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THE MEDICINE

OF THE FUTURE

CONTEXT – TECHNOLOGIES – SCOPE OF APPLICATIONS – OUTLOOK

# Innovation and the Health System

By Ms Agnès Buzyn,  
French Minister for Solidarity and Health



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“By making innovation work for the patients, the medicine of the future carries the seeds of progress: That of creating a fairer and more efficient health system.”

**D**igital technologies, which have already profoundly transformed our daily lives, are today opening the door to a new form of medicine. Medicine tomorrow will no longer resemble what we have always known: It will be more preventive, more personalised, buoyed by innovations in fields as diverse as processing, analysing and storing health data, artificial intelligence and machine learning, connected objects, robotics, virtual reality and so on.

This transformation represents a wonderful opportunity for our health system. By encouraging the emergence of precision medicine, the service provided to the patients will be improved. The use of these exceptional tools, whose potential is enhanced by advances in genomic medicine, offers hope for healing, for preserving and improving our health and our quality of life. Our health system will thus eventually focus more on prevention, patient history – from the medical to the medico-social – and on the quality of care, by opting for a holistic approach to health. The hospital will once again concentrate on high value-added activities, with sophisticated technical units and better coordinated urban health care to take account of the specific needs of each individual.

So that this transformation is of benefit to everyone, throughout the country, these tools must be made accessible and an appropriate ethical framework must be

defined for their applications. This is also a very real economic challenge, given the high cost of individualised diagnostic and care, in a context of increasing chronic illnesses and an ageing population, at a time when the sustainability of our French model of solidarity-based health care is being regularly called into question.

Finally, it is an organisational challenge: Changing practices (greater emphasis on outpatient care, coordinated exercise of primary health care, sharing of information between all healthcare and medico-social stakeholders, etc.) will require a fresh and in-depth look at the organisation of our health care system, its financing and the training of health care professionals.

To meet these challenges and faced with the American and Chinese players who are already extremely active in the digital and artificial intelligence fields, France has a number of key advantages, not only through its tradition of excellence in research – both fundamental and applied – and in medicine, but also thanks to its top-tier industrial health firms as well as those in materials, computing and data processing. The success of French digital start-ups in this field gives our country a competitive edge.

By making innovation work for the patients, the medicine of the future carries the seeds of progress: That of creating a fairer and more efficient health system. ■

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## OUTLOOK & AFTERWORD



# Do Advances in Biotechnologies Always Mean Progress for the Patients?

## An Ethical Question



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**BY PROF. JEAN-FRANÇOIS DELFRAISSY,**  
Chairman of the National Consultative Committee on ethics for the life and health sciences (CCNE)

The question may appear to be surprising when one looks at the immense progress achieved by medicine over the past 20 years and at what is promised by the “medicine of the future”, notably the potential of digital & health. However, this is one of the questions that arose from the Bioethics Conference held by the National Consultative Committee on Ethics (CCNE).

### The Bioethics Conference

This Conference was held in the first half of 2018 and all the work, arguments and opinions were summarised in a report [1] published in June 2018.

The CCNE then proposed issuing an opinion on all the topics which had been debated.

Opinion 129 [2] and the reflections it contains, is above all an orientation guide for the context, points of reference, main subjects and future prospects. It is intended both for civil society, which was extensively engaged in the public debate, but also the public stakeholders who are preparing to build, propose and then vote on the new Bioethics Act 2018-2019.

One key question arises from everything that was heard during the conference: That of the place of the citizens in the health care system and the medical assistance they will receive. How

does one manage uncertainty and risk in medicine? What are the consequences of the growing lack of patient trust in the health care personnel? What bioethical training and information should be given to the citizens, the health care personnel and how should this be done? How to conceive of and ensure access to health care for all in a context of growing health system costs?

If the Conference revealed a common core of fundamental values shared by the participants, sometimes contradictory principles came to light, of two distinct orders: The individual and the collective. This duality between what is personal/intimate and what is public/political is one of the major areas for reflection in terms of bioethics. The CCNE is aware that the indisputable reality of this tension requires that the public debate be continued, with the implementation of a policy of information and education concerning all the issues raised by changes in science, technology and how humans perceive the singular identity of their species.

## Changes since the 2011 Act

### Scientific and Technological Innovations in the Field of the Life Sciences

Without being exhaustive, some fields and orientations in which major scientific events have occurred could be mentioned:

- innovation has reached significant milestones in recent years, for example in techniques for analysis and targeted modification of the genome, but also the epigenome, medical imaging, developments in digital technologies which are spreading ever faster into all health sectors;
- our understanding of the complexity of living beings is constantly increasing thanks to the considerable growth in analysis capabilities and changes in the experimental approach (interdisciplinarity, biology of systems);
- there are new therapeutic possibilities for certain diseases (for example in oncology, with personalised therapies, regenerative medicine, artificial devices) while for others there is still no solution (neurodegenerative and chronic diseases);
- these advances come at a time of globalisation, with a context that is being turned on its head by environmental issues (concept of “one health”);
- there is a lack of information and a mistrust of science and medicine on the part of society.

### Changes to the Health System

If changes to the health system represent progress, they also create new areas of fragility at the same time: An increasing trend towards prevention; equal access by all to diagnostic tools and to innovative treatment molecules, which represent a major ethical challenge.

Chronic diseases are frequent (20% of the French population) and constitute a new paradigm for our health system. The arrival, alongside “curative” medicine, of preventive medicine for which we are as yet unaware of the real impact, means that medicine is increasingly focused on anticipating. The medical field (organisation of care, drugs, medical devices, etc.) is also increasingly becoming a major economic issue. These changes are destabilising the health care system and accentuating inequalities.

### The Emergence of New Vulnerabilities Raises Ethical Questions

Even if progress in knowledge and its application to health care collectively represents a step forward towards improved health, it also generates new risks and individual situations of great vulnerability. One of its characteristics is the situation of tension created between the collective interest (public health, economy) and that of the individual (individual autonomy and well-being).

In the face of all these transformations, it is hardly surprising that one of the new aspects that have appeared since 2011 is the intensification of the societal debate, precisely around bioethical issues. What is at stake is a change in the representations of the human being, triggering a fierce debate, to the extent that the organisation of a major conference to debate controlled legislative changes in order to address this on the basis of clear and robust bioethical principles, would seem to be useful, even essential.

### Ethical Reflections: Reference Points, Balance, Applications

Scientific advances are major sources of progress in the field of health but, at the same time, there is a gap between what is technically possible and what is ethically desirable – a gap which underpins the legitimacy of ethical reflection, taking account of what can be expected from the impact of today’s scientific and technological applications on the future of humanity. Not all technical advances can be considered to be progress: Some of them can actually contribute to degrading the quality of life and the health of a part of humanity, sometimes with dramatic consequences. Just because something is possible does not mean that it is always justified.

To shed light on the questions of biomedical research and innovation, we have points of reference which must serve as unwavering principles. They may contradict each other and demand that a balance be found: They will then be able to help us on the various subjects to which they should be applied. For example, the principle of respect for the dignity of the human individual, which can lead to differing general definitions, is nonetheless an ethical and legal requirement measured by how the material life of the individual conforms to their status as a human being. It requires that the person is never considered simply as a means, but always as an end, that they never be instrumentalised.

“The arrival, alongside “curative” medicine, of preventive medicine for which we are as yet unaware of the real impact, means that medicine is increasingly focused on anticipating.”



“The tension between the individual and the collective, between the most subjective and the most general, is a core issue and one that makes it complex to talk of principles alone.”

Does not the ethical approach also help consolidate the notion of free and informed choice and consent ensuring that the person is able to take decisions concerning their health, with the support of the physician, thus reinforcing their autonomy? Moreover, what happens to the affirmation of the rights of the person and their loved ones, their autonomy, their freedom, the right to know or not know, to the acceptance of and respect for differences or even the affirmation of their identity, when the very notion of a “person” is no longer limited to their body, but takes multiple forms in the digital health data concerning them and which are exchanged, stored, traded and are, more generally, beyond their control?

It should also be pointed out that one of the ethical reference points - that of individual liberty, is often subjected to extreme tension when seen from the collective viewpoint. The tension between the individual and the collective, between the most subjective and the most general, is a core issue and one that makes it complex to talk of principles alone.

The question of individual autonomy is not therefore an end in itself. It has to be supplemented by principles of solidarity and responsibility, failing which one could see the emergence of contradictory autonomy needs or even a misguided concept of autonomy, in conflict with the protection of the general interest.

Finally, scientific and technical advances require that we take a fresh look at the definition and purpose of medicine, more specifically introducing the notions of predictive medicine and personalised medicine. At the same time, French medicine and the health system are faced with challenges that must be addressed: Improving prevention, preserving the financing of health care by the social security system, reducing regional inequalities. Moreover, the risk of a loss of expertise by the physician, the transition to medicine focused on technology and sometimes forgetting the relational aspects, the very definition of health care, are creating upheavals in the practices

and traditional roles of medicine, which is also called on to deal with all forms of suffering.

Many questions are thus left unanswered: Can we claim that scientific and technical discoveries always lead to medical progress? How do we today even define the notion of progress, of benefit for the patient? How can the patients themselves take part in and be a real player in this process of reflection, given the major issues for democratic health? How far must medicine go for a particular individual and for the collective whole? Is the individual benefit of the patient always compatible with the general interest, in other words that of the greatest number? How should one imagine access to costly care and techniques at a time of increasingly tight budgets? What criteria should determine the allocation of scarce resources?

All these questions go beyond the very notion of the medical purpose, that of the definition of “good”. To define what could be the “good” of the patient may be particularly complex given that various viewpoints must be taken into account: That of the patient him or herself, with regard to what they consider to be their “well-being”, but also that of the medical concept of well-being or a more collective idea of what the benefit of a medical procedure could be and which can vary widely (healing a disease, relieving a symptom, effectiveness of the medical technique for example).

The bioethics conference was an ideal opportunity for collective deliberation, in other words an opportunity for wide-ranging, open questioning, for calm reflection and discussion about the end-purpose of research and the human consequences of biomedical practices. Is it not this collective and transparent deliberation that will demonstrate our responsibility and our ability to ensure the survival of democracy?

The 2018-2019 Bioethics Act should take account of all these aspects to ensure legislation that is transparent and trusted. ■



[1] (In French) <https://etatsgenerauxdelabioethique.fr/blog/le-rapport-des-etats-generaux-de-la-bioethique-2018-est-en-ligne>

[2] (In French) Opinion 129 is available on the CCNE website: [www.ccne-ethique.fr](http://www.ccne-ethique.fr)



# What Will the **Medicine** of Tomorrow Look Like...

The medicine of the future means introducing disruptive technologies for precise, preventive, predictive, participative and reactive practice, guaranteeing respect for the individual and constituting a source of economic growth.

**W**estern medicine, which is based on evidence, is a rational art arising from an understanding of the causes and mechanisms of diseases. France stands out with a health system of a high technological level that is accessible to all, underpinned by a principle of solidarity and fairness. It sometimes comes up against a constrained economic model and difficulties due to partitioning between medical specialisations and insufficient links between hospitals, ambulatory care and social players. It is only recently that patient care has tended to move away from frameworks based on average data, paying no heed to the specific nature of each individual, towards precision medicine which is the new health care paradigm. Today's medicine probably pays too little attention to prevention, not as a political will, but through the difficulty experienced in convincing the citizens. We could hope that the medicine of the future, in France and elsewhere, could become more predictive, preventive, participative and precise. The overhaul of the health care system organisation will help break down barriers and more clearly specify the place of the real and virtual players around the patient, with the goal of achieving democratic health care and ethical issues (see p. 4).

## Exploring the Genome, the Metagenomes and the Exposome for Precise, Predictive and Preventive Medicine

The genome, **metagenomes** and **exposome** make us what we are and to a large extent determine the prevalence and particularities of disease in each of us.

The crucial place of the genome and its **epigenomes** in the development and definition of the individual was experimentally validated a long time ago. However, it is only in the last few decades that these data have invaded health research and medical practice. From key areas such as bone marrow and organ transplants, rare diseases with single-gene transmission and cancers, the researchers have turned their focus on other frequent multifactorial diseases. The weight of genes in prevalence and clinical forms of diseases is beginning to be established, against the backdrop of the complexity arising from genetic variations between populations. This field of research has been radically altered by technological developments and the falling cost of

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### Metagenome

All the genomes of the bacterial populations of a given environment. The method used to analyse it – metagenomics – consists in collectively studying the genes, without detailing them individual by individual.

### Exposome

Concept corresponding to all exposures of a human organism to environmental (that is non-genetic) factors, from conception to end of life, supplementing the effect of the genome.

### Epigenome

Additional information "layer" which defines how the genes contained in a cell will be used by it, or not, according to the information it receives from the environment in the broad sense.

sequencing, placing the clinical use of genomic approaches within the grasp of the physician and facilitating the interpretation of related approaches – transcriptomics, proteomics, metabolomics (see p. 12). Avoiding the diagnostic uncertainty affecting families suffering from genetic diseases, adapting cancer treatment on the basis of the genome of the individual and of the tumour, better understanding and perhaps predicting and preventing frequent multifactorial diseases, this is the roadmap that France has set out in the France Genomic Medicine Plan 2025 (PFMG) [1].

Only recently, researchers and physicians returned to the notion that man and the other living beings are symbiotic creatures. It would be an artificial construct to consider humans independently of the micro-organisms that inhabit their intestines, skin and mucous membranes. These micro-organisms exchange signals with our organism and play a decisive role in numerous diseases such as obesity or certain neurological or psychiatric diseases. These germs can also be critical to the effectiveness of therapies, such as cancer immunotherapy. Evaluating the diversity of our flora through “omic” approaches could be a useful supplement to the tools of the PFMG in the future.

Even if genomics define what is possible for each individual from conception onwards, what we become at every stage in our life is to a large extent determined by our exposure to the outside world, by our lifestyle and social influences, our working environment and, more generally, our environment as a whole, which – since the industrial period – has been extensively influenced by man. The body is shaped by food (by extension this can be considered as exposure). It is altered by exposure to toxic substances or by an encounter with infectious agents or their carriers. In this context, it is clear that human health cannot be isolated from a more global health, which includes all living beings (One Health).

Collecting and integrating these data into clinical aspects and the quantitative data obtained in particular from imaging is a major challenge for the precision medicine of the future. This can only be achieved by developing a specialised industrial sector and medical devices to investigate the genome, epigenome and exposome, a sector in which the centre for reference, innovation, appraisal and transfer (CREFIX) of the PFMG should be a first building block and a major coordinator (see p. 12).

**Transcriptomics**

Study of all the messenger RNA produced during the genome transcription process with a view to the production of proteins. By systematic quantification of these mRNA, an indication of the level of transcription of the various genes in given conditions is obtained.

**Proteomics**

Study of all the proteins (proteome) of a cell, organelle, tissue, organ or organism, at a given moment and in given conditions.

