13	120
OSTEOARTHRITIS	62	17	31	12	60
PARKINSON'S DISEASE	183	37	24	4	65
ALZHEIMER'S DISEASE	276	68	52	23	143
MULTIPLE SCLEROSIS	-	19	11	2	32
IMMUNOLOGY	1,157	200	176	60	436
PSYCHIATRY	261	76	100	29	205
SKIN	428	103	222	59	384
TOTAL	14,863	3,723	4,424	1,257	9,404

MÉTHODOLOGY

The global figures from the academic, collective and industrial research cited in Health 2030 are taken from the document published by PhRMA in July 2017, The Biopharmaceutical Pipeline: Innovative Therapies in Clinical Development.

This document provides a snapshot of the number of drugs in development worldwide in July 2017 and their distribution throughout the research and development chain: preclinical and clinical phases (phases I, II, III). PhRMA's analysis focuses on new drugs (immunotherapies, gene therapies, cell therapies, etc.) and on first-in-class therapies, i.e. ones that use a new mechanism of action. It lists all clinical trials, whether from academic, collective or industrial research.

Figures extracted from the Evaluate database and analysed by PhRMA, July 2017.

PRECLINICAL DEVELOPMENT AND PHASE I, II, III CLINICAL TRIALS

Figures extracted from the Evaluate database and analysed by PhRMA, July 2017.

THE INNOVATION WHEEL

THINKING GLOBALLY ABOUT PROGRESS AND R&D BASED ON FOUR PILLARS THAT RANGE FROM UPSTREAM RESEARCH TO PATIENT WELL-BEING

Progress by disease entails the revival of an old approach consisting of four pillars: advances in our knowledge and understanding of diseases; prevention and screening (with considerable progress yet to be made); targeted treatments; and support in quality of life for patients (medical, social, psychological, empowerment).

Innovation must combine these different advances holistically to identify weaknesses, drivers, etc.. For ecosystem actors, it is a question of going beyond translational approaches and integrating the issues and links to the other pillars.

The choice of diseases covered in this section was made primarily on the basis of the expectations of the French in terms of advances in therapy.

Each factsheet has therefore been designed according to a deliberately integrated approach that connects the four inseparable aspects of innovation:
1. advances in disease understanding through research and epidemiology;
2. advances in diagnosis, screening and prevention;
3. advances in treatment;
4. advances in patient support.

Since 2018, advances have been identified
- as a result of ongoing clinical or technological developments;
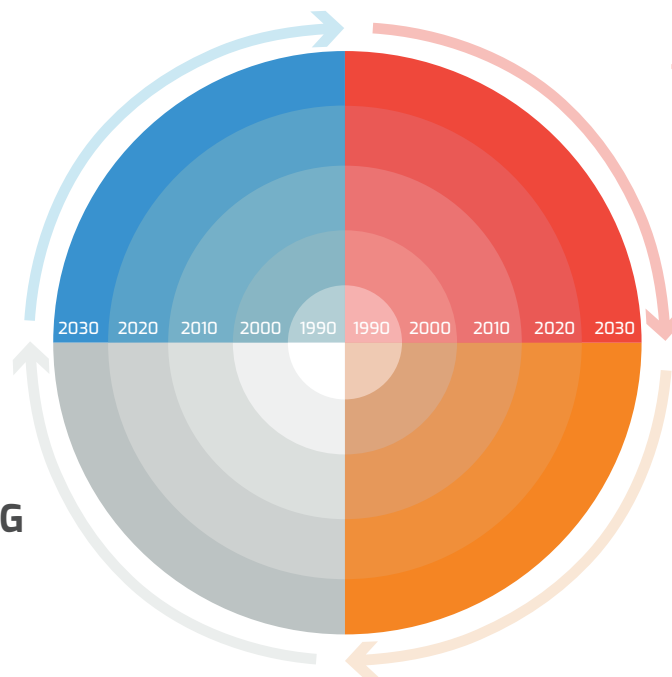- as a result of analyses, forecasting by the experts consulted for each factsheet.

DIAGNOSIS
PREVENTION
SCREENING

TREATMENT

2030 2020 2010 2000 1990 | 1990 2000 2010 2020 2030

UNDERSTANDING
RESEARCH
EPIDEMIOLOGY

SUPPORT

THERAPEUTIC PROGRESS BY DISEASE AS SEEN BY THE EXPERTS AND DOCTORS

- CANCER **GILLES VASSAL** Gustave Roussy Institute, Villejuif

- CARDIOVASCULAR DISEASES **EMMANUEL TEIGER** Henri Mondor Hospital, Créteil

- AUTISM **MARION LEBOYER** Henri Mondor Hospital, Créteil

- DEPRESSION **LUCILE CAPURON** INRA, Bordeaux

- DIABETES **CHRISTIAN BOITARD** Cochin Hospital, Paris

- ALZHEIMER'S DISEASE **HERVÉ CHNEIWEISS** Pitié-Salpêtrière Hospital, Paris

- PARKINSON'S DISEASE **STÉPHANE PALFI** Henri Mondor Hospital, Créteil

- RARE DISEASES **MARC PESCHANSKI** I-Stem, Corbeil

- LIVER DISEASES **GABRIEL PERLEMUTER** Antoine-Béclère Hospital, Clamart

- VIH-AIDS **JEAN-FRANÇOIS DELFRAISSY** National Ethics Committee, Paris

- MULTIPLE SCLEROSIS **DAVID BRASSAT** CHU Toulouse-Purpan, Toulouse

- VISION DISORDERS **SERGE RESNIKOFF** Sydney University, Australia

CANCER

WHAT ARE WE TALKING ABOUT?

The word cancer encompasses a group of diseases characterised by the abnormal, uncontrolled multiplication of cells. These cancer cells can form a malignant tumour or spread throughout the body. There are several hundred different malignancies.

Cancers are complex diseases observable from birth to the other end of the age scale, and the risk of developing cancer increases with age. The treatment is by definition multidisciplinary, as it combines surgery, radiotherapy, chemotherapy, immunotherapy or hormone therapy, depending on the type of cancer and its stage of development (local, locoregional or distant).

CHALLENGES

Detecting cancer as early as possible

Developing prevention

Expanding the therapeutic arsenal

Anticipating the phenomenon of malignant cell resistance

PREVALENCE [1]

400,000 new cases each year in France

161,000[2] deaths each year in France

186,000 women

214,000 men

Most common cancers:

Colorectal Lung

Prostate Breast

Leading cause of death before cardiovascular diseases

MAIN DRIVERS

Creating structured, shared and accessible databases

Bringing together mathematicians, bioinformaticians, etc.

Conducting a rigorous and ethical approach to genetics

Modelling the biological pathways involved in cancer

IN 2030?

A new cancer atlas will have condensed all knowledge from a therapeutic and integrative perspective.
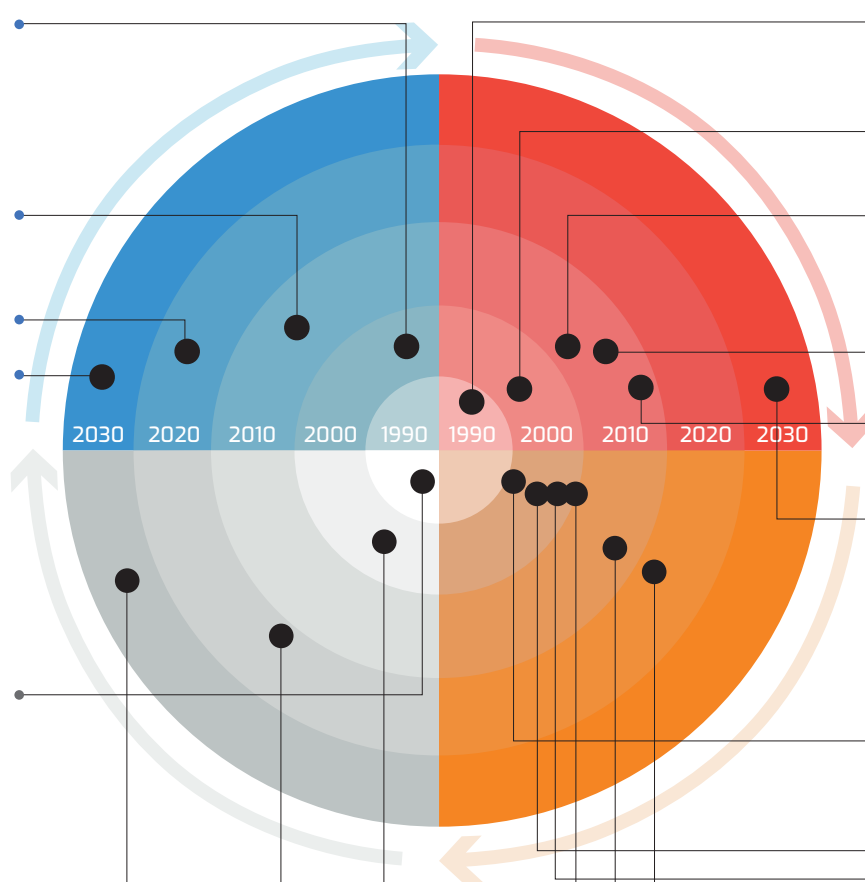
MEDICINES IN DEVELOPMENT

3,463 industry-sponsored[3] clinical trials were ongoing in France in 2018.

[1]Source: INCa Report, 2017/ [2]Cancer Observatory. Institut Curie. 2017/ [3]Source: Leem's Innovation Database, April 2018.

DIAGNOSTICS

2000 - Scanners and MRIs are widely deployed to refine the diagnosis and staging of cancer. High-throughput molecular biology techniques can provide an expression profile of all genes in a tumour

2010 - Establishment of an academic network of 28 molecular genetics platforms (100,000 tests per year)

2020 - Development of liquid biopsy

2030 - New artificial intelligence-driven decision-making algorithms

TREATMENT

1990 - Chemotherapies kill malignant cells non-specifically with many side effects - First kinase inhibitors

2000 - First targeted therapies: Trastuzumab and Imatinib - First anti-angiogenic agents

2010 - Some twenty targeted drugs available for cancers of the kidney, colon, lung, breast and for chronic myeloid leukaemia

2016 - First immunotherapies (CTLA-4 and PD-1/PD-L1) for metastatic melanoma

2018 - Efficacy of CAR-T cells in acute lymphoblastic leukaemias and lymphomas

2030 - Immunotherapy combinations, epigenetic treatments and targeted treatments will be the established treatments

UNDERSTANDING

1990 - Identification of oncogenes that when mutated or altered contribute to converting a normal cell into a cancer cell. - Knowledge of genes predisposing to BRCA cancer (breast cancer)

2000 - Discovery of checkpoint inhibitors CTLA-4, PD-1, PD-L1

2012 - CRISPR-Cas9

2030 - Immunology atlas of cancer

SUPPORT

2000 - Haematopoietic growth factors - New antiemetics and painkillers to improve quality of life during chemotherapy

2003-2007 - 1st Cancer Plan

2005 - Creation of the French National Cancer Institute (INCa)

2009-2013 - 2nd Cancer Plan

2014-2019 - 3rd Cancer Plan

2020 - Quality of recovery and post-cancer care become important fields of research and patient care, in the same way that cancer is

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

CARDIOVASCULAR DISEASES

WHAT ARE WE TALKING ABOUT?