**Metabolomics**

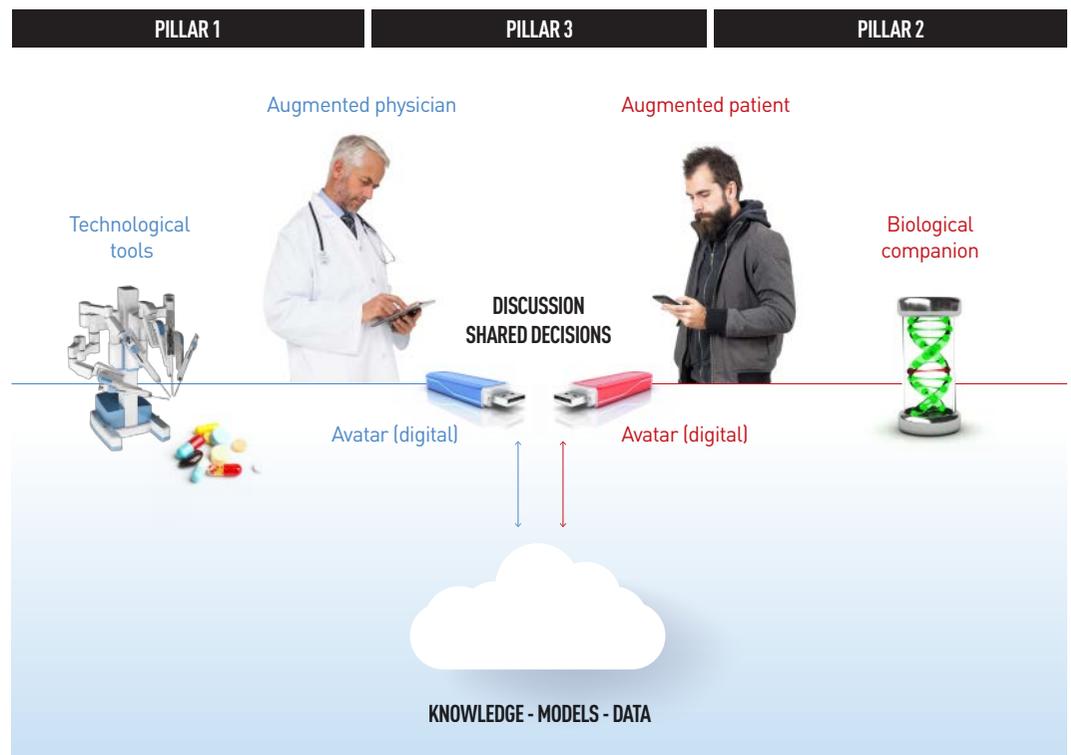
Study of all the primary metabolites (sugars, amino acids, fatty acids, etc.) present in a cell, an organ or an organism. This is the equivalent of genomics for DNA.

**Flora**

All the micro-organisms (bacteria, viruses, parasites, non-pathogenic fungi) which live in a specific environment (called the microbiome). In the human organism, there are various flora, for example on the skin, in the mouth or in the intestine.

Fig. 1

# The Medicine of the Future





## Placing the Patient, the Physician and their Avatars in a Clinical Situation for Participative Digital Medicine Adhering to the Principles of Transparency and Fairness

There are many possible organisational solutions for individual medicine, up to and including the disappearance of health professionals, replacing them by algorithms and diagnostic and treatment devices supplied by industrial companies from a worldwide catalogue. Although less ambitious, but certainly more equitable, the scenario I suggest maintains the relationship between patient and physician, both sentient beings, while incorporating technological companions to optimise the joint approach (Fig. 1).

In this model, the patient is associated with a digital representation, or digital twin, and a biological companion grouping together all the personalised resources extracted from or built up from his or her body. For their part, the physicians are aided by the digital representation of their knowledge and decision-making rules (digital physician). They are also associated with diagnostic sensors and tools, which construct the digital patient by converting the biological, imaging or clinical data into digital files. The physician has a number of conventional approaches for intervening on the patient (drugs, surgical procedures, physical agents, re-education, psychotherapy), enhanced by emerging technologies, such as those derived from biotechnologies (gene and cellular therapies). The digital physician and digital patient interacting with the knowledge space optimise the decision-making shared by the patient and the physician who, unencumbered by the technical details, should have the time needed to find a common language in a context of mediation, transparency and equity.

## Together with Industry, Building the Three Technological Pillars of the Medicine of the Future for Integrated Medicine Generating Economic Growth

The medicine of the future will be significantly affected by three technological pillars, major sources of economic R&D (see p. 29). The first pillar is that of the multidisciplinary approaches to the development of medical devices for diagnostic, therapeutic or combined purposes. They will benefit from chemistry, synthetic biology, various forms of physics, including electronics and materials science, robotics, nanotechnologies and information sciences. The second pillar is that of the biological companion, grouping all personalised biotechnological developments constructed from elements of the patient's body, such as the development of organs on chips, or the genetic modification of cells for precision medicine purposes. Finally, the last pillar is digital, integrating the medicine of the future and building a health system endowed with self-learning.

### Hybrid Nano-objects, "Living-electronic" Interfaces and Robotics

Nanotechnologies already play an important role in medicine. In the field of diagnostics, they are crucial to increasing the sensitivity of in-vivo imaging, the ultimate goal of which (notably for magnetic resonance imaging) is cell scale visualisation. In therapeutics, nano-objects are used to deliver active ingredients, or boost the effectiveness of radiotherapy, for which the procedures are changing with advances in technology and in radiobiology. The possibility of combining devices from synthetic biology and electronics within the same object could open the door to multi-function communicating objects that are both biological and physical data sensors and therapeutic tools delivering active



“Only recently, researchers and physicians returned to the notion that man and the other living beings are symbiotic creatures.”



“Progress in biotechnologies and in particular in 3D bio-printing is opening the door to the reconstruction of tissues and organs able to retain the biological functions. It also allows the reconstruction of malignant tumours the same as those of the patient.”

[1] [https://solidarites-sante.gouv.fr/IMG/pdf/genomic\\_medicine\\_france\\_2025.pdf](https://solidarites-sante.gouv.fr/IMG/pdf/genomic_medicine_france_2025.pdf)

[2] (In French) <https://dg.dk/wp-content/uploads/2017/04/M%C3%A9decine-du-Futur.pdf>

ingredients in a controlled manner (see p. 35). In this context, the development of biocompatible and, as applicable, biodegradable electronics, will be a key step. The ageing of the population is increasing the number of patients suffering from degenerative diseases, for which the therapies offer relatively little effectiveness. These diseases lead to major handicaps. Over and above providing replacement organs, such as the artificial retina (see p. 25), or exoskeletons (see p. 15), medicine should increase the well-being of disabled persons in their usual environment. The design of robots to assist them in their daily lives will be crucial in this respect. Apart from technological developments, building these robots will require significant artificial intelligence algorithm developments participating in the creation of a personalised, intelligent and connected living space. Remote-controllable robots will increasingly help surgeons in less and less invasive procedures, benefiting from an augmented vision of the operating area and personalised pre-operational simulation based on the patient’s imaging data.

#### **Patient’s Biological Companion and Reconstruction of Tissues and Organs**

The considerable progress in stem cell research means that practically all types of cells making up the organism can be obtained ex or in vitro and be modified, if necessary, by editing their genome. Progress in biotechnologies and in particular in 3D bio-printing is opening the door to the reconstruction of tissues and organs able to retain the biological functions. It also allows the reconstruction of malignant tumours the same as those of the patient. At an individual level, these biological companions can be used to optimise the personalised treatments through ex-vivo study of the effects of therapies, with the data obtained enhancing the patient’s avatar (see p. 32). The reconstituted organs could also be reimplanted in the donor patient with no immune rejection, reducing the need to take organs from the deceased. Creating collections of a large number of biological companions annotated with the individual’s genome sequences will allow simulation of ex-vivo therapeutic trials and thus reduce the risks of toxicity and ineffectiveness.

#### **Digital Medicine, Integrating the Medicine of the Future**

The possibility of converting practically all medical

data (clinical, genomic, imaging, functional exploratory, for example) into digital data readable by a computer (the digital patient) opens the door to a new medicine based on these data (see p. 29). In this context, the physician-patient relationship is an interface between the real world and a virtual world in which three partners interact: Scientific knowledge and data, the digital representation of the patient (digital patient or digital twin) and the artificial intelligence algorithms (or digital physician). These latter interpret the digital patient and provide assistance with making medical decisions by proposing precise diagnostic and therapeutic recommendations. The physician becomes a critical mediator of information and guarantees the human character of this new medicine.

The inclusion of cohorts of digital patients in a data collector and analyser (such as the CAD in the PFMG) will make it possible to apply algorithms based on artificial intelligence, the science of data and the simulation of biological processes, which will guide the physician and the patient in defining optimum care and treatment. Everyone’s data will work for everyone else, contributing - through a system of collective appraisal and assessment - to personalised medicine that is less dependent on the experience of a single physician or a single medical team. Over and above treating diseases, this digital medicine will also apply to prediction and prevention, notably via connected objects creating an internet of health (see p. 38). It is probable that the question of the sequencing of the genome of all the individuals will one day arise, triggering ethical debates and requiring changes to legislation and regulations (see p. 4). The variability of genomes defines the populations and constitutes a true asset. Its analysis can help anticipate the individual and collective ability to react to the ambient environment. These data must therefore be conserved in a highly secure place, providing full guarantees against fraudulent or malicious use (see p. 41).

Imagining the innovations of the three pillars of the medicine of the future and taking them to the patient requires effective interaction between health care professionals, academic and industrial researchers and companies who can bring them to market. Organisational innovations are also needed. Proposals along these lines are given in the “Medicine of the future” report [2]. ■

# CHALLENGES FOR HEALTH

Building on its electronics and digital expertise and its life sciences skills, CEA is heavily engaged in addressing the major health challenges.

**Biomedical imaging**

**12**

**Neurosciences**

**15**

**Medical genetics**

**16**

**Infectiology**

**19**

**Gene therapy**

**22**

**Cancerology**

**23**

**Vision disorders**

**25**

**Metabolic diseases**

**27**

→  
**Fig. 1 : installation of Iseult, an 11.7 Tesla magnet, at NeuroSpin in Saclay, for a new imaging generation**



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•  
**BY**  
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# Redrawing the Landscape of Brain Pathologies Using Imaging?

“As well as fingerprints, cortical foldings are specific to each person. AI is near to decipher them, on the basis of millions of digital images produced by MRI. Occurring during the second half of pregnancy, this folding signs deleterious events at the root of developmental disorders.”



## To find out more

The CATI platform:  
<http://cati-neuroimaging.com>

Progress in cerebral imaging is revealing more and more information about pathophysiology. When applied to large populations, this new imaging could lead to a more detailed classification of cerebral pathologies, creating a new and personalised form of medicine for homogeneous patient groups.

**I**t is considered that one third of the population will one day be concerned by a brain-related pathology. Only a small part of these pathologies leads to satisfactory treatment. All too often, we do not know how to cure them and are unaware of their origin. To crown it all, two similar clinical pictures can have completely different causes: A large part of these pathologies are heterogeneous syndromes comprising several illnesses, which entails a significant degree of confusion in the therapeutic trials. In such a context, brain imaging is perceived as being one of the main hopes for improving our understanding of these pathologies, hence the massive CEA investments in this field. Imaging is often associated with genetics, but it could prove easier to use insofar as it reveals the state of the brain after the action of complex mechanisms governing gene expression (fig. 2).

The advances being seen today are partly due to changing imaging technologies and partly to the study of very large populations. CEA is particularly present in the field of innovative sensors, as it has decided to draw on the know-how of its physicists to design a new generation of MRI (fig. 1). Iseult, an 11.7 Tesla magnet currently being installed at NeuroSpin in Saclay, should for example give access to small brain structures which are currently inaccessible to conventional imagers: Increased resolution can reveal lesions in the subdivisions of the hippocampus specific to Alzheimer's disease; the rich iron content of the small neuron clusters involved in Parkinson's disease enables them to stand out in high magnetic field images. This exceptional imager will also be able to cause chemical species other than water protons to resonate with enough of a signal to generate clear resolution images. An ongoing project thus aims to

map lithium, one of the oldest neuroleptics, which is effective in treating bipolar disorders, but whose biological action is as yet little understood.

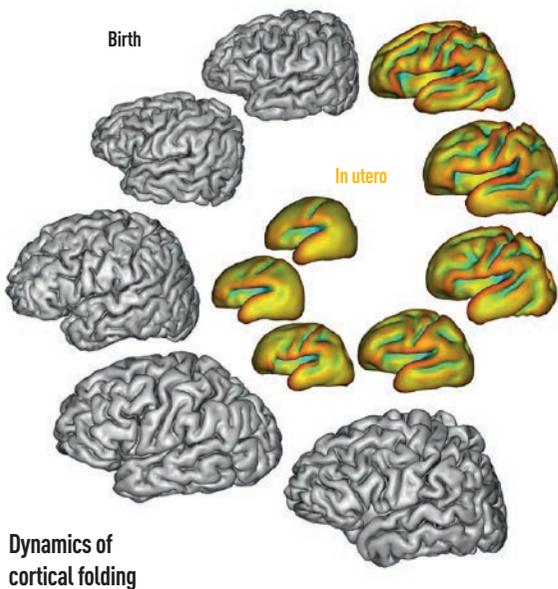
The imaging technologies specific to nuclear medicine are also a spearhead of CEA research (see p. 14). New labelled markers are regularly appearing and allow in vivo access to essential biological processes such as the deposition of amyloid plaques specific to Alzheimer's disease. The new PET ligands targeting the different configurations of the Tau protein are for their part in the process of revolutionising the differential diagnosis of several forms of dementia, which lead to highly distinct types of binding in the brain. The new and highly promising PET-MRI imager installed in the Frédéric Joliot hospital (SHFJ) in Orsay enables these two technologies to be used simultaneously. A map of the functional networks and of a type of synaptic receptor is for example opening up a new field of investigation for the study of neuroleptics. Finally, CEA's imaging research resources include a significant translational part based on animal models, headed by the Molecular Imaging Research Centre (MIRcen) in Fontenay-aux-Roses but also the 17 tesla MRI at NeuroSpin.

CEA is also heavily involved in "population imaging", a step that is today key to converting AI technologies to "bio-markers", specifically for diagnosis, for example, but also for prognosis of the evolution of a disease or the success of a therapy. Jointly with the Pitié-Salpêtrière hospital, CEA is coordinating a national platform, the CATI, running a network of about

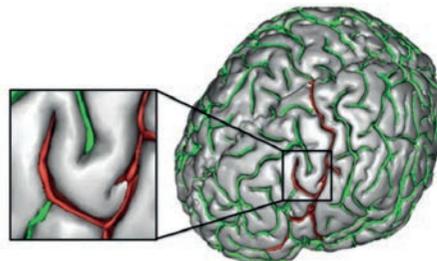
a hundred MRI and PET imagers around the country (fig. 1). Thirty or so clinical trials in progress have enabled standardised images to be collected concerning more than 10,000 patients. This national database will make it possible to discover signatures specific to sub-groups of patients (fig. 2). These signatures are often invisible to the radiologist's eye because they for example correspond to barely perceptible atrophy patterns distributed throughout the entire brain. It is also probable that such signatures could be able to detect the early warning signs of certain pathologies with the same initial symptoms, allowing screening of the populations at risk and paving the way for early therapies.

Owing to the exceptional storage and computing resources needed, brain imaging has become a new use case for the high-performance computing (HPC) centres. It appears on the roadmap of the Human Brain Project (HBP), one of the "flagship" projects of European research. The HBP aims to create a dedicated and lasting infrastructure including CEA's very large computing centre CEA (TGCC).

The most disruptive field of research in population imaging consists in attempting to redraw the brain pathologies landscape by combining clinical signs, imaging and genetics, in order to bring out a more detailed classification of the diseases. The aim is both to sub-divide the syndromes and to reconsider the artificial boundaries which separate them, in order to create personalised medicine, not for each individual, but for homogeneous patient groups. ■



Distortion in the motor cortex, linked to a seizure

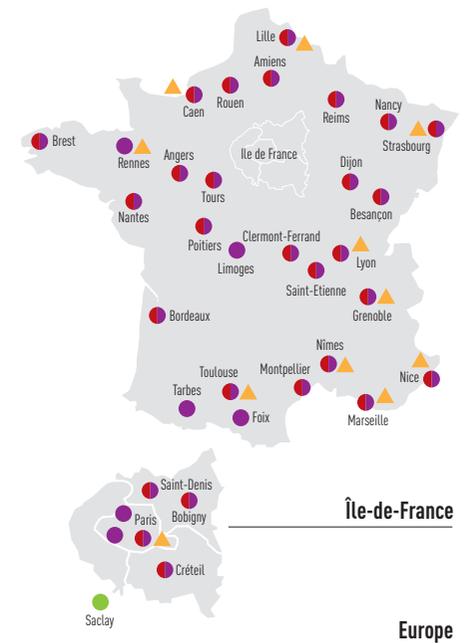


**Fig. 2:** As well as fingerprints, cortical foldings are specific to each person. AI is near to decipher them, on the basis of millions of digital images produced by MRI. Occurring during the second half of pregnancy, this folding signs deleterious events at the root of developmental disorders.

# CATI

## ACQUISITION NETWORK

- Harmonised MRI
- ▲ Affiliated labs
- Harmonised PET
- Affiliated labs



•  
BY  
**PROF. VINCENT LEBON AND  
LE DR FRÉDÉRIC TARAN**

(Fundamental Research Division)



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**Frédéric Taran** is Head of Bio-organic Chemistry and Labelling Service (CEA Joliot Institute /Drugs and Health Technologies Department).

#### Radiopharmaceutical

Molecule containing a radioactive isotopic which can be used for diagnostic purposes, notably for PET scans.

#### Bioorthogonal chemistry

Set of chemical reactions taking place within an organism without interfering with its biochemical environment.

#### Immunohistochemistry

Selective imaging of the proteins in the cells of a tissue, generally used to detect and monitor cancers by detecting cancerous tumours.

# Radioisotopic Imaging and Personalised Medicine

Biomarker needs are significant: The future of therapeutic innovations – notably targeted therapies and immunotherapy – depends on the ability to identify responsive patients, assess an early response and detect the appearance of treatment resistance.

**M**edical imaging has entered the molecular era with positron emission tomography (PET) using fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), a radioactive analogue of glucose, which has been available in hospitals for a decade. Although this technique plays a major role in diagnosing numerous diseases, it is lacking in specificity because glucose hypermetabolism is common to numerous pathological processes.

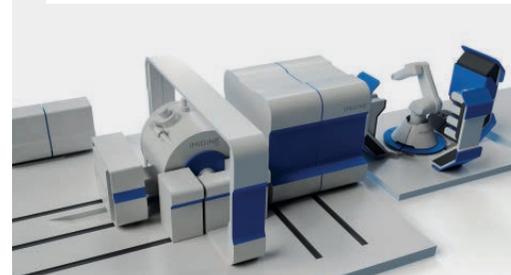
PET offers far greater potential than imaging of  $^{18}\text{F}$ -FDG: Any molecule labelled with  $^{18}\text{F}$  (or  $^{11}\text{C}$ ) can be an imaging biomarker. The needs for biomarkers are significant: The future of therapeutic innovations – notably targeted therapies and immunotherapy – depends on the ability to identify responsive patients, assess the early response and detect the appearance of treatment resistance. The development of **radiopharmaceuticals** specific to a pathology or a therapy will enable these challenges to be addressed.

They are based on innovative chemistry research focusing on clinical transfer. This “fundamental/clinical” synergy is embodied by two departments at CEA. The Bio-organic Chemistry and Labelling Service (SCBM) is a recognised player in the field of isotopic labelling applied to the field of health and is pioneering the design of new **bioorthogonal chemistry** tools. It is developing ultra-rapid reactions allowing specific “click and release” of chemical entities. The Frédéric Joliot Hospital Service (SHFJ) has expertise in the development, evaluation and clinical transfer of original radiopharmaceuticals for PET imaging. The radiochemists at the SHFJ are producing radio-tracers compatible with this click and release for in-vivo molecular chemistry applications.

In the field of cancerology, for example, PET using monoclonal antibodies will provide “in vivo tumoral **immunohistochemistry**”, similar to standard immunohistochemistry on biopsies. The advantage of PET lies in the whole body mapping of tumour populations, unlike biopsies; which only represent a fraction of the actual tumoral picture. The immunoscore obtained in PET will thus be

representative of the total tumour volume and acquired non-invasively by means of molecular imaging. The SCBM and the SHFJ are together drawing up disruptive strategies to develop radiopharmaceuticals specific to the tumoral environment and its immune system. This combination of know-how, in collaboration with the clinicians at Gustave Roussy Hospital, the leading centre in the fight against cancer in Europe, will enable these new bioorthogonal radiochemistry tools to be transferred to clinical uses. Mapping anti-tumour receptors in the patient by molecular imaging will release the full clinical potential of personalised anti-cancer immunotherapy.

**LOTUS system** for “on-demand” production of radiopharmaceuticals, being installed at the SHFJ in Orsay.



© PMB

In neurology, similar approaches are being developed for early diagnosis and therapeutic evaluation of neurodegenerative diseases. Targeted radiopharmaceuticals will allow quantification of protein aggregation in the brain characteristic of these diseases, such as the neurofibrillary tangles of Alzheimer’s disease or the Lewy bodies in Parkinson’s disease.

CEA is also working on a disruptive technological approach to automated production of radiopharmaceuticals: The LOTUS project. This industrial partnership with the PMB company, supported by Bpifrance, aims to develop an integrated and automated “on-demand” radiosynthesis system, from the production of the radioisotope to syringe filling for patient injection. It will eventually enable a personalised radiopharmaceutical to be produced in the hospital in just a few minutes. ■



View of the exoskeleton in clinical trial in Grenoble

© Pierre Jayet/Clinattec

# Technology Aiding Those with Motor Disabilities

The idea of collecting information at source, in the cerebral cortex, to activate effectors and muscles in particular, is not a new one. In 1985, the proof of feasibility, obtained on a patient with an implant in the brain, supplied a signal enabling them to move a computer mouse.

**H**aving proven the concept, there remained the problem of technological developments to convert this situation into a procedure usable on patients. Over the past 10 years, progress has been impressive and recent publications have mentioned practical applications in patients suffering from motor disabilities.

In recent months, several publications, including two from Lausanne, have excited the medical world and, more importantly, the patients, who will be the ultimate beneficiaries of these developments. These spectacular results have shown that one can significantly increase the speed and intensity of motor recovery in paraplegic patients with major sequelae in the lower limbs, as a result of damage to the dorsal spinal cord.

The approach undertaken at Clinattec by CEA/Leti and CHUGA, was from the outset to target the most dramatic problem of complete tetraplegia (that is the lack of movement in the lower limbs and a part of the upper limbs, as well as the loss of sensitivity in these same areas). Here there is no longer any

question of accelerating a recovery which is impossible, but of restoring a degree of mobility by taking information directly from the brain and, after decoding it, using it to control motors to actuate the four limbs of an exoskeleton surrounding the patient.

For the past 17 months, following an injury, a tetraplegic patient has been fitted with two implantable continuous, wireless recorders, transmitting the electrical activity of the motor cortex of the two hemispheres. These data are transmitted and decoded on-line to translate the subject's movement intentions into a motor command executed by the limbs. This patient at present controls 8 degrees of freedom in the upper limbs and can start and stop walking, although still supported.

The results obtained at this level of experimentation hold pole position in the international competition currently under way. This programme is the subject of a clinical research project, to which three other patients should be added in the coming months. ■

•  
**BY PROF.  
ALIM-LOUIS BENABID**



**Alim-Louis Benabid** is member of the French Academy of Sciences, Professor Emeritus of Biophysics, former head of neurosurgery department, former director of Inserm 318 Unit. He runs the Edmond J. Safra biomedical research centre, Clinattec, in Grenoble.



“The results obtained at this level of experimentation hold pole position in the international competition currently under way.”

**CHUGA**

Grenoble Alpes University Hospital

•  
BY  
**JEAN-FRANÇOIS DELEUZE**

(Fundamental Research Division)



**Jean-François Deleuze** is Director of the National Human Genomics Research Centre (CEA Jacob Institute) and Scientific Director of the Fondation Jean Dausset-CEPH.

The NovaSeq6000,  
CNRGH latest acquisition.



# CEA, a Major Player in Genomic Medicine in France

Whether a major revolution, a disruptive innovation or a necessary development, genomic medicine is today one of the driving forces in addressing the challenges of the medicine of the future: Meeting medical needs as yet unsatisfied (access for all, therapeutic and technological innovation, diagnostic delay, drug effectiveness and safety, etc.) and helping to control health spending.



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## Background

During the course of the 20<sup>th</sup> century, no fewer than four Nobel prizes (James Watson, Francis Crick and Maurice Wilkins in 1962, Frederick Sanger in 1976, Jean Dausset in 1980 and Kary Mullis in 1993) were awarded for scientific and technological discoveries ushering in the era of personalised genomic medicine. The 1960s discovered DNA, the 70s sequencing, the 80s revealed that DNA profiles of donor and receiver had to be matched in order to avoid graft rejection and finally, the 90s led to automated, democratic DNA reading thanks to **PCR**. Through large-scale use of these technologies, the 2000s saw the complete decryption of the human genome and the characterisation of its variability on the scale of human populations, triggering an avalanche of discoveries of associations between genetic variations and neutral or pathological **phenotypic traits**. Among the most significant innovations, the disco-

very that the amplification of the Her2 gene was a predictive marker of the response to Herceptin (anti-cancer drug) in women suffering from breast cancer, laid the foundations for targeted therapies in oncology: Today, more than about fifteen therapies are prescribed following the identification of a genomic variation. Rare diseases also benefited from these innovations, thanks to which about a hundred genes have been identified, leading to molecular diagnostics, which for certain patients meant an end of years of waiting. The world of common illnesses is also beginning to be affected, first of all thanks to the identification of genetic variations involved in the metabolism of drugs. Faced with the economic potential of the analysis of the human genome, an international industrial sector was created (from which France is still far too absent today) and some players are engaged in a race, having clearly understood that beyond “simply” analysing the genome, the data it contains are where the true added

### PCR

Polymerase Chain Reaction, a molecular biology method for in vitro amplification of DNA (gene concentration and amplification by polymerase chain reaction).

### Phenotype

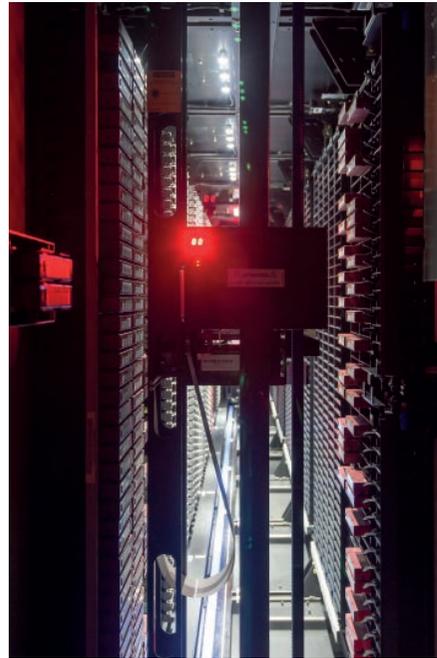
All the observable traits of an organism (anatomical, physiological, molecular or behavioural).

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**On the left**, the Cobalt supercomputer at CCRT (Research and Technology Computing Centre) is used by CNRGH for genomic analysis.

**On the right**, view of the storage and data processing infrastructure of the France Génomique project.



© P. Stroppa / CEA

value lies. Hence the shift from sequencing technology to the digital industry and big data. These were all factors that convinced CEA to join the game ten years ago: It today runs the National Human Genome Research Centre (CNRGH), one of the largest European centres in this field and a key player in genomic medicine in France.

## CEA's Genomic Medicine Assets

The role of the CNRGH is to address scientific questions requiring high-throughput sequencing and genotyping, by developing and implementing innovative and integrated technologies through in-house and collaborative projects. The CNRGH possesses and controls latest-generation genomic technologies enabling it to be competitive and it can rely on a bioinformatics team using the capabilities of CEA's very large computing centre (TGCC) which houses petaflop scale supercomputers on the CEA military applications division (DAM) site in Bruyères-le-Châtel. This collaboration with the DAM experts enables the CNRGH to carry out hundreds of genomic analyses simultaneously on a daily basis.

A cross-cutting, multidisciplinary programme comprising the teams of the Fundamental Research Division (DRF) and the Technological Research Division (DRT) at CEA is currently being carried out to assess the development of new processors offering speed of analysis and data integration. This combination of expertise, which is unique in France, positions the CNRGH among the top 3 in Europe and has already enabled it to become a partner in major

scientific discoveries, including the characterisation of new rare disease genes [1] and the identification of a bio-marker explaining the onset of severe side-effects when a statin type drug is taken [2]. These two iconic examples clearly illustrate the ability of genomics to impact both diagnostics and treatments. Owing to its expertise and its tools, the CNRGH is very regularly associated with major national and European projects. Together with the French Centre for the Study of Human Polymorphism (CEPH), it is therefore jointly running the GenMed (for Medical Genomics) laboratory of excellence, the aim of which is to help genomics make the transition from research to clinical applications, more particularly based on national initiatives and plans. It has seen the launch of pioneering, ground-breaking projects, in particular the first project to sequence the complete genomes of individuals representative of France, in order to produce a map of the neutral genetic variations which exist in the population. These benchmark sequences produced and analysed at the CNRGH constitute a collaborative database which has already led to the identification of disease genes, by filtering the pathogenic variations from the neutral variations and thus identifying the genes responsible.