The term cardiovascular disease covers various diseases, the most frequent of which are myocardial infarction, heart failure, stroke, and venous thrombosis.

In France, 100,000 people are treated each year for myocardial infarction, 130,000 for stroke. Myocardial infarction and stroke are the leading cause of physical disability among adults, the second leading cause of death, the second leading cause of dementia, and a common cause of depression.

CHALLENGES

Combating the rise of sedentary behaviour, obesity and diabetes

Controlling high blood pressure

Anticipating the ageing population

Controlling cholesterol

PREVALENCE

Leading[1]
cause of death
worldwide in 2017

150,000[3]
deaths each year
in France in 2017

17.7 million[2]
million deaths worldwide
in 2017

400[4]
deaths each day
in France in 2017

MAIN DRIVERS

Screening high-risk subjects

Developing innovative therapeutics

Preserving and regenerating vascular capital

Transferring skills to nursing staff and patients

IN 2030?

Artificial intelligence will make it possible to personalise the treatment of cardiovascular diseases by 2030[5]

+3%
Increase in all heart diseases by 2030

+8%
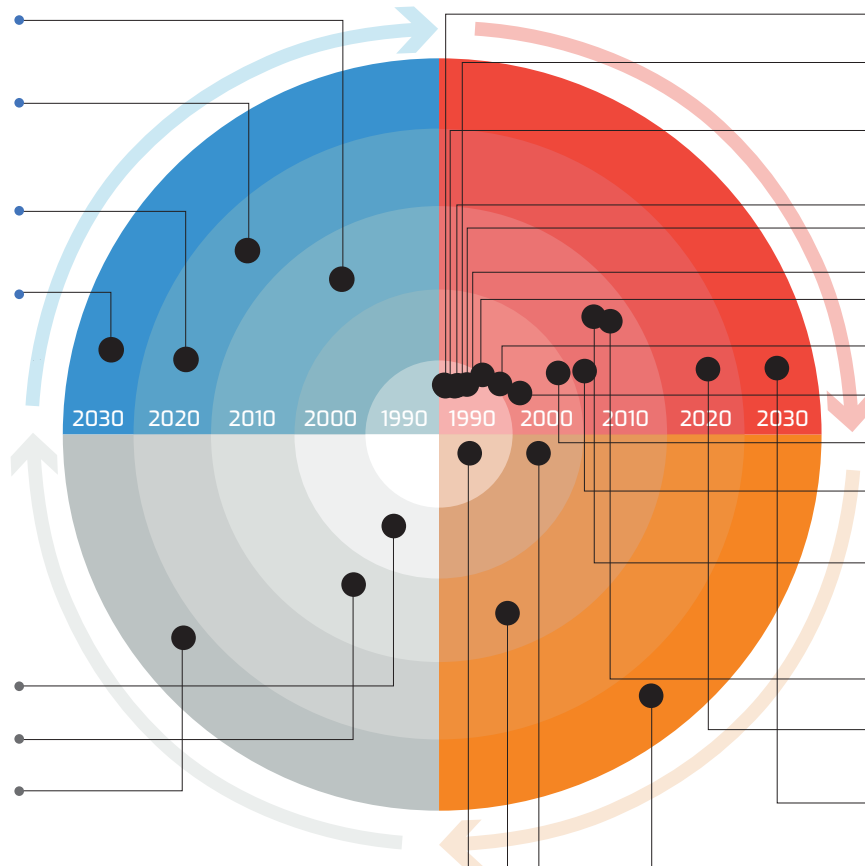Increase in stroke by 2030

MEDICINES IN DEVELOPMENT

234 industry-sponsored clinical trials were ongoing in France in 2018

DIAGNOSTICS

2010 - Link between atherosclerosis and digital applications used to combat heart disease

2019 - Use of artificial intelligence to improve our understanding of the early signs of cardiovascular events

2020 - Coordination between genomic approaches and data processing using artificial intelligence

2030 - New biomarkers of risk

TREATMENT

1956 - First aldosterone antagonists

1975 - First use of beta-blockers in heart failure

1981 - First ACE (angiotensin converting enzyme) inhibitor

1987 - First statins

1990 - Second-generation ACE inhibitors

1995 - First sartans

1998 - Widespread use of antiplatelet drugs

2000 - New classes of antihypertensive agents

2001 - First drug-eluting stent

2009 - New oral anticoagulants (NOACs)

2010 - Widespread use of conversion enzyme inhibitors and beta-blockers

2014 - First embryonic stem cell transplantation to alleviate heart failure symptoms - First implantation of a fully artificial heart

2015 - First anti-PCSK9 monoclonal antibodies

2020 - Innovative therapeutics to preserve and regenerate the patient's vascular and myocardial capital

2030 - Pacemakers will be run on AI and coordinated using systems that deliver the drug to the right person at the right time

UNDERSTANDING

2000 - Cell therapy applied to myocardial preservation

2010 - Genetic characterisation of many heart diseases

2030 - Role of inflammation in cardiovascular disease - Convergence between hypertension, obesity and diabetes

(circle axis labels: 2030 2020 2010 2000 1990 1990 2000 2010 2020 2030)

SUPPORT

1990 - Identification of risk factors (cholesterol, hypertension, smoking, diabetes)

2000 - French National Health and Nutrition Programme (PNNS)

2010 - Primary prevention programme launched by the National Health Insurance Fund (CNAM)

2030 - AI-driven integrative prevention policy

AUTISM

WHAT ARE WE TALKING ABOUT?

Autism Spectrum Disorders (ASDs) are a heterogeneous set of lifelong neurodevelopmental conditions which manifest in early childhood (before the age of 3). They are characterised by impairment in social interactions and stereotyped behaviours, combined, to varying degrees, with communication difficulties, mental retardation, sleep disorders, attention deficit hyperactivity disorder, mood disorders, but also somatic conditions such as epilepsy or gastrointestinal problems.

According to the DSM-5 criteria, autism is defined according to two main domains: impaired social interaction and stereotyped behaviours.

CHALLENGES

Developing an inclusive approach: improving schooling

Avoiding the exclusion of the 600,000 adults with autism

Identifying ASD early and improving diagnosis

Promoting research and data processing

PREVALENCE

1 in 100 people[1]
is affected by autism worldwide, versus
1 in 59 people[2]
in the United States

3 to 5 years
Age[4] when the diagnosis is made

1%
of autistic people in France[3], with a ratio of three boys for every girl

40%
of autistic people[5] are in school

IN 2030?

Effective therapies will be identified for each subgroup of patients

MAIN DRIVERS

Identifying the subgroups of people with autism by improving its clinical and biological characterisation

Promoting multidisciplinary approaches that bring together psychiatrists, general practitioners, paediatricians and specialists, as well as researchers in genetics, epidemiology, immunology, brain imaging, etc.

Training front-line health professionals to identify people with autism so they can be offered a specialist diagnostic assessment, and introducing psychosocial therapies countrywide
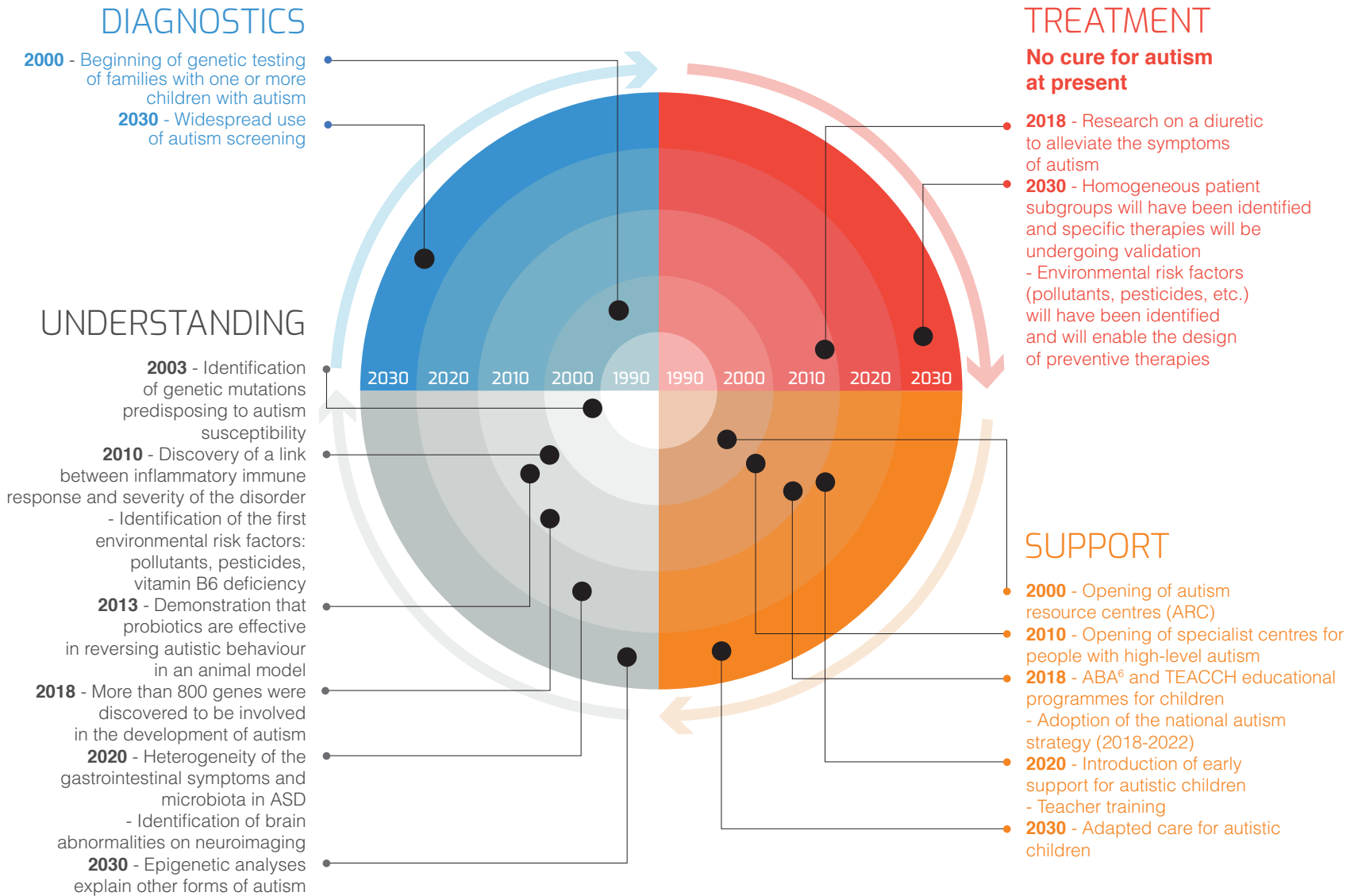
Gaining a better understanding of genetic and environmental risk factors