In collaboration with CEA/List, a pilot data security approach was implemented. After homomorphic encryption, it was possible to make basic diagnostic analyses such as determination of the blood group, paving the way for future genomic data protection strategies. This first database is today one of the foundations of genetic diagnostics in France and

**Pr. Stanislas Lyonnet**,  
(Université Paris Descartes, AP-HP)  
Director of the Genetic Diseases Institute  
(Imagine, Inserm / Université Paris  
Descartes)



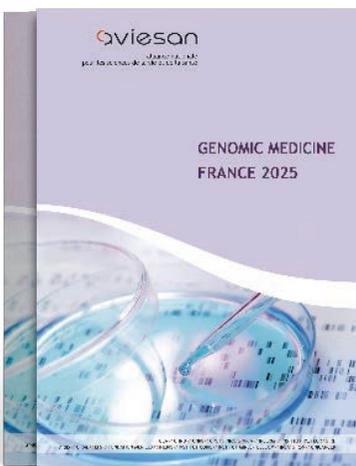
"The conjunction of the 3<sup>rd</sup> version of the rare diseases plan, just adopted by France, the PFMG 2025 and a proactive and open strategy by the national genomics centre (CNRGH and CEA) finally gives us hope that modern genomic medicine will find a place in health care and in the research devoted to rare genetic diseases. Its success will not (only) be measured by the very high-level production of DNA sequences but also and above all by the impact it will have on reducing diagnostic waiting times, on the budgetary economies of scale to which it will lead in our public health system and, finally, on its link with academic research, as carried out in a teaching hospital institute such as Imagine, as well as on clinical research and industrial partnerships. It is in all these respects that the genomic medicine of rare diseases must impose a French model for genetic medicine; quality and multidisciplinary oversight of the prescription of tests, the essential precondition for the quality of the results and their interpretation."

### Petaflop scale

Ability of a supercomputer to carry out several million billion "simple" calculation operations in one second.

**Aviesan**

National alliance for life sciences and health, comprising the leading French players in the field.



was the starting point for a far more wide-ranging project, which will complete the map to cover the entire country, as part of the French genomic medicine plan.

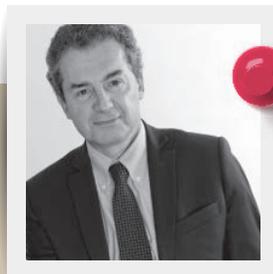
## The France Genomic Medicine Plan 2025

Unsatisfied medical needs, spiralling health expenditure, falling sequencing costs and scientific evidence are today converging to see genomics make their entry into the medical world. Under the leadership of the Government and in the same way as in the United Kingdom, United States and China, France recently adopted a ground-breaking national plan to integrate sequencing into the care pathway and make the country a leader in the field. Under the supervision of Prof. Yves Lévy, Chairman of Aviesan, with the notable strategic support of CEA, this plan aims to deploy 12 diagnostic sequencing platforms – the first two are being installed in Paris (SEQOIA) and Lyon (Auragen) – backed up by a reference, innovation, expertise and transfer centre (CREFIX). This centre, co-managed by CEA and Inria, in partnership with Inserm, occupies the same site as the CNRGH, on the Evry genetics hub. CREFIX works on reference baselines and procedures, conducts a technological and scientific watch and

coordinates innovation in collaboration with industry, or by promoting the emergence of a French industrial fabric, such as the recent spin-off from the CNRGH, the TRAASER start-up, in the field of bioinformatics applied to diagnostics. CREFIX has a major role to play in maintaining the competitiveness of the plan, by fostering the deployment of appropriate innovations on the diagnostic platforms. The genomic data generated and the corresponding clinical data will be centralised in a national data collector and analyser (CAD) accessible to the experts who will be able to complete the interpretation process and organise feedback to the patient. Finally, to identify and eliminate all the obstacles to the implementation of medical genomics, from first consultation up to reimbursement, three pilot clinical research studies, headed by Inserm, are under way and will address all the steps on the genomic pathway. Several thousand patients suffering from a rare disease (mental retardation), a cancer (colon or sarcoma) or metabolic illness (diabetes) will be sequenced at the CNRGH, their data pre-analysed at the TGCC and then transferred to the groups in charge of final interpretation. At the same time, the platforms and the CAD will be ramped up and will become operational so that they can begin diagnostic sequencing on selected indications in collaboration with the French National Authority for Health. ■

[1] Further delineation of the clinical spectrum of de novo TRIM8 truncating mutations. M. Assoum, MA. Lines, O. Elpeleg, V. Darmency, S. Whiting, S. Edvardson, O. Devinsky, E. Heinzen, RR. Hernan, C. Antignac, JF. Deleuze, V. Des Portes, A. Bertholet-Thomas, A. Belot, E. Geller, M. Lemesle, Y. Duffourd, C. Thauvin-Robinet, J. Thevenon, W. Chung, DH. Lowenstein, Faivre L. *Am J Med Genet A*. 2018 Sep 23.

[2] SLC01B1 variants and statin-induced myopathy - a genomewide study. SEARCH Collaborative Group, E.Link, S. Parish, J. Armitage, L. Bowman, S. Heath, F. Matsuda, I. Gut, M. Lathrop, R. Collins - *N Engl J Med*. 2008 Aug 21; 359(8):789-99



**Prof. Yves Lévy,**  
Councillor of State, former CEO of Inserm

“Over and above the technological advances which are allowing or will allow large-scale and low-cost genetic diagnostics, the major challenge is to find out how to guarantee access to this genomic medicine, in ethical and secure conditions and in a health care system that guarantees fairness. The other challenge is also to be able to ensure the integration of scientific advances resulting from innovation into medical follow-up, in order to speed up access to innovation. In addition to the genetic diseases characterised by mutations and/or anomalies, our ability to meet the challenges of interpreting “real life” variants in order to get back to the patient, their family and physician rapidly, has yet to be proven. Addressing these issues is the challenge for the PFMG 2025.”



© L. Godart/CEA

IDMIT is equipped with a two-photon microscope system tailored to ex and in vivo imaging at cellular scale and, in particular, to the follow-up of interactions between a pathogenic agent and the host organism.

# Very Promising Avenues

CEA is fully committed to research and development in therapeutic and preventive approaches of infectious diseases, which are the second cause of mortality worldwide.

**T**he main challenges for infectiology tomorrow will be to identify new host defence mechanisms and new targets against bacteria, viruses and parasites and to develop new treatments or vaccines, develop diagnostic tests to rapidly target the “resistant” patients, in order to limit propagation and facilitate treatment and care and, finally, to anticipate health crises linked to emerging infectious diseases. Several teams from the CEA Fundamental Research Division (DRF) are fully involved in this work in Grenoble, Marcoule, Fontenay-aux-Roses and Saclay (see box).

## Identifying New Anti-infective Agents

For nearly a century now, antibiotics such as penicillin and vancomycin have been used as anti-infective treatments worldwide. However, the resistance

developed by several pathogens is now widespread and represents a major global health problem: It is therefore crucial to identify new anti-infective agents by characterising new potential targets. The Structural Biology Institute (IBS) is working on deciphering the main components of the bacterial wall, the ‘peptidoglycane’, a “mesh” surrounding bacteria and essential for their stability. The biosynthesis of peptidoglycan requires complex steps regulated by proteins and enzymes. Understanding the interactions between these proteins and with other elements of the bacterial wall, as well as their activation processes, remains a scientific challenge and a prerequisite for the development of new antibacterial agents. The recent characterisation of the structures of the PBP2-MreC (Fig.1) and MurT-GatD complexes, as well as the MapZ bacterium division factor has for the first time brought to light the surfaces used by these proteins for the interactions essential to survival of the cell. These results open the door to the design of completely original antibacterial agents.

## CONTRIBUTORS

(Fundamental Research Division)



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**Christophe Junot** is Head of the Health Drugs and Technologies Department (CEA Joliot Institute).



**Roger Le Grand** is Director of the IDMIT (CEA Jacob Institute).



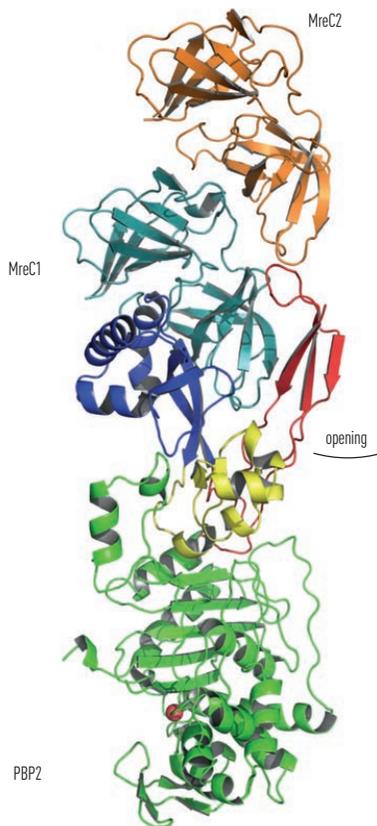
**Winfried Weissenhorn** is Director of CEA's Structural Biology Institute.

**Nucléocapsid**

Assembly comprising the capsid of the virus (structure surrounding its genome, DNA or RNA) and the viral genome.

**Glycoprotein**

Group consisting of proteins and carbohydrates.



**Fig. 1:** The crystal structure of the PBP2 and MreC complex shows conformational changes of PBP2. It provides a structural basis for developing new small molecules able to prevent interactions essential to survival of the cell.

In the field of virology, the IBS is looking at the structure and working of replication mechanisms in negative RNA pathogenic viruses, such as those of measles and influenza. The most recent works include the atomic resolution of the structure and kinetics of the process of assembly of the **nucleocapsid** of the measles virus. These results are used to develop inhibitors of measles and other RNA viruses.

Other work concerns the inhibition of HIV-1. In collaboration with IDMIT under European programmes, structural biology approaches are being used to develop new vaccines utilising HIV-1 envelope **glycoproteins** in order to introduce extensively neutralising antibodies (bnAbs) by vaccination. This approach is based on the fact that certain patients develop bnAbs spontaneously. These bnAbs are also isolated and characterised in order to better understand the evolution of the immune response to infection. This work is associated with innovative chemical approaches to develop sugar-based mimetics which interfere with the function of the glycoprotein at the viral entry level.

## Improving Prevention of Infection Transmission

The research being carried out at the IDMIT concerns the interaction between pathogens and the host organism and the defence mechanisms to be exploited to develop new treatments or new vaccination strategies.

Improved prevention of the transmission of infectious diseases, by vaccination or by medical prophylaxis, entails a detailed understanding of the mechanism whereby the pathogens penetrate and are disseminated within the host organism. The IDMIT teams are more particularly recognised for their study of the mechanisms of the sexual transmission of HIV. They revealed the role of sperm, in particular the infected cells it contains, in the virus's penetration of the mucosal barriers of the vagina and the cervix. In collaboration with researchers from the SPI and IBS, they tested the effectiveness of new molecules (small peptides mimicking the structure of the cell receptor for the virus) in animal experimental infection models.

Vaccination is one of the most effective strategies for fighting the dissemination of infectious diseases, for example tetanus, polio or diphtheria, the number of cases of which has significantly dropped. However, there is still no vaccine for major pathologies such as aids, tuberculosis or malaria. To achieve this, we

need a clearer understanding of the basic mechanisms which, through vaccination, lead to a long-term "immunological memory". The IDMIT is studying the installation of this memory, from the very first steps following vaccine injection up to the characterisation of cellular and molecular events involved in subsequent exposure to the infectious agent and the disease. The new technologies available to research, notably for the study of gene expression or infected cells, today offer a detailed view of all these phenomena. The long-term objective is to use these data for in vitro and in silico modelling of the response to vaccines and thus speed up the exploration of new hypotheses, before carrying out pre-clinical and clinical trials.

The IDMIT thus has unique in vivo imaging resources for molecular, microscopic or whole organism time and space visualisation of the interactions between a pathogenic agent and the host organism. When an infection takes place, these interactions are highly dynamic and are often to be found in a variety of complex environments (tissues, organs) with the possibility of rapid development.

New microscope technologies are opening the door to the in-depth study of micro-organisms in living tissues, including a visualisation of the complexity of the phenomena in a whole, living organism. By increasing the precision of observation and the characterisation of the elements visualised, it is now for example conceivable that one could identify a virus, bacterium, fungus or parasite in the deep tissues of a patient. The IDMIT thus has the first two-photon microscope system tailored to exploration in a large animal, in a biologically confined environment.

On this same topic, the IDMIT is developing other approaches, based on positron emission tomography (PET) and computed tomography (CT). The aim is to provide whole-body mapping of the replication of a virus, such as HIV, or of a bacterium, for example the one responsible for whooping cough and at the same time visualise the host's response or the distribution of drugs. These approaches should in the future enable patient treatments to be more closely tailored and help understand the persistence of pathogens which escape the effect of drugs or the action of vaccines.

## Detecting Infectious Agents

Therapeutic treatment of an infectious disease requires that the diagnosis (detection of the infectious agent or corresponding biomarkers) be closely associated with treatment. So that treatment can begin

as early as possible, the diagnosis must be rapid, precise, personalised and connected. The fight against emerging infectious diseases must also be considered in its entirety, in other words not only in terms of public health, but also taking account of veterinary and environmental aspects. It is therefore necessary to produce tests that can be used clinically on humans and animals, in the environment and on food, both in low-income countries with limited infrastructure and in high-income countries.

In addition to these “point of care” approaches in the field, sophisticated and high-performance technologies are also required. Some, such as high-speed genome sequencing, were designed for deployment in the field (MinION sequencer) but still require R&D efforts. Others, such as the “omic” analyses using mass spectrometry, are used for detailed characterisation of infectious agents and their interactions with their hosts and environments and for identification of biomarkers to improve diagnoses and provide new therapeutic targets.

In this context, the SPI has for the past few years been carrying out both Point of Care Tests (POCT) and “omic” analyses. The POCT developed in the Laboratory of Innovations for Detection and Diagnosis (Li2D) and the Laboratory for Study and Research in Immunoanalysis (LERI) are immunological tests (Fig. 2). There are three challenges:

- To shorten the development time for providing a rapid solution for health crises involving new agents which, as they evolve very fast, render the existing tests obsolete;
- To improve their performance through miniaturised innovative approaches (microfluidics), which

are both robust and compatible with extreme conditions;

- To increase their multiplexing capability, for simultaneously detecting different biomarkers, thus reinforcing the level of certainty of the test, at the lowest possible cost.

These tests will also need to be connected, in order to rapidly identify the emergence of a pathogen anywhere in the world, map and model its spread or combat medical desertification.

Illustration of the rapid mobilisation capability of the Li2D and the LERI when faced with major health crises, the development and marketing of a POCT for the Ebola virus during the 2014 crisis or, more recently, a POCT for bacterial resistance to antibiotics.

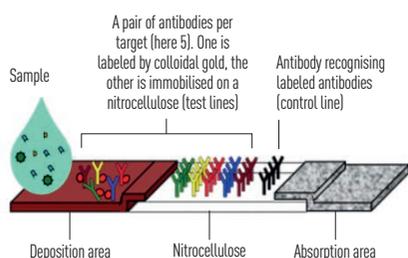
The Laboratory for the Study of Drug Metabolisms (LEMM) and the Li2D are developing global metabolomic, metaproteomic and proteogenomic approaches. By combining high-resolution mass spectrometry, with statistical and bioinformatic analyses, they are able at the molecular level to characterise the pathogenic agents and identify new protein variants/mutants, or metabolites and reaction products specific to resistance phenomena, with an excellent level of precision. Although lengthy, costly and as yet reserved for the experts, these techniques complement the field tests. They could help lift diagnostic uncertainties, conduct epidemiological surveys (identification and monitoring of variants, mutations, etc.), identify new biomarkers of use for the development of new POCTs, or measure treatment effectiveness or resistance and new therapeutic targets. ■

## Infectiology at CEA Complementary approaches



1. **IBS:** Research in molecular and structural microbiology. It benefits from unique platforms that are part of the FRISBI French national platform and of the Instruct-Eric European infrastructure, and also from the access to its European partners' platforms, ESRF, ILL and EMBL through the "Partnership for Structural Biology" (PSB).
2. **IDMIT:** Study of mechanisms involved in the transmission and dissemination of pathogens and the spread of diseases in humans.
3. **SPI:** Development of diagnostic tools.

### Structure of the Dipstick Assay



### Immunological Test



### Result

- The control line appears: The test worked out
- One or several test lines appear: The test is positive for the corresponding target
- No test line: The test is negative for the five targets

**Fig. 2: Principle of the multiparameter Point of Care “dipstick” assay.** It is based on the recognition of the target by a pair of antibodies: One is immobilised on the solid phase (nitrocellulose) and the other is gold-labeled for visualizing the reaction. In this case, it has been conceived for recognizing five different targets.

BY

PROF. PHILIPPE LEBOULCH

(Fundamental Research Division)



**Philippe Leboulch** is Senior Adviser for medical innovation at CEA. He is also Honorary Scientific Director of the DRF and Chairman of the Board of CEA Jacob Institute.

# Gene Therapy is Booming

As this 21<sup>st</sup> century begins, gene therapy has burst onto the scene and there is every reason to believe that it will enjoy a major place in the therapeutic arsenal of the medicine of the future.

**G**ene therapy can be defined as a specific modification of the genome for therapeutic purposes, for innate and usually hereditary diseases as well as for acquired genetic illnesses, such as cancer. It combines a specific genome modification approach with a tailored choice of target cell population, either to obtain a permanent effect (case of hematopoietic stem cells), or one that is intentionally temporary – as in cancer immunotherapy using modified T cells (CAR T Cells). Gene and cell therapies thus work hand in hand.

After pre-clinical developments in animals and in human cell systems, a large number of phase I/II then phase III clinical trials carried out in recent years confirm the long-term effectiveness and the safety of several approaches, even if the very first trials led to serious side-effects in a few patients. A number of gene therapy products have already been authorised for release to the market in the United States and/or in Europe: Glybera<sup>®</sup> and Strimvelis<sup>®</sup> respectively for lipoprotein lipase and adenosine deaminase deficiency, Kymriah<sup>®</sup> and Yescarta<sup>®</sup> for the immunotherapy of certain leukaemias and lymphomas and Luxturna<sup>®</sup> for Leber congenital amaurosis.

The genome is modified by means of vectors – the main ones being lentiviral vectors and those derived from the virus associated with the adenovirus – which enable a therapeutic gene surrounded by its regulatory elements to be input. The aim is to make up for the absence or functional deficiency of a given gene (most frequent cases, such as **beta-thalassemia** or **adrenoleukodystrophy**), or to obtain a product that will positively interfere with a pathological process (case of **sickle cell disease**), or even express a product with artificial functions (chimeric T cell receptor). With recent vectors, the theoretical genotoxi-

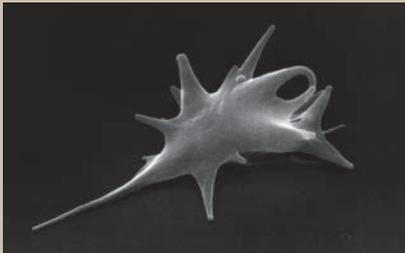
city linked to undirected chromosomal insertion would appear to be low and enjoys a high “risk/benefit ratio”, although this does need to be reassessed for each project.

Another approach at an early stage in development is in-situ “gene editing” using special enzymes such as CRISPR/CAS9. This is awaiting theoretical proof of sufficient clinical effectiveness in humans with no major genotoxicity.

France has played a leading role in the emergence and current growth in gene therapy. At CEA, researchers laid the scientific foundations for the world’s first two clinical trials using lentiviral vectors for the gene therapy of hereditary diseases. They then took part in development up to the EMEA application in October 2018 for marketing in Europe of a gene therapy product for non-beta beta-thalassemias.

Our country is in a position of strength to assist with the global development of gene therapy, at scientific and industrial levels. CEA has experts in each of the scientific fields essential for innovation in this area, such as vector optimisation (targeted integration of lentiviral vectors, selection of transduced cells, etc.) and the enzymatic development of CRISPR/CAS9 for greater effectiveness and fidelity. Its scientists and dedicated infrastructures give it a clear advantage for large-scale clinical grade (cGMP) production and for sophisticated pre-clinical trials in animals. Another advantage is its experience in relations with industry, valorisation, economic studies for determining a fair but competitive price for biological therapies and their reimbursement, as well as international relations with countries of widely varying socio-economic levels. Finally, with its genomics institute, CEA is able to provide new targets for gene therapy and new therapeutic genes. ■

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Abnormal red blood cells in patients suffering from sickle cell disease.



Healthy red blood cells.

## Beta-thalassemia

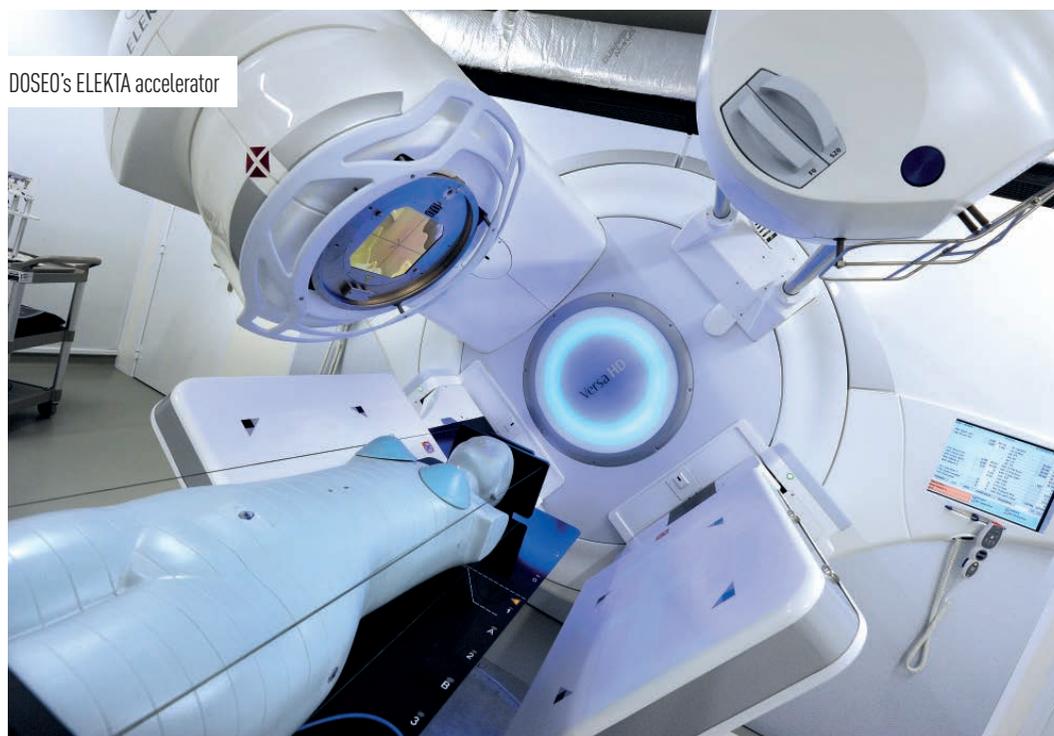
Genetic blood disease caused by insufficient production of haemoglobin.

## Adrenoleukodystrophy

Genetic disease linked to the X chromosome, affecting the myelin of the brain.

## Sickle cell disease

Genetic blood disorder due to abnormal production of haemoglobin.



DOSEO's ELEKTA accelerator

© CEA / Gardat

# Towards Personalised Radiotherapy

Optimising and personalising radiotherapy treatments to preserve healthy tissues and organs: This is CEA's goal, through the development of a two-fold physical and biological approach.

**M**ore than half of all cancer patients are treated every year using radiotherapy. With the arrival of intensity-modulated conformal radiotherapy and then volumetric modulated arc therapy, the radiotherapist can better tailor the delivered dose to the target volume. This increases the therapeutic effectiveness of radiotherapy while reducing unwanted side-effects.

Despite this progress, there are avenues of development for further optimising and personalising radiotherapy treatments. These include predicting and reducing the toxicity of this treatment. In order to meet these two major challenges, CEA is engaged in research aimed on the one hand at achieving a precise and personalised determination of the dose of radiation absorbed by the healthy tissues and, on the other one, on characterising individual sensitivity and susceptibility to radiation, in order to avoid secondary toxicity as a result of radiotherapy.

## Towards Complete, Precise and Personalised Dosimetry

During **radiotherapy** treatment, radiation can reach peripheral areas remote from the site of the tumour and additional low doses are thus delivered to the healthy tissues. Numerous epidemiological studies show **iatrogenic effects** and the existence of a relationship between low doses and the risk of late onset of cancer or heart disorders. The adaptation of the "as little irradiation as reasonably achievable" technique then proves to be of major benefit but implies that these additional doses are known precisely and in advance, which is not at present the case.

The teams working on the DOSEO platform, supported by CEA/List, are attempting to address this issue by developing software based on Monte Carlo simulation codes, allowing an extremely precise calculation of the physical dose.

•  
**BY**  
**BÉNÉDICTE POUMARÈDE**  
Technological Research Division  
**ET PAUL-HENRI ROMÉO**  
(Fundamental Research Division)

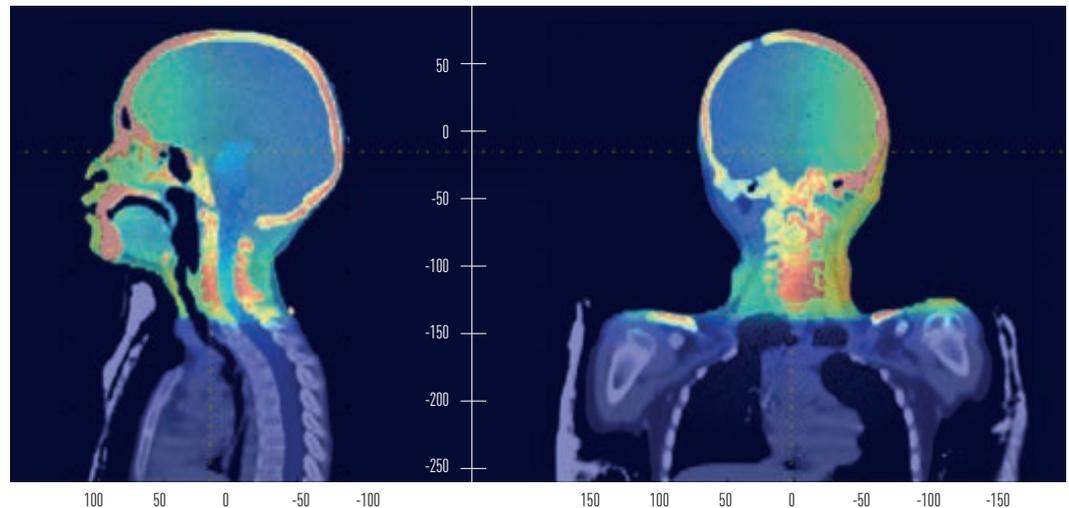
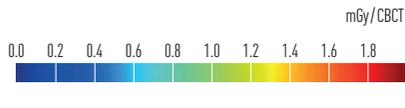


**Bénédicte Poumarède**  
is Head of the DOSEO platform  
supported by CEA/List.



**Paul-Henri Roméo** is Head of the  
Cellular and Molecular Radiobiology Institute  
(CEA Jacob Institute)

Example of dosimetry during the positioning imaging of a seven-year-old child



### Radiotherapy

Locoregional treatment of cancers using radiation (beams of high-intensity X-rays or electrons produced by an accelerator) to destroy the cancer cells while preserving the healthy tissues and neighbouring organs as far as possible. There are different techniques, including intensity modulated radiotherapy (IMRT) which enables the radiation beam to permanently adapt and volumetric modulated arc therapy (VMAT) for circular irradiations continuously adapted to the angle of incidence of the beam with respect to the target and the organs at risk.

### Iatrogenic effects

Refers to the harmful effects of a medical procedure or drugs, even if there is no error on the part of the physician.

A first step is to develop a software which makes a precise, personalised calculation of the doses delivered to the patient during the positioning imaging. This tool thus makes it possible to optimise the protocols used for this treatment phase so that the healthy tissues are the least irradiated. These doses linked to the positioning imagery are combined with those delivered to the healthy tissues during the radiotherapy treatment. The origin of these doses is leakage radiation from the accelerator itself and the radiation scattered by the accessories and patient. The particles must then be transported throughout the geometry of the accelerator as well as in the patient, including regions outside the field of treatment, which are by their very nature sampled less frequently. The researchers at DOSEO are developing a special code using an appropriate variance reduction method, based on the pseudo-deterministic transport technique, for ensuring convergence of the calculations.

The software developed are then all validated by the experimental irradiation and detection facilities on the DOSEO platform.

## Individual Sensitivity and Susceptibility

Of the patients treated with radiotherapy, 5 to 15% are liable to present secondary toxicity phenomena (dermatitis, rectitis, fibrosis, etc.), owing to hyper-radiosensitivity. The lack of radiosensitivity tests able to predict these harmful late onset side-effects observed in a small number of patients treated by radiotherapy leads to a limitation of the dose delivered and thus a probable reduction in the effectiveness of radiotherapy in most of the patients treated. Over and above the technical developments allowing increasingly targeted irradiation of the tumour, the optimisation of radiotherapy requires

characterisation of the mechanisms, cells and genetics governing individual radiosensitivity, with the aim of developing individual predictive radiosensitivity tests that are robust, fast and validated. The Cellular and Molecular Radiobiology Institute (iRCM) is conducting research directly concerning this issue.

The researchers at the iRCM have developed a simple test to determine the radiosensitivity of human cells and have used it to determine the genetics of this radiosensitivity. They identified a gene, called TRAIL, whose expression is directly linked to this radiosensitivity. The study of the genetic link between TRAIL and the radiosensitivity of the cells, led to the identification of three nucleotide polymorphisms of this gene linked to this radiosensitivity. This work shows that radiosensitivity is genetically predetermined, which opens up a field of research into the personalisation of radiotherapy. The study of a cohort of 113 breast cancer patients with complications after radiotherapy treatment, also revealed a link between two of the TRAIL gene polymorphisms and the occurrence of a radiotherapy complication, acute or sub-acute radiodermatitis.