DIAGNOSTICS

2000 - Beginning of genetic testing of families with one or more children with autism
2030 - Widespread use of autism screening

TREATMENT

No cure for autism at present

2018 - Research on a diuretic to alleviate the symptoms of autism
2030 - Homogeneous patient subgroups will have been identified and specific therapies will be undergoing validation
- Environmental risk factors (pollutants, pesticides, etc.) will have been identified and will enable the design of preventive therapies

UNDERSTANDING

2003 - Identification of genetic mutations predisposing to autism susceptibility
2010 - Discovery of a link between inflammatory immune response and severity of the disorder
- Identification of the first environmental risk factors: pollutants, pesticides, vitamin B6 deficiency
2013 - Demonstration that probiotics are effective in reversing autistic behaviour in an animal model
2018 - More than 800 genes were discovered to be involved in the development of autism
2020 - Heterogeneity of the gastrointestinal symptoms and microbiota in ASD
- Identification of brain abnormalities on neuroimaging
2030 - Epigenetic analyses explain other forms of autism

SUPPORT

2000 - Opening of autism resource centres (ARC)
2010 - Opening of specialist centres for people with high-level autism
2018 - ABA[6] and TEACCH educational programmes for children
- Adoption of the national autism strategy (2018-2022)
2020 - Introduction of early support for autistic children
- Teacher training
2030 - Adapted care for autistic children

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

[6] ABA: Applied Behaviour Analysis / TEACCH: Treatment and Education of Autistic and Related Communication Handicapped Children.

DEPRESSION

WHAT ARE WE TALKING ABOUT?

Depression is understood as experiencing five or more symptoms for a period of at least two weeks. The patient is in the grip of emotional pain (unusual sadness) and/or loss of pleasure and inability to perform daily activities (getting up, going to work, cooking). Fatigue, loss of energy, decreased appetite, sleep disorders, poor attention and concentration, irritability, suicidal thoughts, low self-esteem and psychomotor slowdown are also observable.

Refractory depression is characterised by depression that persists despite at least two successive courses of appropriate antidepressant medication or is insufficiently relieved by these treatments. It is thought to account for between 15 and 30% of major depressive episodes.

CHALLENGES

- Rethinking the approach to mental health
- Developing more effective treatments (they are only effective in 70% of cases at present)
- Promoting holistic physical and mental healthcare
- Destigmatising depression

MAIN DRIVERS

- Finding new therapeutic targets
- Improving the diagnosis of refractory depression and identifying homogeneous clinical forms
- Harnessing the advances in genetics, medical imaging and immunopsychiatry
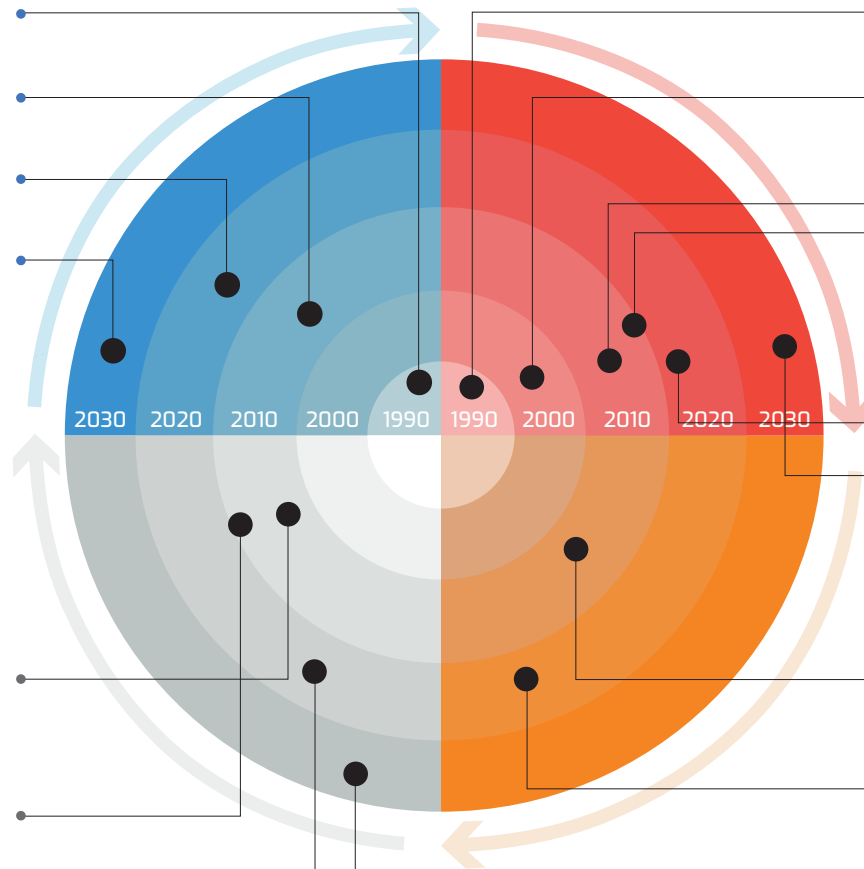- Establishing patient stratification platforms to promote precision medicine

PREVALENCE

322 million[1]
worldwide in 2017

+ 18%[2]
Increase in the number of cases worldwide between 2005 and 2015

- 50%
of depressions are treated

1 out of 5 French people[2]
has suffered or will suffer from depression during their lifetime

800,000[2]
Number of depression-related suicides worldwide each year

IN 2030?

12 billion[3]
working days will be lost each year between now and 2030 unless better support is provided

Development and implementation of strategies to enable precision medicine in psychiatry

MEDICINES IN DEVELOPMENT[4]

39 DRUGS
in development in 2017, including 2 specifically targeting refractory depression

DIAGNOSTICS

1990 - Initial framing based on the concept of major depressive episode according to DSM-III criteria

2010 - Heterogeneity of depression: distinction between recurring and non-recurring forms

2020 - Categorisation of depression and refractory forms

2030 - Effective biomarkers for diagnosis and treatment follow-up: pharmacogenetic profiles, magnetoencephalography

TREATMENT

1990 - Development of antidepressants (SRI)[5], MAOI[6], SSRI[7]: the antidepressant decade

2000 - Therapeutic innovations: cognitive behavioural therapy (CBT) and modulation of brain activity or deep brain stimulation

2010 - Ketamine trial

2018 - Application for funding in the United Kingdom for ketamine in the treatment of refractory depression - Several clinical trials underway for refractory depression targeting altered inflammatory mechanisms

2020 - Development of guidelines on refractory depression

2030 - Targeted and personalised therapeutic strategies (including immunopsychiatry, nutritional psychiatry, etc.)

2030 2020 2010 2000 1990 | 1990 2000 2010 2020 2030

UNDERSTANDING

2010 - Identification of genetic variations, gene-environment interactions, inflammation factors and the role of microbiota

2018 - Study launched: "How to prevent inflammation from disrupting neurotransmitter metabolism"

2020 - New treatment response biomarkers
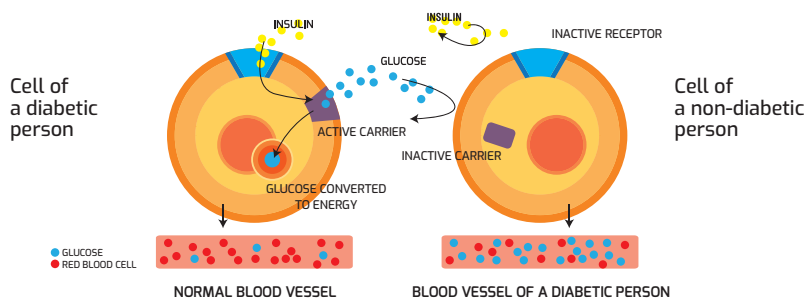
2030 - Understanding genetic vulnerability

SUPPORT

2010 - Creation of the FondaMental Foundation and a network of expert centres for treatment-refractory depression (2012)

2020 - Better monitoring of disease progression (anxiety disorders, eating disorders, OCD, etc.)

DIABETES

WHAT ARE WE TALKING ABOUT?

Diabetes is a chronic disease that cannot be cured, but can be treated and controlled. It is caused by the inability of the body to produce (case of type 1 diabetes or T1D) or use (case of type 2 diabetes or T2D) a hormone called insulin, which is produced by the pancreas. Diabetes is an issue that involves medical factors (complications), social factors (diagnosis and prevention are overlooked in some patients), scientific factors (many unknowns surrounding the mechanisms involved), and industrial factors.

INSULIN
INSULIN
INACTIVE RECEPTOR
GLUCOSE

Cell of a diabetic person

ACTIVE CARRIER
INACTIVE CARRIER

Cell of a non-diabetic person

GLUCOSE CONVERTED TO ENERGY

- GLUCOSE
- RED BLOOD CELL

NORMAL BLOOD VESSEL

BLOOD VESSEL OF A DIABETIC PERSON

PREVALENCE[1]

422 million
cases worldwide in 2017

+ 2.9%
diabetics each year

1 in 11 people
is affected

3.3 million
cases in France in 2017

IN 2030?