This pioneering study illustrates how, in conjunction with functional cell radiosensitivity tests, genetics can open the door to personalisation of the dose delivered during radiotherapy treatment of cancer.

## Conclusion

The end-purpose of the research being carried out at CEA into radiotherapy is personalised treatment. The two approaches used, physical and biological, as well as the industrial and medical applications of this research, show the important position that CEA occupies and must indeed strengthen further in the personalisation of radiotherapy. ■



### To find out more

The DOSEO platform:  
<http://www.platformedoseo.com>

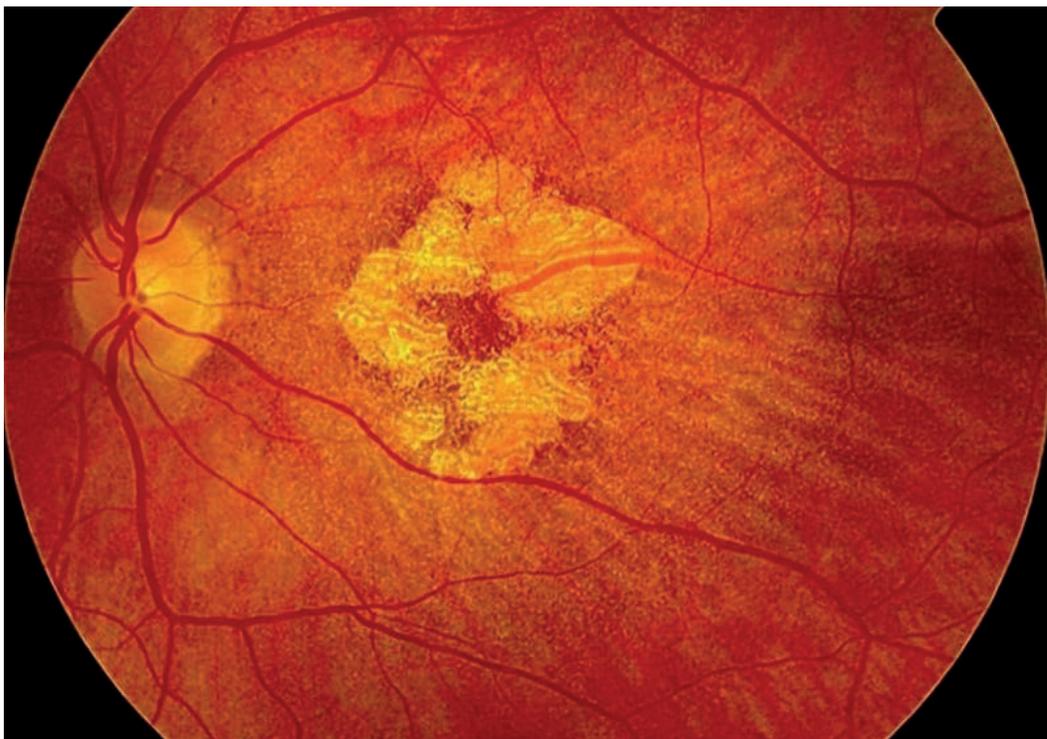
# Fighting Visual Disabilities

The loss of eyesight is among the primary fears of our fellow citizens. Whether partial or total, it arises during the development of chronic diseases, whether genetic in origin or related to age (ARMD, glaucoma, etc.), or to vascular or metabolic pathologies. In our country, there are still problems of access to health care (cataract surgery for institutionalised elderly persons, poorly reimbursed optical correction, screening and follow-up of complications from diabetes, screening and compliance in the case of glaucoma).

One of the paradoxes of modern ophthalmology is that large numbers of people continue to be affected by a visual handicap, despite massive progress in therapies and diagnostic tools. The explanation lies mainly in the rise in age-related pathologies, a global phenomenon, which is why ARMD has become the leading cause of visual impairment. Another paradox is the belated and insufficient treatment of numerous pa-

thologies (diabetes, glaucoma) even though screening tools exist. Finally, visual rehabilitation is only accessible for a very small proportion of those affected by a visual handicap.

Yet technological progress and the prospect of connected, personalised medicine taking advantage of the power of artificial intelligence (AI) methods gives us hope that there is a partial solution to these problems.



© Inserm / Jean-François Korobelnik

•  
**BY PROF.  
JOSÉ-ALAIN SAHEL**  
(Université Pierre et Marie Curie, AP-HP)



**José-Alain Sahel** is an ophthalmologist and Director of the Institut de la Vision (Sorbonne University / Inserm / CNRS).

## ARMD

Age-Related Macular Degeneration



“The explanation lies mainly in the rise in age-related pathologies, a global phenomenon, which is why ARMD has become the leading cause of visual impairment.”

← Fundus image of an atrophic ARMD

**Anti-angiogenics**

Or Anti-Vascular Endothelial Growth Factor: Treatments designed to stop the growth of malignant tumours by preventing the formation of new blood vessels.



In a laboratory of the Institut de la Vision

Very high resolution imaging of eye tissues exploits technologies such as optical coherence tomography, adaptive optics (derived from astronomy), holography and signal processing methods such as the Fourier transform, convolutions. These powerful computing tools for observing the cornea, the retina or the optical nerve at the molecular level allow precise detection of lesions and monitoring of evolution, both spontaneous or during the course of therapeutic interventions, with a better assessment of their effectiveness. The application of Deep Learning to reference images and to independent cohorts is of predictive value and shows impressive precision. AI, which exploits imaging data, and patient self-monitoring applications via smartphone or tablet, should help reduce current difficulties with screening and follow-up of numerous pathologies, partly compensating for the shortfall in the treatment offered.

Recent progress in therapy concerned improvements to cataract surgery (ultrasounds, laser, small incision, etc.) which is today very fast, reliable and performed on an out-patient basis, to the treatment of neo-vascular and/or oedema complications of ARMD and diabetes, thanks to **anti-angiogenics**, with the limitations being the palliative and belated nature of these interventions reserved for certain clinical forms, and the need to carry out intra-ocular injections several times a year and the high cost involved. Improving the mode of delivery and the development of earlier approaches are needed.

In the field of genetic diseases, progress in gene therapy and cell therapy is highly promising, with approval of the first gene therapy in the United States and in Europe, at a very high cost, which will require the creation of viable models for financing these innovative therapies. Artificial retinas have also obtained conditional reimbursement and are continuing to evolve, now also applying to ARMD.

Other approaches are being developed, directly targeting the cortical neurons.

The whole process must be accompanied by treatment of the residual and still major visual handicap, underlining the importance of developing a wide-ranging and innovative visual rehabilitation programme. Progress in virtual reality technologies is making them accessible and extremely useful for these patients.

Even if this progress is being proposed by integrated reference centres, a service involving all health professionals have to be created to provide appropriate treatment that is whenever possible local, keeping to the strict minimum the need to resort to complex care.

At the same time, the impact of innovation will only be measurable by precisely assessing the weight of the disorder, the handicap, the burden of treatment and the benefit gained in the day-to-day lives of the patients. ■



The Institut de la Vision

© Brunet Saunier Architecture

**To find out more**

The Institut de la Vision:  
[www.institut-vision.org/fr/en](http://www.institut-vision.org/fr/en)

# Artificial Intelligence for Treating Diabetes

An auto-immune disease which in the vast majority of cases appears before the age of 30, type 1 diabetes affects 200,000 people in France and 2 million in Europe. Diabeloop, which was created in Grenoble in 2015, is developing artificial intelligence for autonomous treatment of this pathology.

In the case of type 1 diabetes, the pancreas is incapable of producing the insulin needed to regulate blood sugar levels. The diabetic must therefore inject the insulin they need on a daily basis. This requires complex calculations - taking account of blood sugar levels, carbohydrates in meals and physical activity - 4 to 6 times a day. Too much insulin leads to short-term hypoglycaemia, resulting in tremors, impaired awareness and vision and even ultimately coma. Many patients are therefore cautious regarding the quantity of insulin injected and have a high average blood sugar level. This can have serious long-term complications: Blindness, dialysis, amputation or cardiovascular problems.

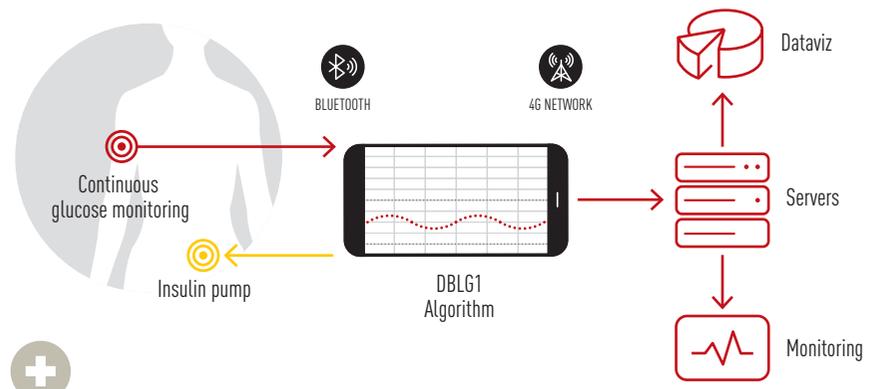
The calculation of the exact dose of insulin is particularly complex because blood sugar levels change rapidly and significant variations are possible in just one hour. The insulin/blood sugar ratio also varies according to the patients and, for a given patient, is determined on the basis of many other parameters: sport, stress, coffee consumption, fatty meals, insulin infusion site, even minor infections, hormonal cycle and so on. Insulin also has a significant inertia, with peak activity between 1 and 2 hours after injection with subsequent prolonged action of up to 4 to 6 hours. Finally, this inertia varies within and between patients by a factor of up to 3, further complicating matters.

Diabeloop has developed a closed loop which automates the delivery of insulin: Every 5 minutes, the system calculates the optimum dose to be injected and directly controls a miniaturised insulin pump stuck to the patient's skin. The extreme complexity of the problem and the considerable variability, even for a given person, owing to factors that are impossible to measure and which are sometimes poorly understood, drove the development of several algorithms. Self-adaptive artificial intelligence (AI) is thus coupled with an expert system which reproduces the principles followed by the diabetologist or expert patient and takes over when the reliability of the AI is considered to be insufficient. This was made possible by close and continuous collaboration between algorithm and data

science specialists, developers, diabetologists and, above all, the patients. The quality and regulatory aspect is also crucial: The system must be both perfectly safe and comply with standards which have not always kept pace with technological change.

After 4 series of clinical trials of its DBLG1 System, the last of which involved 70 people over 3 months, in real life situations, Diabeloop has recently obtained CE approval and is going to set up its commercial deployment in France and Europe.

Other developments are however needed to further improve the system: Even greater personalisation to take account of individual lifestyles and incorporation of other sensors for a clearer understanding of physiology, thus improving the clinical results and reducing the discomfort of living with type 1 diabetes. This will require the integration of new AI technologies, such as recurrent neural networks (attention mechanism or LSTM), in addition to continuously improving those currently being used. ■



## To find out more

The Diabeloop website: [www.diabeloop.com/](http://www.diabeloop.com/)

BY ERIK HUNEKER



Erik Huneker is CEO of Diabeloop.



Diabeloop is derived from a project initiated by a diabetologist, Guillaume Charpentier, in cooperation with CEA/Leti. The company, which today has 50 staff, raised initial funds of €13.5 M in 2017, with the participants including the venture capital subsidiary of Air Liquide.

# TECHNOLOGIES FOR MEDICINE

In collaboration with the other players in the field, CEA is working on offering health professionals rapid diagnosis tools, innovative therapies and efficient decision-making aids.

**Introduction**

**29**

**Biological Companions**

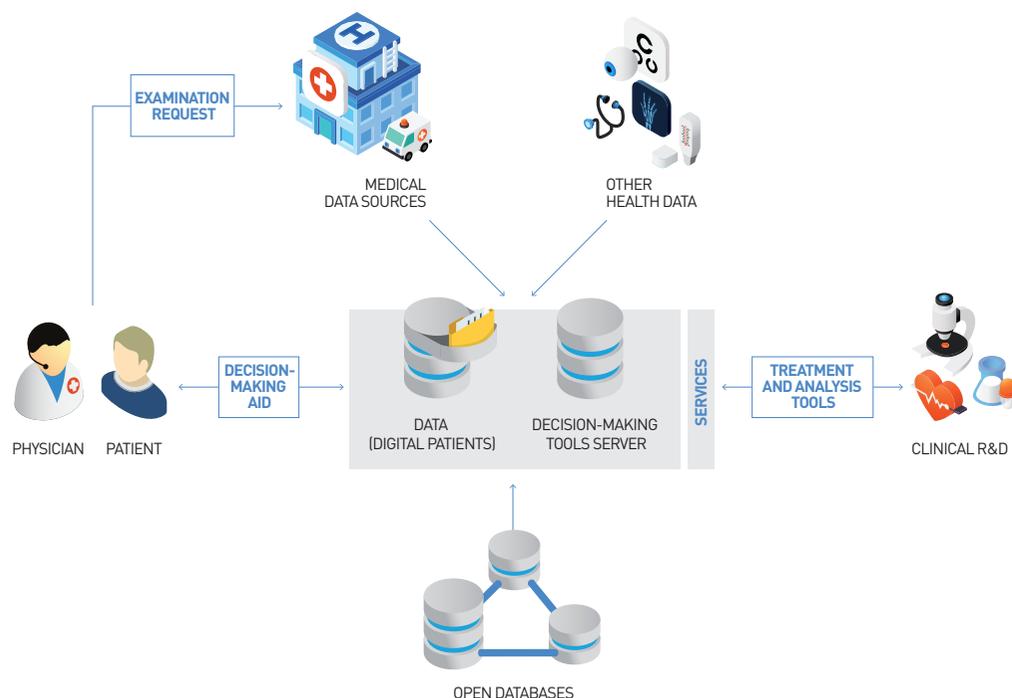
**32**

**Multi-disciplinary Technological Tools**

**35**

**Health Data Security**

**41**



← Fig. 1: the digital medicine value chain

•  
**BY PROF.  
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 (Fundamental Research Division)

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**Christophe Calvin** is head of the IT, numerical simulation and supercomputing sector (Partnerships and Programmes Division) at CEA/DRF.



**Jean-Noël Patillon** is Scientific Director of CEA/List.

# Digital Medicine, Coordinating Medical Practices of the Future

The merging of medicine with all aspects of the internet, personalised numerical modelling of biological functions, cells and organs and the data sciences, including artificial intelligence, will be creating precision medicine and breaking down the barriers within the health system. This digital medicine will create a new form of relationship between the patient and the care personnel, shifting the centre of gravity of health from the hospital, which is useful for medical R&D in its collaboration with the industrial sectors, to the GP's surgery. Via health data sensors, it will expand the health landscape to include the home and the workplace.