552 million
people will be diabetic in 2030[2]

Soaring costs of diabetes

CHALLENGES

Understanding the function of the genes involved in T1D and T2D

Detecting diabetes early

Preventing the complications of diabetes (blindness, amputation)

Preventing the explosion in obesity

MAIN DRIVERS

Improving treatment compliance (40% of T2D patients do not adhere to their treatment)

Using artificial intelligence to improve support

Investigating changes in the intestinal flora

Moving to a holistic, systemic and integrative approach: understanding the links between diet, body weight, lifestyle, etc.
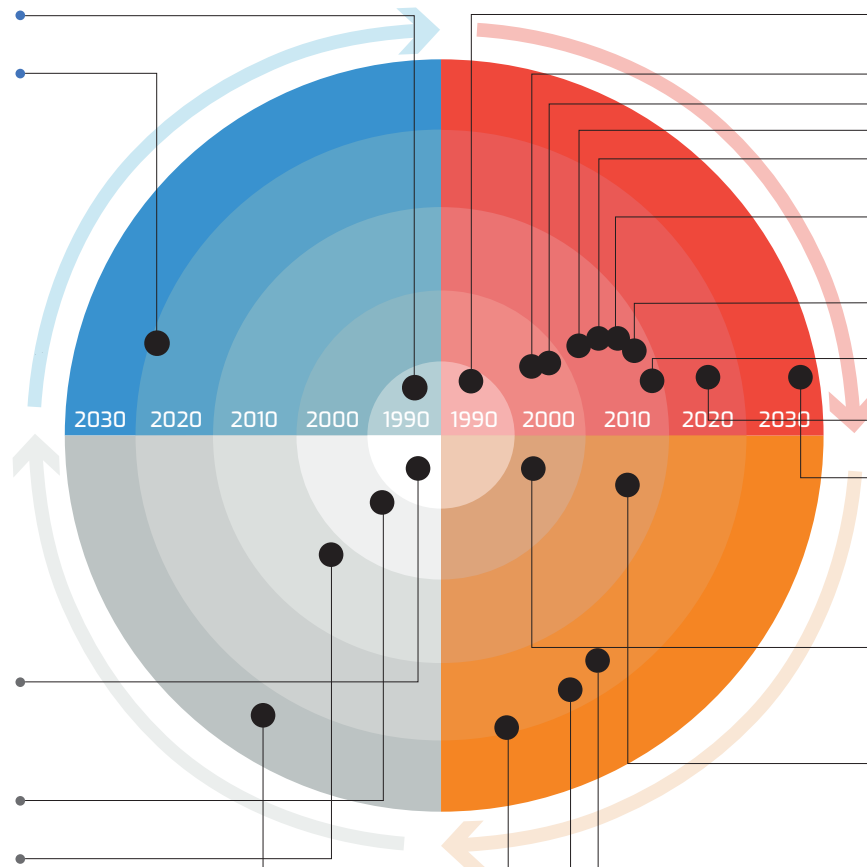
MEDICINES IN DEVELOPMENT

170 industry-sponsored[3] clinical trials were ongoing in France in 2018

DIAGNOSTICS

1990 - Measurements of glucose (sugar level) in the blood

2020 - Need to improve the diagnosis of diabetes, as 700,000 French people are reported to have diabetes without knowing it understanding

TREATMENT

1990 - Old treatments: insulin (1921) and biguanides (1957)

2006 - First GLP-1 analogues

2007 - First DPP-4 inhibitors

2013 - First SGLT2 inhibitors

2016 - New long-acting GLP-1s

2017 - Promising results of clinical trials o n the artificial pancreas

2018 - Application for approval of nasal glucagon

2019 - Availability of the artificial pancreas

2025 - Combined GLP-1/GIP and anti-IL 21 + GLP-1 for T1D

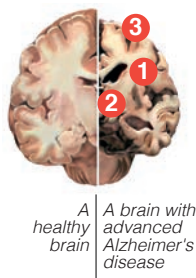**2030** - Development of smart insulin, which is activated in response to rising blood sugar levels

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

UNDERSTANDING

1990 - Characterisation of the main mechanisms by which insulin is produced by the pancreas

2000 - Role of adipose tissue - Link with obesity

2010 - Identification of markers that classify the different forms of T2D

2030 - Clinical trials testing immunotherapy for T1D

SUPPORT

2000 - Widespread use of self-monitoring of blood glucose and recombinant human insulins

2010 - Interstitial continuous glucose monitoring system/combined pump and glucose sensor system - Dedicated diabetes websites

2017 - First sensor to measure blood sugar attached to the skin. Blood glucose levels can be viewed on a smartphone and blood tests are no longer required

2018 - First closed-loop insulin pump capable of interrupting insulin infusion when blood glucose reaches critical levels

2020 - Availability of integrated solutions combining digital technologies and insulin injection

ALZHEIMER'S DISEASE

WHAT ARE WE TALKING ABOUT?

Alzheimer's disease (AD) is a neurodegenerative condition associated with ageing. It manifests as a decline in cognitive function that eventually progresses to dementia, with memory impairment, mood and behavioural changes, severe confusion about events, time and place, etc.

A healthy brain | *A brain with advanced Alzheimer's disease*

Progression of lesions and symptoms

During the course of Alzheimer's disease, the characteristic lesions gradually invade several regions of the brain

1 The hippocampus involved in memory processes
2 The limbic system which manages emotions
3 The cortex involved in the control of space-based attention, language, memory and control of executive functions

CHALLENGES

Having reliable data and information on trends

To facilitate caregivers's role

Understanding the mechanisms of the disease Facilitating the role of caregivers

Detecting functional difficulties very early on at the first signs of the disease

MAIN DRIVERS

Increasing the number of cohort studies

Maintaining physical, intellectual, social activity

Identifying high-risk populations

Developing drugs capable of fighting AD at a very early stage

PREVALENCE

900,000[1]

people, equivalent to the population of Marseille, in 2017

50 million[2]

worldwide in 2030

Prevalence of Alzheimer's disease and related diseases[3]

before age 70	< 👤	/ 100
between age 70 and 79	👤	/ 25
between age 80 and 89	👤	/ 5
after age 90	👤	/ 3

IN 2030?

75 million[4]

sufferers in 2030

Alzheimer disease will be better described and understood and will benefit from an upstream treatment.
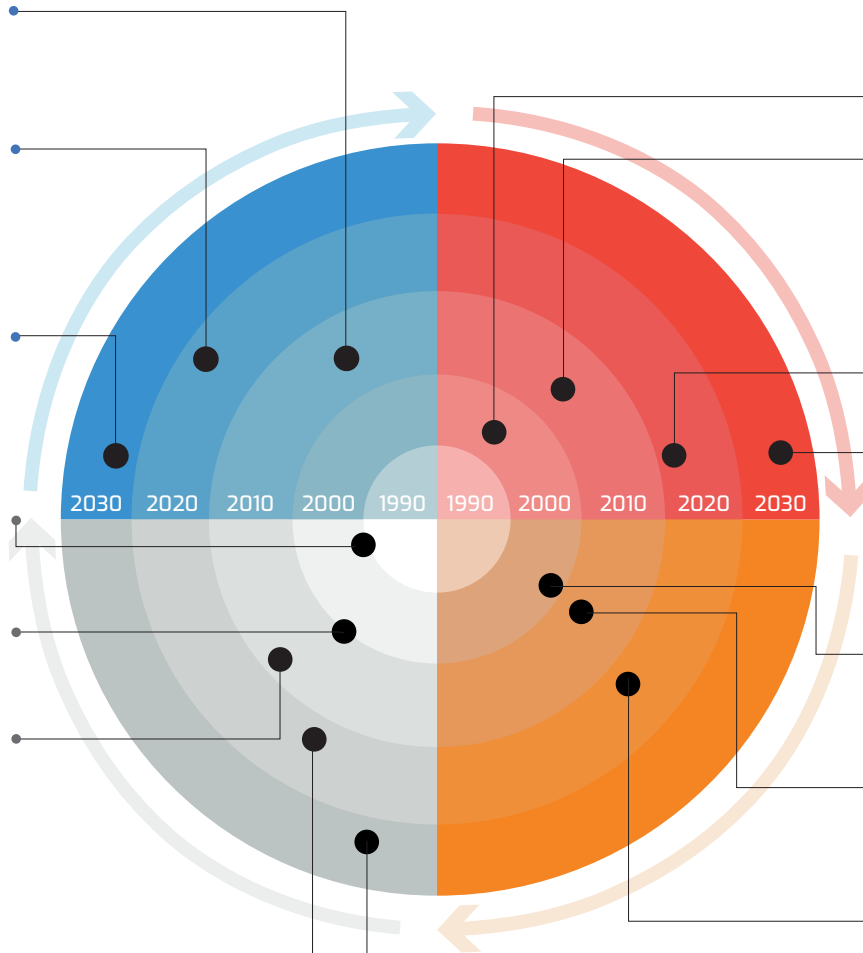
MEDICINES IN DEVELOPMENT

82 industry-sponsored[5] clinical trials were on-going in France in 2018

DIAGNOSTICS

2010 - Use of biological markers for early diagnosis (amyloid-beta protein, Tau proteins and phosphorylated Tau)

2018-2020 - A reliable early diagnosis can now be made based on cerebrospinal fluid biomarkers (amyloid ß to phosphorylated Tau ratio) and amyloid plaque brain imaging

2030 - Development and use of risk biomarkers (genetic, metabolic, etc.)

UNDERSTANDING

2000 - Identifying the neurotransmitter circuits involved in memory and the biochemical composition of lesions

2010 - Paquid study: discovery of fine cognitive changes ten to fifteen years before disease onset

2018 - Results of the Insight study highlighting compensation mechanisms in people with lesions - Studies have shown that even before the first symptoms of Alzheimer's disease appear, the functioning of the neuronal mitochondria (cell powerhouses) is disrupted. This energy deficit causes a molecular cascade that leads to the disease

2020 - Towards detection of Alzheimer's disease years before its onset

2030 - Understanding Alzheimer's disease

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030
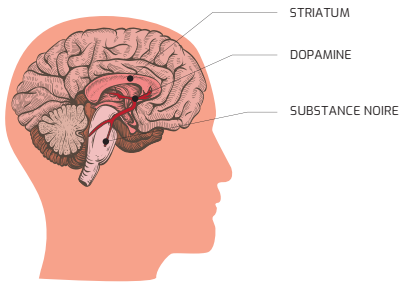
TREATMENT

No treatment to cure the disease

2000 - First symptomatic drugs

2010 - Many trials were conducted using anti-amyloid antibodies that yielded weak but encouraging results if treatment is started very early, hence the ongoing trials in symptom-free patients in an attempt to delay the age of disease onset

2021/2022 - A first effective treatment for AD (a drug is currently in phase III clinical trials)

2030 - Development of preventive strategies

SUPPORT

2008 - Alzheimer's Plan - Introduction of memory consultations within MAIA (Houses for the autonomy and integration of Alzheimer's patients)

2013 - LabEx DISTALZ's work on understanding the ethical issues raised by the possibilities of increasingly early diagnosis or detection of AD

2020 - Secondary prevention: high cognitive reserve, high intellectual activity, physical exercise, general disease management (diabetes, hypertension, hypercholesterolemia), delaying disease onset and slowing its progression

PARKINSON'S DISEASE

WHAT ARE WE TALKING ABOUT?

STRIATUM

DOPAMINE

SUBSTANCE NOIRE

Parkinson's disease is a neurodegenerative disease characterised by the destruction of a specific population of dopamine-producing neurons in the substantia nigra of the brain.

As it progresses, patients will face an increased risk of dependency, due largely to motor complications (dyskinesia, motor fluctuations, falls) and cognitive complications (cognitive impairment, hallucinations, dementia).

CHALLENGES

Diagnosing the disease early enough (60% of neurons are already lost in a late diagnosis)

Understanding the mechanisms of the disease

Improving the treatment of impairments

Managing patients at different stages of their disease

PREVALENCE[1]

6.3 million
cases worldwide in 2017

1.2 million
cases in Europe in 2017

150,000
people with Parkinson's disease in France in 2017

58 years
average age of diagnosis in France

MAIN DRIVERS

Identifying genetic and environmental risk factors

Using digital applications to monitor patients on a daily basis

Identifying prognostic and predictive markers using an integrated approach that combines genetic, metabolic, physiological and clinical information

Administering treatment before the onset of symptoms

IN 2030?

More personalised treatments

for Parkinson's disease

MEDICINES IN DEVELOPMENT

47 industry-sponsored[2] clinical trials were ongoing in France in 2018

DIAGNOSTICS

No blood test or imaging method can diagnose the disease

Nuclear imaging can only monitor the progression of dopaminergic degeneration

TREATMENT

1960-1970 - Compensation of dopamine loss with the contribution of its precursor Levodopa

1990 - Cell therapy trials

1993 - Deep brain stimulation to treat tremor, akinesia and rigidity

2000 - Gene therapy, neuroprotection and dopamine replacement trials

2007 - Dopamine continuous-delivery pump

2010 - Form of continuous transdermal delivery of dopamine agonists and Levodopa

2014 - Alpha-synuclein immunotherapy trials
- neuroprotective iron chelator trials

2017 - First directional brain stimulation electrode

2018 - Neuroprotection trials by injection of a homeoprotein
- Continuation of cell therapy trials with the transplantation of foetal dopamine neurons (from IPs or ES cells)

2030 - Patient-controlled deep brain stimulation
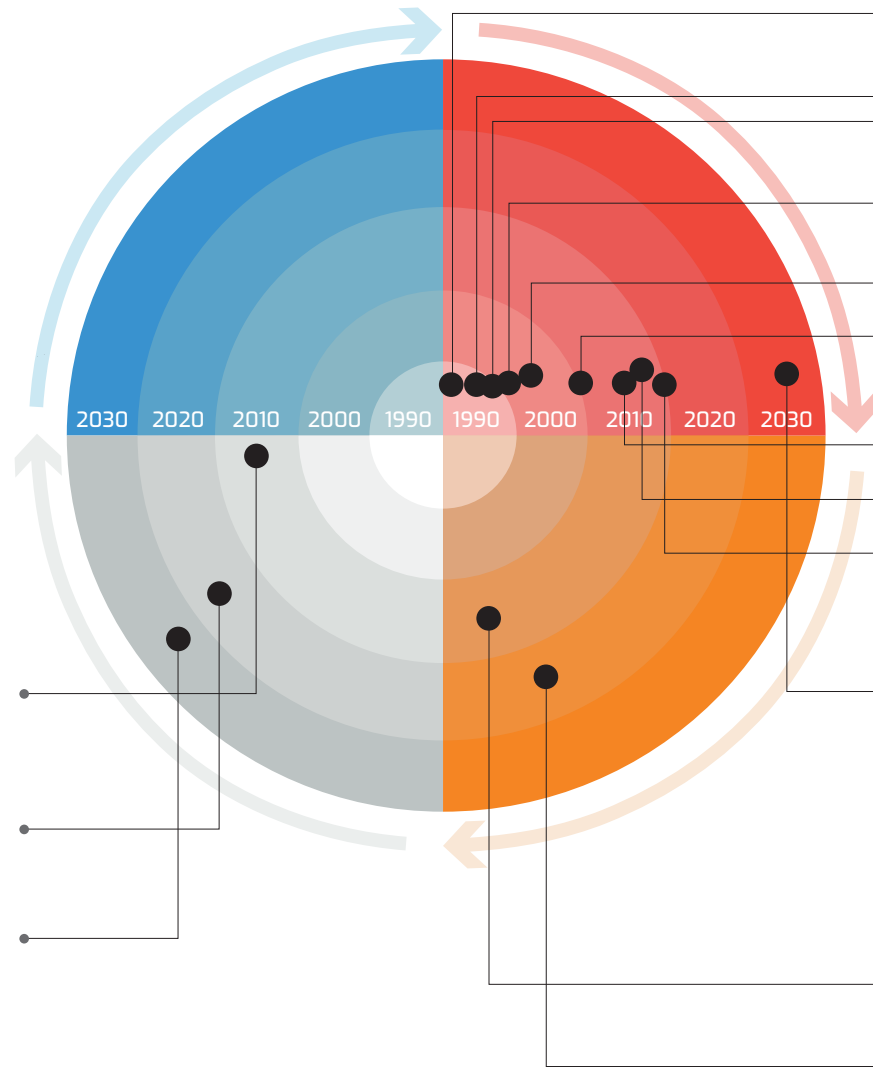- Precision treatments personalised according to phenotype and genotype
- Stopping the spread of alpha-synuclein

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

UNDERSTANDING

2010 - Identification of a gene involved in early Parkinson's disease
- Investigation of the role of mit chondria

2020 - Identification of the pathogenic role of the protein alpha-synuclein and its spread in the brain

2030 - Identification of patient subgroups

SUPPORT

2010 - Serious Game to rehabilitate balance disorders and falls
- Expert Centres for Parkinson's disease

2020 - Markers to monitor and predict disease progression

RARE DISEASES

WHAT ARE WE TALKING ABOUT?[1]

Of the 7,000 rare diseases (diseases that affect fewer than 1 in 2,000 people) listed to date more than 80% are caused by genetic "bugs" (transcription and coding errors, etc.). Hereditary or accidental errors, these mutations are responsible for genetic diseases that are often serious and difficult to diagnose and treat.

Rare and ultra-rare diseases affect a very small proportion of patients. Rare diseases therefore represent a major public health issue, the specificity of which being largely related to their heterogeneity and their treatment difficult as there is no return on investment under the current framework.

CHALLENGES

Adapting the regulatory system to the specificity of rare diseases

Building an integrated, interconnected and international database

Ensuring patient access to innovative medicines

Developing an incentive system for industry-driven R&D

PREVALENCE[2]

3 million French people have a rare disease in 2018

30 million Europeans are affected

50% of cases relate to children under 5 years of age
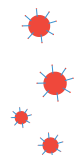
90% of cases affect fewer than one in 100,000 people (ultra-rare diseases)

MAIN DRIVERS

Controlling gene therapy vectors

Enhancing bioinformatics skills

Making technological leaps forward through efficient biomanufacturing

Organising an information system at national and European level that is accessible to doctors and healthcare providers

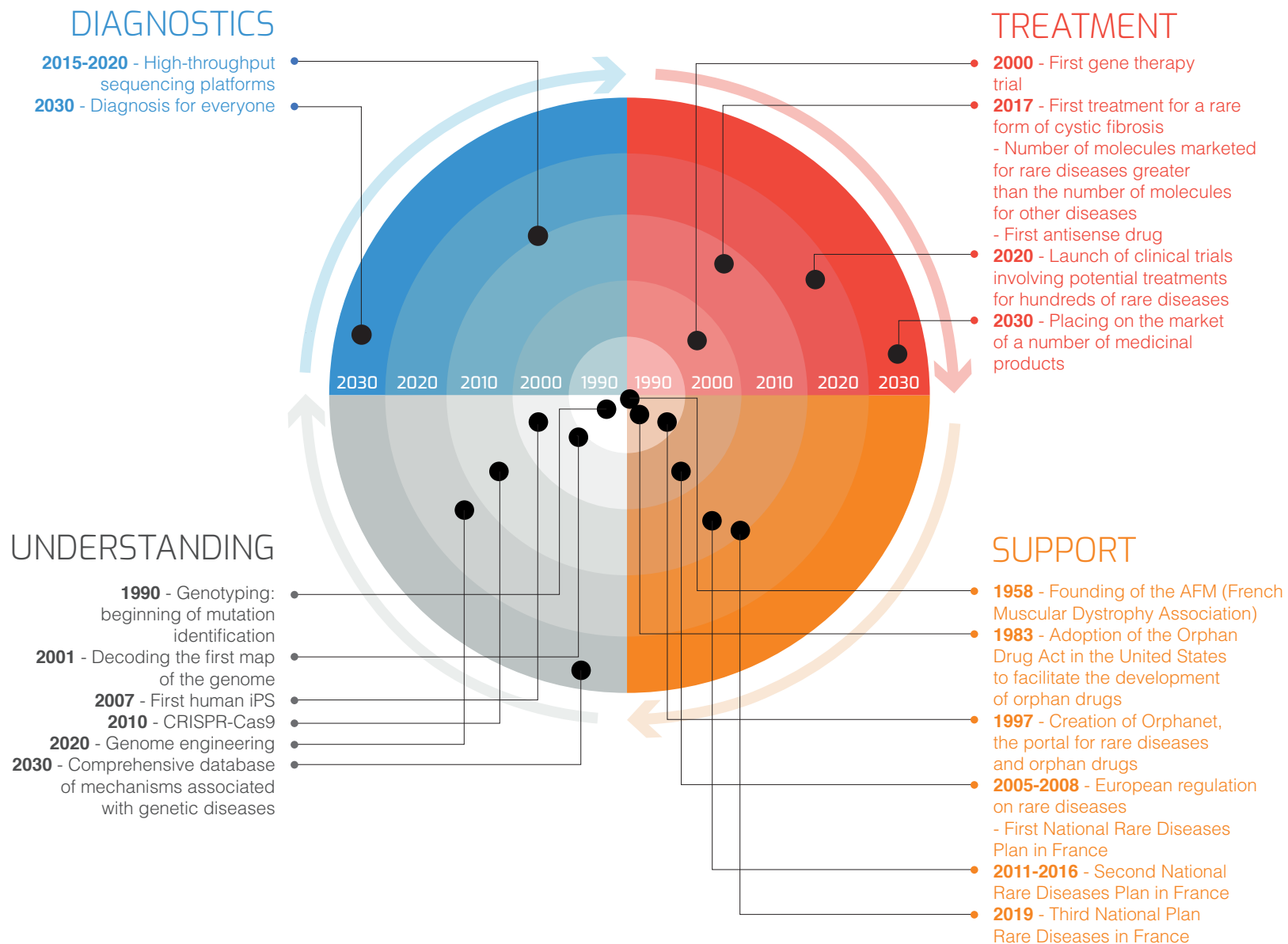## IN 2030?