**T**he scope of digital medicine has yet to be determined, primarily in two areas. The first is telemedicine (e@medecine) the aim of which is to decentralise the patient/carer interface. The second is that of medical practice based on an analysis of the digital representation of the patients and their inclusion in the internet of patients, by calling on data sciences and modelling. It is this latter area that will mainly be covered here.

## The Building Blocks: Digital Patient and Digital Physician

The digital patient (avatar or digital twin) is a set of data consisting of all the clinical, biological, anatomopathological, functional exploration and imaging information that can be transformed into digital data. These data come from connected sensors, from the digital transformation of clinical

data collected from the physician and information gathered through specialised radiology, biochemistry or genomics instruments, for example, obtained in clinics or at the hospital and which can be considered as “living-digital converters”. Over and above the data resulting from the digital transformation, the digital representation contains annotations which can evolve with time and which place these data in the context of the knowledge available at the time. The annotations can be taken from collections of scientific articles, from specialised databases or from computer programmes incorporating the patient’s data into a digital model. The digital representation also includes an integration diagram that can be visualised as connected graphs of data, annotations and concepts.

The use of this digital representation in treating the patient exceeds the capabilities of the physician, who needs to be helped by algorithms (digital doctor). These algorithms will attempt to infer a diagnosis from the patient’s data in the context of a list of illnesses, or nosography. For certain illnesses, this nosography can be based on a statistical analysis of data in large cohorts of patients (see box by Professor Marion Leboyer). In general, the result of the algorithms will be a list of illnesses classified in order of likelihood. The algorithms will also be used to propose therapies. They will be based on the results of published clinical trials, which are ad-

mittedly robust but are lacking in personalisation. They will therefore, if possible, be supplemented by collections of digital patients (Data Collectors and Analysers, CAD). In this context, they will project the patient’s digital representation into the space of other patients in order to identify digital families of similar cases. Based on the clinical evolution of these patients taking different treatments, they will propose documented scenarios. Moreover, datamining the CADs will make it easier to choose the right drugs if pharmacovigilance and pharmacogenomic data are incorporated. These crucial goals for the medicine of the future are the subject of initiatives in France, Europe and elsewhere (see box on ITFoC).

## CEA, a Key Player

An analysis of the digital medicine value chain makes it possible to identify its key segments (see Fig. 1). These segments have very different maturity levels: from that to be created from scratch (such as digital infrastructures for health data storage) to that which is operational in research (for example, high throughput sequencers or MRI), but which require certification or regulatory accreditation. The detailed analysis of these segments allows the identification of activity sectors in which CEA’s unique expertise and technologies could play a key role, in line with its valorisation model and positioning it as

a crucial player in the technologies for the medicine of the future. These fields concern the development of new technologies for data capture, management and analysis. In all these sectors, CEA has competitive assets embodied by one or more of its divisions: Fundamental Research Division, Technological Research Division, Military Applications Division (see FAST box).

### Development of Innovative Technologies for e-medicine and Integration of Medical Devices into the Digital Transition Process

CEA, more specifically the Leti and List institutes of the DRT, have undisputed know-how in the development and integration of digital tools, in the production of sensors and in the creation of cyber-physical systems for medical applications. They were notably developed for monitoring of physiological constants (such as blood sugar levels, see p. 27), or control of the brain-machine interface at Cinatec to propose solutions for patients with reduced mobility (see p. 15). The development of smart robots to help overcome a disability or dependence is also a major goal. Three issues are the subject of intensive study in these institutes. The first aims to ensure that these systems are secure, to protect the patient from data capture or, worse yet, from hijacking of the control of the devices (see p. 41). The second issue is that of overall and context-based optimisation of digital processing which can call on artificial intelligence. The third is that of the integration of technologies (nanotechnologies, biotechnologies, data technologies) into devices and the incorporation of these devices into the Internet of Things and the data they generate into the Internet of Patients.

### Big data Management and Analysis

From the generation of high-quality data up to its analysis, CEA has know-how, expertise and knowledge that position it as a recognised player.

It is first of all recognised for the generation of high-quality data, with the role of operator of technological analysis platforms for multimodal “omic” and phenotype characterisation of patients. We could mention the examples of the National Centre for Human Genome Research (DRF/Institut Jacob) for genomics, the ProFI national infrastructure hub (DRF/BIG) for proteomics, the Metabohub national infrastructure hub and neuro-imaging with the CATI project at NeuroSpin (DRF/Institut Joliot).

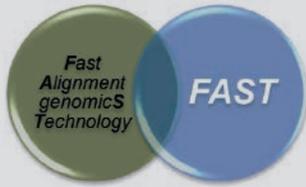
The methods for producing, archiving and ana-

<https://itfoc.eu/> →

## The IT Future of Cancer Project (ITFoC)

Over the last decades, we have made major progress in diagnosing and treating cancer, but these diseases remain one of the leading causes of morbidity and mortality worldwide. Comprising 17 academic and industrial partners from six countries, and coordinated by CEA, the European ITFoC project aims to provide “the right drug to every patient”. It proposes to develop an approach based on a deep molecular characterisation of tumour and patient as input to digital patient models, allowing to explore effects of all therapy options. ■





## The Top Down FAST Exploratory Programme

Launched in 2018 under the France Genomic Medicine 2025 Plan, the FAST programme (Fast Alignment genomicS Technology) brings together the skills of the DRT and DRF to study various means of improving the treatment and exploitation of sequencing data (efficient alignment, automatic annotation) on the one hand and integration and utilisation of various data (structural and functional genomic, clinical, imaging data) on the other. ■

lysing the various data generated are specific to each technological approach but share certain characteristics placing them firmly within the scope of Big Data: their Volume, which requires appropriate infrastructures for archival and analysis, the Velocity of acquisition, their Variety (broad spectrum of phenotype investigations) and their Veracity, guaranteed by the standardisation of operational procedures and the input of the data into public databases.

CEA, or more specifically the DAM, has developed internationally recognised expertise in the management and archival of Big Data and high-performance computing. The infrastructures operated at the TGCC by the DAM are already offering data management and archival services to various national and European academic communities, in the fields of the climate (Pierre Simon Laplace Institute with the international exercises of the IPCC) and the life sciences (data storage and processing platform of the France Genomics infrastructure). The DAM is also open to digital works for various industrial sectors (CCRT).

The multidisciplinary issue of integrating heterogeneous data requires that their specificities be taken into account in order to establish links between them. The challenge consists in integrating experimental data, using biological knowledge with computer tools (databases, networks, standards, data production and analysis path) and mathematical methods (data mining, learning, graphs, visualisation). The DRF (Pariétal Team at Neurospin, CNRGH) and the DRT with List, have developed specific skills over a number of years.

Once these data have been stored and integrated, it is then possible to run a cross-analysis on them, resulting in decision-making tools (personalised diagnosis and therapy). These analyses are based on statistical methods and artificial intelligence, as well as on multi-scale modelling. Collaboration between DRT and DRF or with Inria, has led to the

acquisition of specific know-how in bioinformatics and artificial intelligence, implementing original data analysis methods based on multivariate statistical methods, learning (Machine Learning, Deep Learning) and data mining, including Text Data Mining.

## How to Increase the Chances of Success of Digital Medicine?

Like any major transition, the introduction of digital medicine into the health care system will be exposed to the unpredictability of the changes to the ecosystem bringing together the patients, the health care professionals, the academic and industrial R&D players and the public authorities. We know that in circumstances such as these, an in-depth analysis of the cultural and economic impacts is critical. This analysis has not yet been carried out but, among the measures that will be required, training of the professionals and information of the public are vital.

The development of digital medicine will transform the medical art. Even if in-depth and technical understanding of the algorithms is not necessary, the practitioners will need to learn the principles of data analysis and modelling of decision-making systems and processes, with a level of confidence comparable to that they today give to their own experience. The way in which the patient is informed of the significance of the digital approach must be tailored to each individual case. As the practice of digital medicine is by its very nature multi- and inter-disciplinary, new players such as engineers holding qualifications in multiple fields could find a place in the health care system.

Finally, the ethical question will remain an essential one for a long time to come. The quality of this aspect will clearly determine the way in which digital medicine is viewed in the future (see p. 4). ■

© Fondation FondaMental



**Prof. Marion Leboyer**  
(Université Paris-Est Créteil, AP-HP)

"If psychiatry is to be a part of this drive towards precision medicine, we will have to supplement the subjective diagnostic categories based on symptoms with an objective, precise nosography based on a global analysis of the patient's particularities.

We will need to follow the path traced by research into cancer and cardiovascular diseases, where mortality has been reduced thanks to targeted therapies prescribed for homogeneous sub-groups of patients identified using specific biomarkers.

The classifications of psychiatric disorders are today based on the descriptive collection of behaviours with no objective validation or markers to create a stratification of patients, which leads to the consideration of heterogeneous groups of patients affected by overlapping psychiatric disorders and comorbidities at various stages of progression.

It is however unlikely that isolated markers could be valid predictors of diagnostic sub-groups or the response to therapies.

We will have to combine multi-mode biomarkers for precision psychiatry with the end goal of improving the prognosis for patients who respond only partially to the therapies".

•  
BY **JÉRÔME GARIN**

(Fundamental Research Division)

AND **PATRICE CAILLAT**

(Technological Research Division)



**Jérôme Garin** is head of CEA's Biosciences and Biotechnologies Institute in Grenoble (BIG).



**Patrice Caillat** is in charge of strategic marketing in the field of medical devices (Biology and Health Technologies Department) at CEA/Leti.

# Mimicking the living

The production of “biological companions” will impact our understanding of life, enable us to conduct personalised pharmacological tests and set us on the road to regenerative medicine.

**I**nterest is currently growing in the development of organ substitutes which could act as “biological companions”. The first developments in this field were launched a decade ago and concerned the design of microfluidic chips for mimicking a particular biological function of a tissue, such as the barrier between the alveoli of the lungs and the capillary blood vessels [1]. Since then, the number of scientific publications on this topic has grown considerably, leading to the description of two main types of biological companion families: Organs-on-a-chip and organoids.

An organ-on-a-chip is a miniaturised device, with a design inspired by the architecture of a human organ, in order to mimic its physiological functions [2]. The use of microtechnologies enables cell structures to be

perfused (microfluidics) and the physical and biochemical environment of the cells to be controlled in order to obtain the desired multi-cell architecture (see box below).

Organoids however are “mini-organs” or “mini-tumours”, obtained from stem or progenitor cells, placed in a 3D hydrogel culture mimicking the extra-cellular matrix [3]. Co-cultures of different types of cells are generally used. The concept is to allow the cells to organise themselves into a functional tissue, mainly by adjusting the supplements added to the culture medium (see box p. 33).

The biological companions will be all the more pertinent if we are capable of vascularising them in order to reflect as accurately as possible the situation found

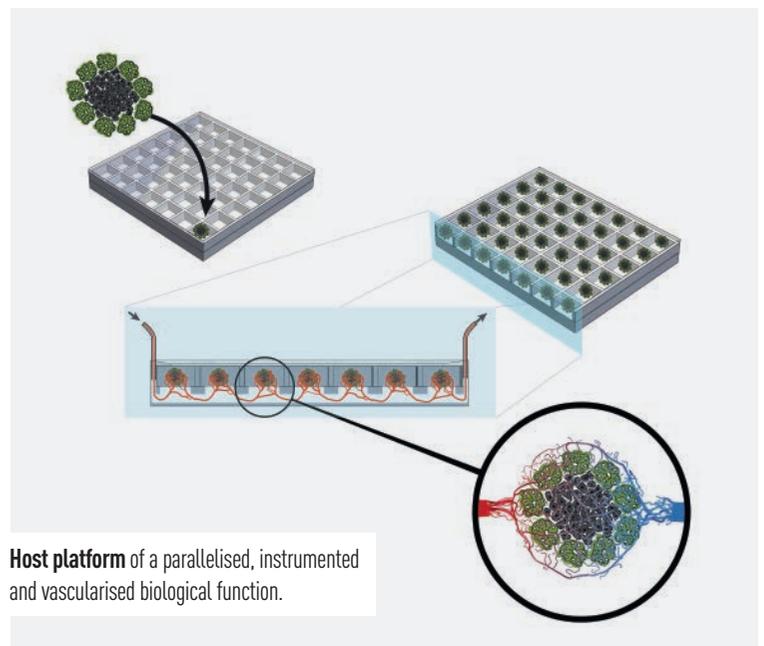
## New Generation Microfluidics

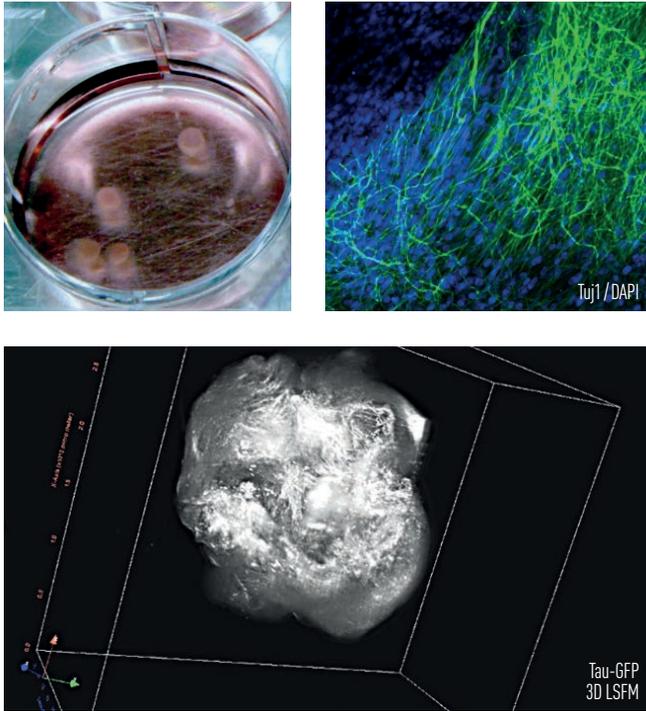
BY **FABRICE NAVARRO,**

Head of the Microfluidic Systems and Bioengineering Laboratory (Biology and Health Technologies Department) at CEA/Leti.

Microfluidics encompasses a range of disciplines aimed at studying and manipulating fluids in media comprising micrometre-sized channels derived from micro-manufacturing techniques.

Microfluidics has really taken off in the past twenty years, driven in particular by the development of DNA chips and “laboratories on a chip”. New devices are today accessible. They are capable of offering the cells a suitable environment for their growth while also guiding it, enabling organs-on-a-chip to be developed. The organs-on-a-chip are equipped with micro-sensors for multi-parameter, highly parallelised monitoring and will increasingly mimic miniature human organs. ■





## The Search for Proofs of Concept

BY JEAN-PHILIPPE DESLYS,

Head of the Prions and Atypical Infections Study Service (CEA Jacob Institute).