End of misdiagnosis

MEDICINES IN DEVELOPMENT[3]

1,362 clinical trials ongoing in 2018
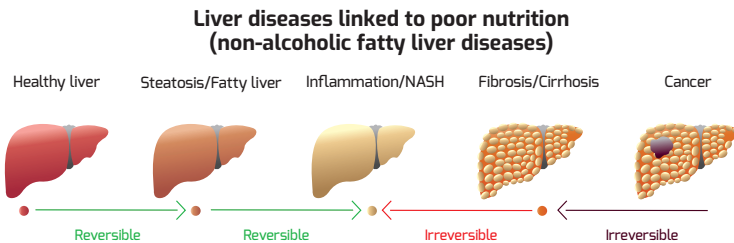**413** in phase I
737 in phase II
212 in phase III

42 drugs in pre-registration phase (phase before their assessment by the regulatory agencies)

DIAGNOSTICS

2015-2020 - High-throughput sequencing platforms
2030 - Diagnosis for everyone

TREATMENT

2000 - First gene therapy trial
2017 - First treatment for a rare form of cystic fibrosis
- Number of molecules marketed for rare diseases greater than the number of molecules for other diseases
- First antisense drug
2020 - Launch of clinical trials involving potential treatments for hundreds of rare diseases
2030 - Placing on the market of a number of medicinal products

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

UNDERSTANDING

1990 - Genotyping: beginning of mutation identification
2001 - Decoding the first map of the genome
2007 - First human iPS
2010 - CRISPR-Cas9
2020 - Genome engineering
2030 - Comprehensive database of mechanisms associated with genetic diseases

SUPPORT

1958 - Founding of the AFM (French Muscular Dystrophy Association)
1983 - Adoption of the Orphan Drug Act in the United States to facilitate the development of orphan drugs
1997 - Creation of Orphanet, the portal for rare diseases and orphan drugs
2005-2008 - European regulation on rare diseases
- First National Rare Diseases Plan in France
2011-2016 - Second National Rare Diseases Plan in France
2019 - Third National Plan Rare Diseases in France

LIVER DISEASES

WHAT ARE WE TALKING ABOUT?

Liver diseases are common. It is estimated that between 23 and 45% of the French population suffers from hepatic steatosis.[1] A real revolution has recently taken place in the treatment of Hepatitis C. Other diseases (hepatitis B, D, alcoholic hepatitis) remain public health problems worldwide. Liver diseases affect people of all ages. They have a major impact on the health and quality of life of those affected.

**Liver diseases linked to poor nutrition
(non-alcoholic fatty liver diseases)**

Healthy liver Steatosis/Fatty liver Inflammation/NASH Fibrosis/Cirrhosis Cancer

Reversible   Reversible   Irreversible   Irreversible

CHALLENGES

Understanding the hepatotoxicity of drugs

Making progress on liver damage linked to overweight, hepatitis D and rare liver diseases

Early screening and eradication of hepatitis C

Better management of the risk factors of liver disease (nutrition, alcohol, etc.)

PREVALENCE

240 million people live with hepatitis B worldwide[2]

280,000 people live with hepatitis B in France[3]

140 million people live with hepatitis C worldwide[2]

75,000 people live with undetected[3] hepatitis C in France

MAIN DRIVERS

Combating alcoholism, rising obesity, sedentary lifestyle, industrial foods

Implementing vaccine recommendations

Bringing therapeutic advances to poorer countries

Evaluating the best non-invasive diagnostic and therapeutic strategies

IN 2030?

Eliminating viral hepatitis as a serious threat to public health by 2030[4]
Stepping up hepatitis B vaccination campaigns

MEDICINES IN DEVELOPMENT

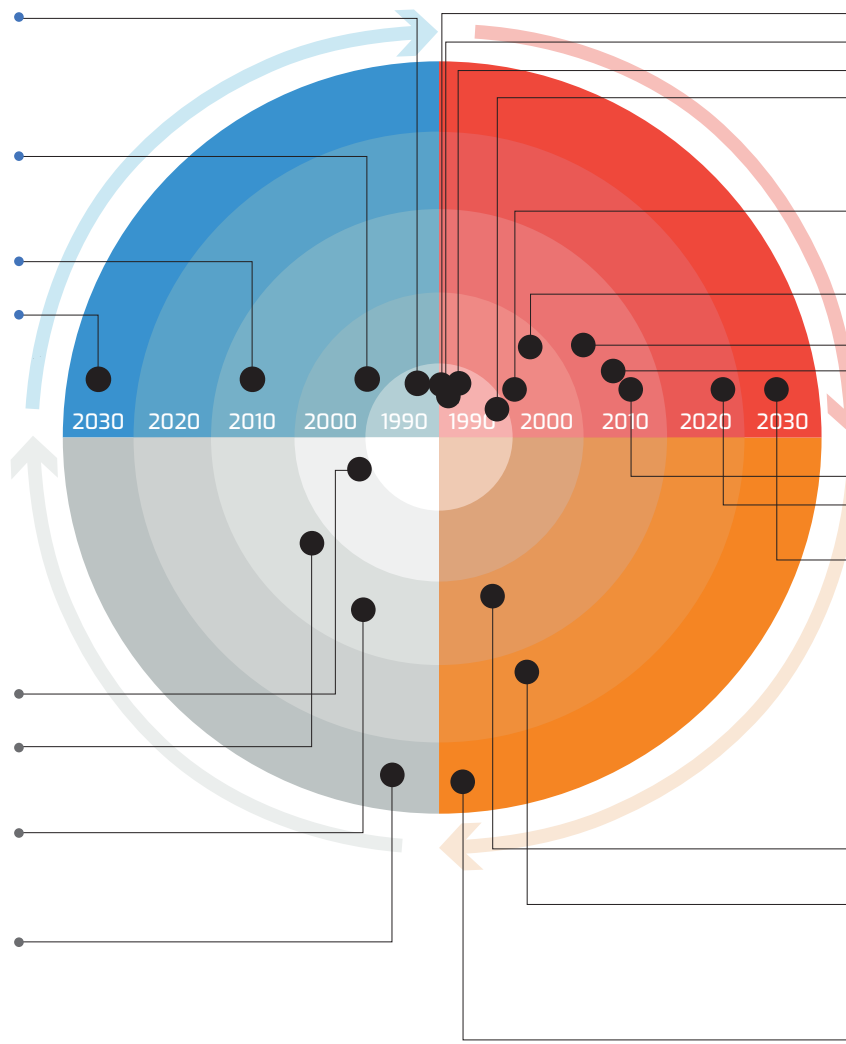**67** industry-sponsored[5] clinical trials were on-going in France in 2018

[1]Between 8% and 27% of people with fatty liver disease will go on to develop inflammation known as NASH (non-alcoholic steatohepatitis), "Nature Clinical Practice Endocrinology & Metabolism", Perlemutter et al., June 2007, vol 3, No. 6. / [2]ANRS figures, 2018 / [3]ANRS figures, 2018 / [4]World Health Organization (WHO) strategy in June 2016 / [5]Leem Innovation Database, April 2018.

DIAGNOSTICS

1989 - Discovery of hepatitis C virus
- Use of anti-mitochondrial antibodies to detect primary cholangitis

2001-2002 - First non-invasive screening tests for fibrosis using pulse elastography FibroScan®)

2015 - More than 3500 Fibroscan® machines worldwide

2030 - Use of microbiome to predict hepatic risk

TREATMENT

1968 - First liver transplant

1981 - Hepatitis B vaccine

1989 - Interferon for hepatitis C

1998 - Ribavirin and interferon combination therapy cures 40% of hepatitis infection, but at the cost of major adverse effects

2001 - New pegylated interferon administered by one injection once a week instead of three

2007 - Sorafenib: first targeted therapy used to treat liver cancer

2011 - New oral antiviral agents for hepatitis C that increase the likelihood of success with interferon therapy

2014 - The "sofosbuvir revolution" in the treatment of hepatitis C

2017 - 1374 liver transplants in France

2025 - First drug to treat NASH (nicknamed the "junk food disease")

2030 - Bioartificial liver
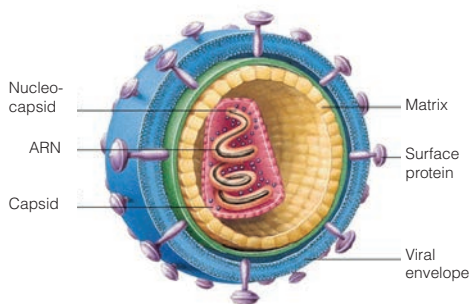- Artificial intelligence-assisted personalised medicine based on the metagenome

UNDERSTANDING

2000 - Link between steatosis and obesity

2010 - Identification of genes predisposing to liver fibrosis

2015 - Integration of gut microbiome into our understanding of the mechanisms of liver disease

2030 - Integration of the metagenome (our genome and that of our microorganisms) into our understanding of the mechanisms of liver disease

SUPPORT

2010 - Informing the public about hepatitis and how it is transmitted

2020 - Alerting the public to the increased incidence of NASH worldwide
- Learning to eat better through adapted coaching

2030 - Improving the quality of industrial food products

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

HIV-AIDS

WHAT ARE WE TALKING ABOUT?

HIV[1] (human immunodeficiency virus) is transmitted sexually, through the blood, and from mother to child. It targets T cells, cells essential to the proper functioning of the immune system. Those infected have weakened defences and develop serious diseases. AIDS is the most advanced stage of HIV infection.

Nucleo-capsid

ARN

Capsid

Matrix

Surface protein

Viral envelope

CHALLENGES

Stepping up basic research and applying new technologies to prevent and treat HIV

Improving the transfer of knowledge between HIV and its co-infections (TB, viral hepatitis, malaria)

Developing an effective prevention policy

Developing drugs with few side effects and few metabolic comorbidities

PREVALENCE

36.9 million[2]
people live with HIV worldwide, including 1.8 million children in 2017

21.7 million[2]
patients are on triple therapy in 2017

172,700[3]
people are HIV carriers in France

6,000[3]
new contaminations are reported each year

24,000[3]
people are HIV positive but do not know it

MAIN DRIVERS

Maintaining the smooth flow of translational research

Promoting access to medicines and self-testing

Relying on patient associations

Administering treatments as early as possible

IN 2030?

Control of the epidemic with antiretrovirals
90-90-90: an ambitious goal for 2020
90% of people living with HIV know their HIV status
90% of infected people are treated
90% of people receiving antiretroviral therapy have a permanently suppressed viral load
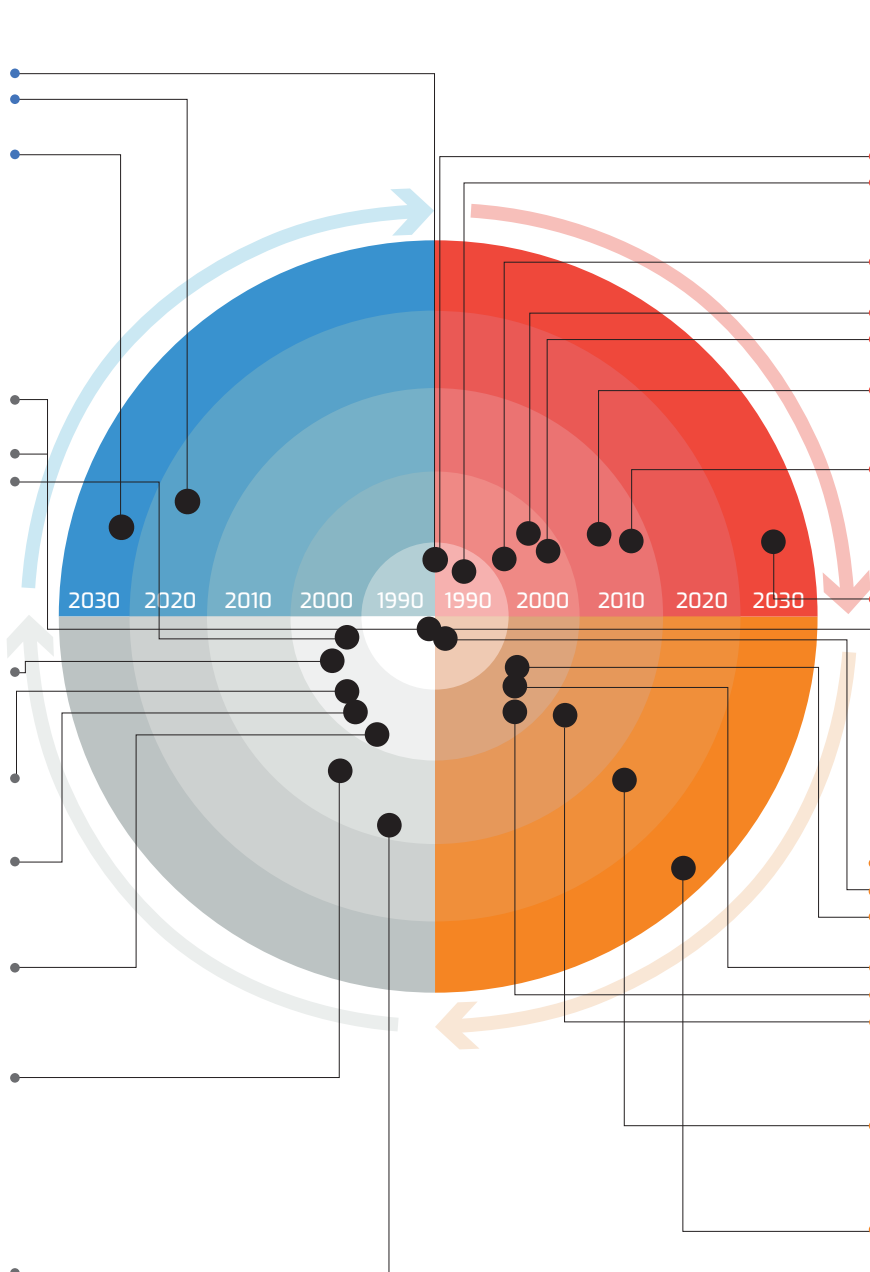**An HIV vaccine**

MEDICINES IN DEVELOPMENT

42 industry-sponsored[4] clinical trials were on-going in France in 2018

DIAGNOSTICS

1981 - First cases
2020 - Widespread use of self-testing
2030 - Viral load detection tests for all children exposed to the virus in the countries that are most affected, in their first two months of life

UNDERSTANDING

1983 - 1983 - Discovery of the HIV virus
1985 - Sequencing of the virus
2003 - Role of the protein APOBEC 36, an immune response activator
- Role of the antagonists of viral restriction factor Tetherin which inhibits the release of viral particles
2005 - Identification of HIV controllers (who spontaneously control the infection with a very effective immune response)
2006 - Link between microbial translocation and immune hyperactivation
2007 - The "Berlin patient", an HIV-positive man with leukaemia cures not only his cancer but also his HIV infection
2008 - Nobel Prize to Luc Montagnier and Françoise Barré-Sinoussi for the discovery of the HIV virus
2014 - Advances in understanding spontaneous Resistance
- Ipergay (on-demand HIV pre-exposure prophylaxis) and Proud (effectiveness of antiretroviral prophylaxis) trials
2018 - Understanding the role and nature of the CCR5 molecule expressed on the surface of immune cells to explain a person's susceptibility to HIV infection

TREATMENT

To date, there is no treatment that can completely eliminate HIV from the body

1986 - AZT, the first antiretroviral agent
1996 - Start of triple therapy with nearly 15 medication sessions at fixed times, night and day
2000 - First generics (2001) - First fusion inhibitor (2003)
2008 - First CCR5 inhibitor
2009 - Clinical trial of the RV144 vaccine candidate
2015 - Temprano and Start trials
- Administration of treatments as soon as possible after infection
2018 - Many vaccines in development
- New once-daily combination (new integrase inhibitor and reverse transcriptase inhibitor)
2030 - HIV vaccine
- Two new very long-acting treatments
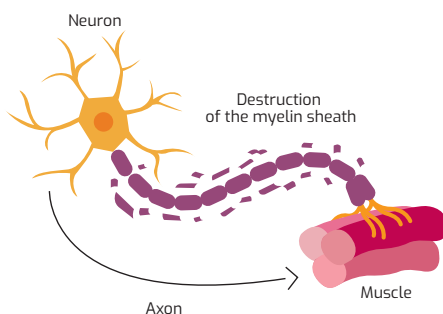- Use of anticancer drugs to eradicate the virus in the reservoir cells

SUPPORT

1984 - Founding of Aides
1989 - Founding of Act-Up Paris
2004 - Together against AIDS becomes Sidaction
2005 - Levying of a tax on airline tickets
2006 - Founding of Unitaid
2012 - First-time participation by France in the International AIDS Candlelight Memorial (campaign led by a coalition 1,200 organisations in 115 countries)
2020 - UN-led Prevention Roadmap focusing on adolescent girls, young women and high-risk populations
2030 Agenda for Sustainable Development: UN strategy for an integrated approach to ending HIV through its links to other key areas such as malaria, tuberculosis, access to medicines and the growing threat of antimicrobial resistance

2030 2020 2010 2000 1990 | 1990 2000 2010 2020 2030

MULTIPLE SCLEROSIS

WHAT ARE WE TALKING ABOUT?

Multiple sclerosis (MS) is an autoimmune disease in which a person's immune defences turn against the central nervous system (brain and spinal cord) and attack the myelin sheath as well as the axon (a projection of a neuron that makes connections with other neurons possible). Myelin and axonal destruction through repeated attacks disrupts the transmission of nerve impulses, which can lead to reduced visual acuity, motor impairments and/or altered sensations (tingling).

Neuron

Destruction of the myelin sheath

Axon

Muscle

CHALLENGES

Better understanding of the early stages of multiple sclerosis

Reforming the myelin sheath and restoring electrical conduction of the neurons

Protecting the axons (neuroprotection)

Modifying progression by treating the subclinical forms (radiologically isolated syndrome)

MAIN DRIVERS

Immunotherapy: lymphocytes play a major role in the demyelination process

Advanced molecular imaging to visualise impairment of neural energy supply

Artificial Intelligence (algorithm to monitor disease progression and drug effects)

Development of molecules to treat the progressive phase of the disease. Two pathways:
- removing the inflammatory component very early on
- promoting remyelination and neuroprotection

PREVALENCE [1]

100,000 sufferers in France in 2017

3 out of 4 are women

400,000 sufferers in Europe in 2017

4,000 new cases each year in France

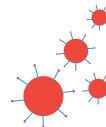**2.3 million** sufferers worldwide in 2017

IN 2030?

MS identity will be broken down into different, more homogeneous diseases.
Diagnosis and monitoring of the disease will be improved through advances in MRI and the advent of reliable blood biomarkers.
It is not inconceivable that imaging techniques (PET scans) will be used routinely for treatment. It will be possible to modify or stop severe disease progression and effectively repair the damage.

MEDICINES IN DEVELOPMENT [2]

32 clinical trials ongoing in 2017

DIAGNOSTICS

1986 - Introduction of MRI,
an invaluable tool
in the diagnosis of MS
- Demonstration of spontaneous
remyelination capacity
2000 - Establishment of MRI-based
diagnostic criteria
2010 - Detection of plaques in the
cerebral cortex
2020 - Successful use
of new imaging tools
(high-field MRI, unconventional MRI,
PET scan, MEG, etc.)
to monitor MS progression
2030 - New tools for biological and
radiological prognosis

TREATMENT

1995 - First interferons 2000
- First monoclonal antibody:
copolymer
2005 - First beta interferons
2010 - First new treatments focusing on
inflammation (attacks):
- Fingolimod (2012)
- Alemtuzumab (2013)
- Dimethyl fumarate (2015)
- Teriflunomide (2015)
- Ocrelizumab (2018)
2020 - Mavenclad, Qizenday
(2018-2020)
2030 - Disease progression can
be modified or halted
by more precise and
personalised treatments.

2030 2020 2010 2000 1990 1990 2000 2010 2020 2030

UNDERSTANDING

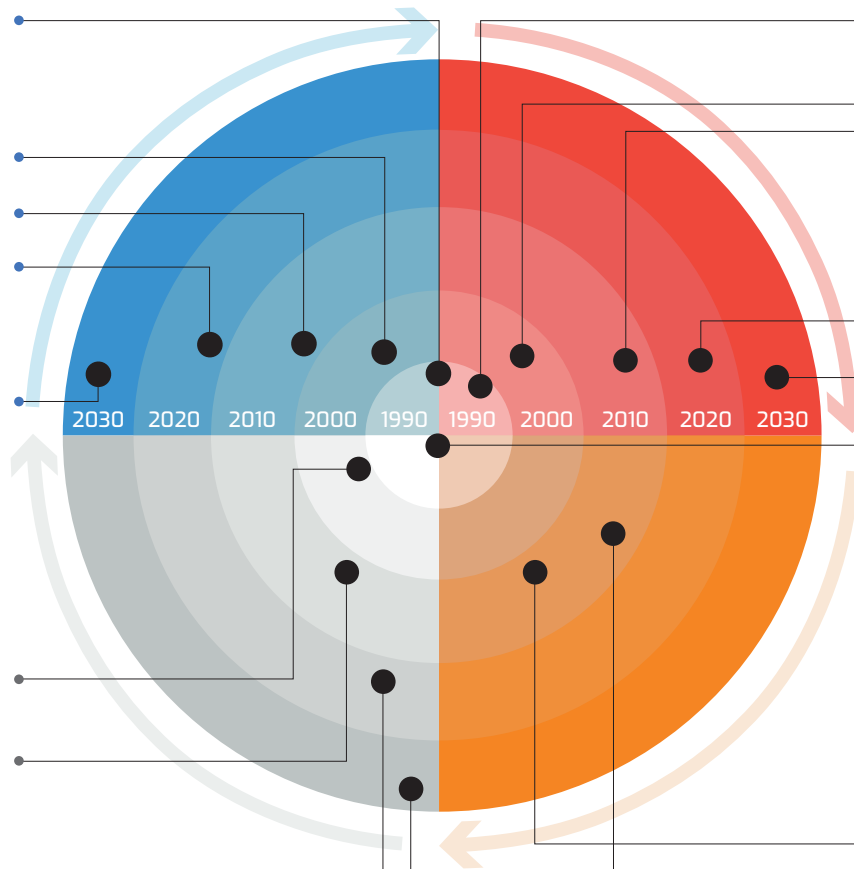**2000** - Understanding
the role of different lymphocyte
subpopulations
2010 - Demonstrating new
susceptibility genes
- Identifying a specific marker for
Devic's disease
- First subtyping of MS
2020 - Removal of the
inflammatory component to reduce
disability in the medium term
2030 - Identification of different
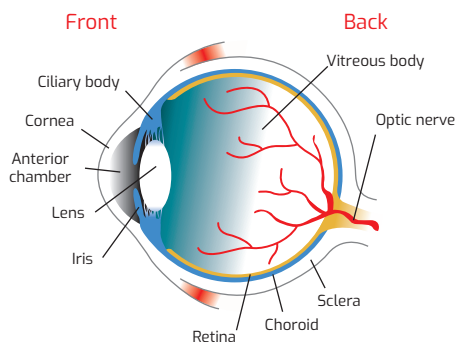diseases within the spectrum of MS

SUPPORT

1960 - Formation
of patient associations
- Establishment of MS networks,
bringing together neurologists,
rehabilitation doctors, nurses,
physiotherapists, etc.
2010 - Introduction of therapeutic
education programmes
2014-2019 - French National
Neurodegenerative Diseases Plan
- Creation and endorsement of
23 Multiple Sclerosis Skills
and Resources Centres
(CRC-SEP)

VISION DISORDERS

WHAT ARE WE TALKING ABOUT?

Vision disorders affect visual perception: visual acuity, visual field, colour perception and contrasts. A distinction is made between diseases of the anterior part of the eye - opacification of the lens (cataract) and damage to the ocular surface - diseases of the posterior part of the eye, i.e. damage to the retina (AMD, retinitis pigmentosa, diabetic retinopathy, retinoblastoma, etc.) and diseases of the optic nerve (genetic defects, toxicity and especially glaucoma).

Front

Back

Ciliary body
Cornea
Anterior chamber
Lens
Iris
Retina
Choroid
Sclera
Optic nerve
Vitreous body

CHALLENGES

Diagnosing and treating early vision disorders

Ensuring access to care for those who need it

Using artificial intelligence (especially in diabetic retinopathy)

Circumventing rejection phenomena (cell therapies)

PREVALENCE [1]

1.5 million French people suffer from visual impairment, of whom 235,000 are blind and 1,265,000 visually impaired in 2017

81% of moderately to severely blind or visually impaired people around the world are 50 years of age or older

253 million people worldwide are visually impaired, of whom 36 million are blind and 217 million have moderate to severe visual impairment in 2017

80% of all visual impairments are preventable or curable

MAIN DRIVERS

Combining very-high-resolution morphological imaging and functional imaging

Developing therapeutic solutions adapted to the needs of patients

Modelling the mechanisms, balances and plasticity involved in vision disorders

Implementing virtual clinical trials

IN 2030?

The number of visually impaired is expected to double by 2030 and triple by 2050. Blindness, poor vision and severe myopia will become, along with Alzheimer's disease, the scourges of old age. AMD is the leading cause of blindness in the elderly and unoperated cataracts in developing countries.
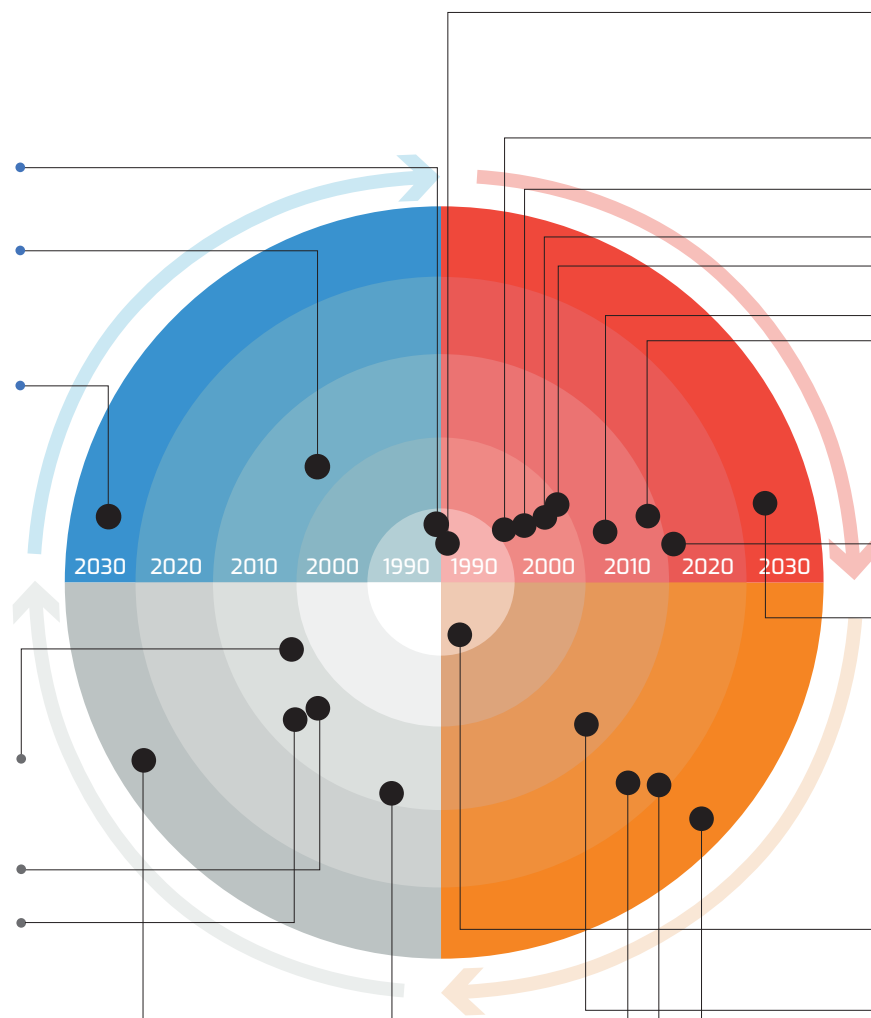
MEDICINES IN DEVELOPMENT

163 industry-sponsored[2] clinical trials were ongoing in France in 2018

[1]*Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis",* Rupert R A Bourne, Seth R Flaxman, Tasanee Braithwaite, Maria V Cicinelli, Aditi Das, Jost B Jonas, Jill Keeffe, John H Kempen, Janet Leasher, Hans Limburg, Kovin Naidoo, Konrad Pesudovs, Serge Resnikoff, Alex Silvester, Gretchen A Stevens, Nina Tahhan, Tien Y Wong, Hugh R Taylor, Santé 2030 on behalf of the Vision Loss Expert Group / [2]Leem Innovation Database, April 2018.

TREATMENT

1978 - Cataracts become easily treatable
- Glaucoma is often controllable by beta-blockers instilled with eye drops
2000 - Prostaglandins for glaucoma
2001 - Micronutrients for the prevention of AMD
2006 - Anti-VEGF agents (AMD)
2007-2008 - Gene therapies (Retinitis Pigmentosa)
2010 - Artificial retina
2018 - First successful retinal cell transplant in humans
- Experimental breakthrough in glaucoma treatment: insulin delivered via eye drops restores communication between neurons and retinal function
2020 - Prospects of cell therapy for patients with retinal dystrophy and dry AMD
2030 - Therapy will be biomolecular and targeted (neuroprotection in tissues, morphofunctional repair of tissues after implants, cell or gene therapies

DIAGNOSTICS

1995 - Revolution in imaging by providing an in-depth view of the retina and the optic nerve
2010 - Imaging of the ocular surface reaches the cellular level, while that of the retina and the optic nerve is on the way to reaching the same resolution
2030 - Vision disorders will be diagnosed at an early stage for everyone. Prevention will combine screening and therapy (diabetes control, systematic control of intraocular pressure, control of environmental and food toxins)

2030 2020 2010 2000 1990   1990 2000 2010 2020 2030

UNDERSTANDING

2010 - Use of the eye, a closed organ with specific properties, as a model for new therapeutic pathways
2014 - Development of optogenetics
2016 - An understanding of vision, combined with microsurgery, and of microelectronics leads to the development of wireless retinal implants
2018 - First gene therapy trial in mice (retinitis pigmentosa)
2030 - Research will have strengthened three key therapeutic pathways:
- discovery and validation of therapeutic markers
- discovery and validation of therapeutic targets
- understanding and modelling of the mechanisms, balances and plasticity of vision

SUPPORT

1999 - Launch by the World Health Organization (WHO) of the Vision 2020 initiative
2008 - Founding of the Vision Institute
2017 - Establishment of an AMD register by 210 hospitals
2019 - Publication of the WHO World Report on Vision
2030 - The maturation of disability technologies will break down barriers between people with visual impairment (sensory substitution, environmental adaptations, home automation, etc.)

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