Brain organoids, or “mini-brains” can be created from reprogrammed patient cells (iPS – Induced pluripotent stem cells), thus paving the way for modelling and studying the pathology of a specific individual. A cell engineering project was thus developed in CEA’s Prions and Atypical Infections Study Department (DRF/Jacob Institute) in partnership with Sup’Biotech. With these organoids, proofs of concept are being sought in various pathologies such as Creutzfeldt-Jakob, Alzheimer’s and Parkinson’s diseases, frontotemporal dementia, or creatine deficiency. ■

**Top left:** Culture of brain organoids in a Petri dish.

**Top right:** Green fluorescent labelling of neural cells within an organoid with the anti-Tuj1 antibody and blue labelling of nuclei (DAPI).

**Down:** 3D reconstitution of a brain organoid expressing the transgene of the human Tau protein mixed with the GFP protein (light sheet microscopy).

in humans. This vascularisation will be provided or guided by technology in the case of organs-on-a-chip, while it will take place spontaneously for the organoids. Meeting this challenge will bring us closer to the organ’s physiological response, legitimising the use of these devices in the development of drugs, to help with the therapeutic choice or to envisage the regenerative medicine of tomorrow.

### In terms of applications, at least four major fields can be identified:

■ **The study of fundamental mechanisms and physiopathological processes.** Multi-parametric characterisation of a biological companion will make it possible to discover the essential molecules and parameters that must be controlled in order to come close to the normal physiological functions of the organ being mimicked. Studying the alteration of these functions, regardless of the origin (mutated cells, infection, drug molecule), will complete our knowledge of the physiopathological processes which can affect the organ [4];

■ **Assistance with pharmacological screening.** The biological companions will allow the search for candidate drugs capable of correcting a malfunction. They will also help achieve a better understanding of

the mechanism underpinning the action of a pharmacological molecule, which is needed when marketing any new drug;

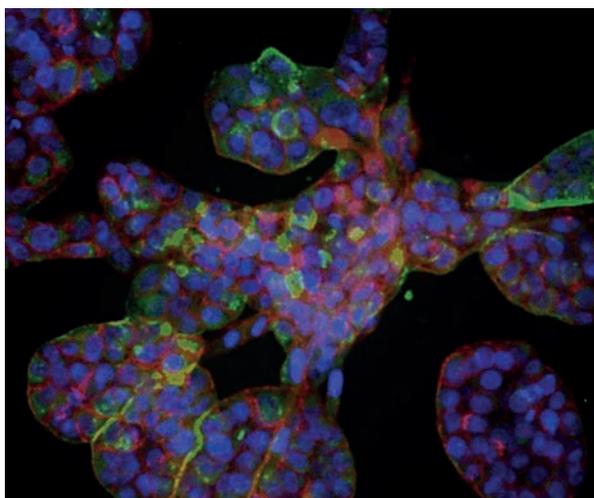
#### ■ Help with personalised therapeutic choices.

In oncology, the cells taken from a patient’s tumour biopsy will be used to manufacture a biological companion. This will then be usable for testing the molecules most effective in treating the tumour. We are here entering the realm of personalised medicine;

■ **Regenerative medicine.** Even if this is still some way off, the controlled and reproducible manufacture of functional organ substitutes will be a significant step forward in regenerative medicine, the goal of which is to replace or repair a defective organ (see boxes p. 34).

The biological companions will also contribute to the digital revolution under way in the field of health. The processing of massive amounts of data produced by “omic” approaches and quasi-continuous monitoring of physiological constants or biochemical parameters measured on the patient will make it possible to develop general digital models of human pathologies. At the same time, the ageing of the population and the correspondingly large number of pathologies will make these models increasingly complex to create

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**Organoid of an exocrine gland**, observed by confocal microscopy. Nuclei appear in blue, actin (cytoskeleton) in red and laminin V (extracellular matrix) in green.

## Towards the Engraftment of Organoids

**BY XAVIER GIDROL,**

Head of the Large-Scale Biology Service (CEA Biosciences and Biotechnologies Institute in Grenoble)

By growing co-cultures of mesenchymal stem cells, endothelial cells and progenitor cells of the adult organ (skin, pancreas, for example), the Biomics team is relying on the 3D self-organisation potential of these cells to generate vascularised organoids. These organ substitutes, possibly obtained with patient cells “repaired” by gene therapy, could eventually be grafted onto the patient to partially and temporarily restore a deficient physiological function while waiting for the availability of an organ transplant. ■

and qualify. This development goes hand in hand with the crucial need to adapt to individual cases. For example, the success of the “Diabeloop” device in treating diabetic patients is based on its ability to adapt a general digital model to a specific patient in real time (see p. 27). However, the impact of the digital approach to health will be limited if the models generated cannot be tested. There is no doubt that in

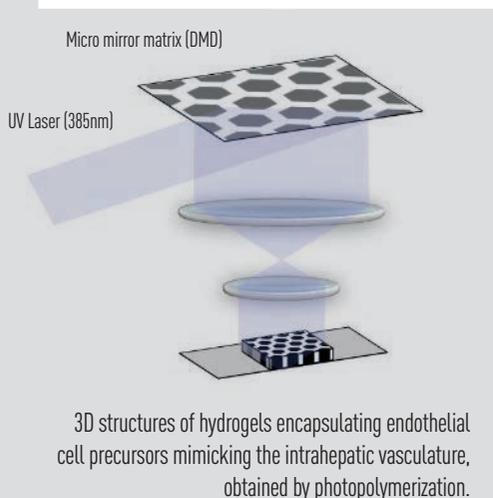
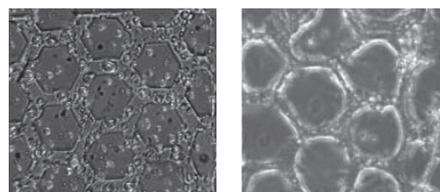
the coming years, progress in cell engineering and microtechnologies will make it possible to produce biological companions that are increasingly “faithful” to the mimicked organs. The analyses carried out on these biological companions will thus generate data which will be increasingly pertinent, enabling the digital models guiding the care given to the patients to be optimised. ■

## Mimicking Liver Structures

**BY ALEXANDRA FUCHS,  
AND FRANÇOIS CHATELAIN,**

Researchers at CEA.

In the Cell Therapy Unit at Saint Louis Hospital, 3D stereolithographic bio-printing of primary cells and hydrogels is being explored in order to reconstitute hepatic, vascular and biliary tissue structures mimicking the liver for regenerative medicine clinical applications. The aim is to create a controlled 3D micro-environment favourable to the auto-organisation of precursor cells and their maturation into functional tissue. ■



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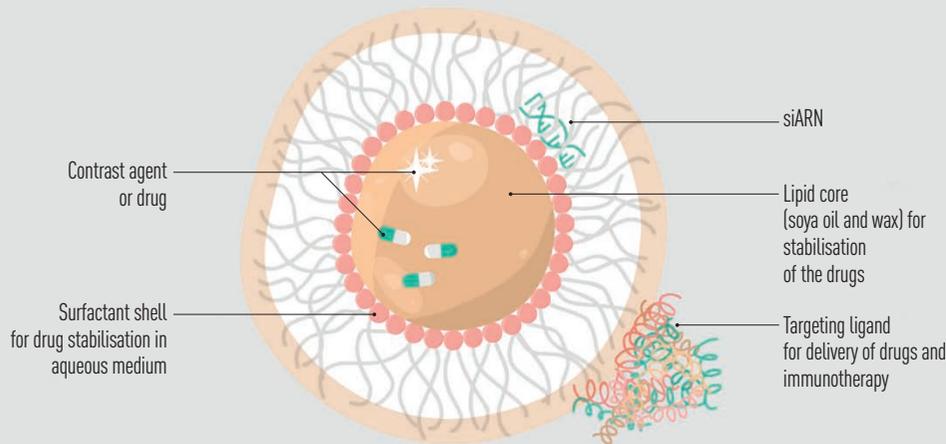
[5] N. Picollet-D'hahan, et al. A 3D toolbox to enhance the physiological relevance of human tissue models. Trends in Biotech. 2016; 34:757-769.

### Mesenchymal stem cells

These cells are present in the mesenchyme (connective tissue) of the embryo and are capable of becoming many different types of cells: Bone, muscle, fat or cartilage cells. They exist in very small quantities in adults.

### Endothelial cells

They line and protect the inner wall of blood vessels.

**Fig.1** : Diagram illustrating the Lipidot<sup>®</sup> technology and its applications

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**BY**  
**PASCAL MAILLEY**  
 (Technological Research Division)



**Pascal Mailley** is research director and scientific director at the Biology and Health Technologies Department of CEA/Leti.

# Electronics and living organisms

For several years, CEA has been working on interfacing living organisms with electronic technologies and/or micro-nanotechnologies. Its research ranges from monitoring vital functions or the metabolism to the delivery of active substances. This scientific position enables it to interface various compartments of the body: the skin, with sensors worn on the person or smart bandages, the subcutaneous compartment, with the development of micro-needles, or the whole body with lipid carriers, the lipidots<sup>®</sup>.

## Lipidots<sup>®</sup> lipid nanoparticles

The Lipidots<sup>®</sup> lipid nanoparticles are colloidal systems with a controlled diameter of 50 to 120 nm, manufactured from an oily core (mixture of saturated and unsaturated triglycerides) encapsulated in a molecular shell (Fig. 1). This formulation, which enables them to store active hydrophobic molecules in an aqueous medium with increased bio-availability, enables them to be used as molecular carriers to deliver drugs for example.

For about ten years, CEA has been developing Lipidots<sup>®</sup> technology, initially designed for in-vivo fluorescence imaging applications. For this purpose, tracers had to be developed offering high-quality brightness factors at the same time as adequate bio-compatibility for future clinical application [1-3].

Since then, these lipid particles have been extensively characterised from a physico-chemical viewpoint [4, 5] and have been the subject of several pre-clinical demonstrations for applications in oncology ranging

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from the imaging of solid tumours [2, 6-11] to the delivery of therapeutic molecules, such as photosensitisers [12, 13]. Bio-distribution studies have shown that they accumulate in the liver through the liver sinusoids, in solid tumours through the permeabilised endothelium of the tumour microenvironment (EPR effect) and also in the lymph nodes and steroid hormone biosynthesis areas [1, 2, 8, 14]. Since 2012, bio-therapeutics such as siRNA or antigen peptides/proteins have also been carried for applications primarily in the field of inflammatory disorders or infectiology (European NAREB and NEW DEAL project). This approach notably led to the development of a new vaccine methodology based on the administration of the p24 protein, used as a model antigen of the AIDS virus, validated by a 7-month pre-clinical trial [15].

In addition, the Lipidots® manufacturing processes were scaled up in a pilot unit enabling large volumes of concentrated nanoparticles to be prepared (> 500 ml) and the entire physico-chemical characterisation chain needed to control them was developed. We are nearing industrial level transposition with a broadened panel of applications ranging from contrast imaging, from vaccination to therapy.

## Biosourced biomaterials

Synthetic or biosourced biomaterials are used in implantable or injectable form, for medical purposes, to replace or restore parts or functions of an organ or tissue. They must evidently be biocompatible and contain no toxic substances. Most of the available biomaterials have been produced to deal with significant and regular mechanical stresses (prosthetics). At CEA, in the light of our involvement in the field of drug delivery, our activity focused on formulating and implementing active biosourced biomaterials (derived from plant or animal biomass). Various materials have been studied, including polysaccharides, collagen, or nanocellulose. This activity involves strong strategic partnerships with leading research institutes, who are experts in the functional synthesis of biomaterials.

If the lipid nanoparticles developed at CEA improve the delivery of active molecules thanks to the increase in their stability and their solubility with active molecules, there are nonetheless limits, such as the slow and controlled kinetics of drug release. The encapsulation of the nanoparticles in an appropriate matrix - hydrogels or networks of bioresorbable biopolymers - would appear to be a good solution for improved control of the release kinetics of the active molecule. Various composite biomaterials incorporating biopolymers and lipidots® have been developed and the incorporation of nanoparticles

containing organic fluorophores (used as the drug model) in hydrogels produced from carboxymethyl cellulose cross-linked with polyethylene glycol has been demonstrated [16]. The release kinetics of the nanoparticles can then be controlled by adjusting their diameter and/or the hydrogel crosslinking rate. In another development, cross-linked CMC was replaced by an interpenetrated polymer network, allowing improved control of the porosity and mechanical properties of the aerogels formed [17]. These various biomaterials could be used as skin patches or post-surgical implants in order to promote the implantation or repair of damaged tissues.

Finally, we are working on producing materials capable of minimally invasive or implanted delivery of active ingredients. Soluble micro-needles were developed by moulding bioresorbable polymers as well as bioresorbable filling gels (intended for cerebral exploration surgery following cancers).

Lipidots, lipid nanoparticles for the delivering of drugs or fluorescence imaging



© Godard / CEA

A 3<sup>rd</sup> area of research around biomaterials concerns the encapsulation of functional cells. For several years, CEA has been developing a method for encapsulating pancreatic islets in alginate gels, which could allow the stealthy reimplantation of healthy islets in patients suffering from diabetes. This research is being carried out under the European BioCapan project, notably in collaboration with Grenoble Alpes University Hospital and aims to achieve routine production of these islets to restore pancreatic functions in diabetic patients [19]. This work also acted as a basis for the development of an organ-on-a-chip to study the secretome from an artificial prostate grown in a microfluidic system [20]. This work paves the way for the study and early diagnosis of prostate cancers.



Fluorescent tracers for imaging

© Cottet/CEA

## (Bio)electrochemical sensors and effectors

Bioelectrochemistry is an essential method of transduction for characterising most of the exchanges that take place inside the human body, whether metabolic, bioelectrical, or energetic. Two main approaches are used to investigate the body: Electroanalysis and neuroprosthetics (monitoring of bioelectrical signals or electrostimulation)

With electroanalysis, the biological targets are numerous and a variety of research has been carried out, either on in vitro diagnostic devices, or for measurements worn on the person. In any case, they require multiparametric measurement platforms to produce a precise physiological and/or metabolic profile linked to a particular pathology. Our initial work thus concerned the evolution of sodium concentrations and the pH of perspiration, which could be envisaged as biomarkers of the condition of fire-fighters. More recently, amperometric biosensors have been developed to detect lactic acid or glucose [18]. We have also looked at a new class of electrochemical detectors - electrochemical organic transistors - the configuration of which enables several sensors to be coupled within the same bioelectronic structure and thus offer smart multiparametric devices which do not need the measurements to be centralised for processing.

Neuroprosthetic applications (monitoring, electrostimulation and impedance measurements) are based on electrophysical rather than electrochemical measurements, which measure or stimulate a local physical value. Historically, monitoring electrodes were developed for transcutaneous measurements (electrocardiograms, electroencephalograms, etc.). They were highly polarisable (noble metals, carbon) and offered high measurement impedance (and thus a low signal/noise ratio) making them relatively insensitive to low-amplitude, high-frequency bioelectrical signals such as those emitted by the brain.

Then, electrodes referred to as non-polarisable replaced this first generation. However, in order to function correctly, the electrode/skin interface must be perfectly hydrated, hence the use of gels containing physiological concentrations of conducting ions. Although this pre-requisite is relatively well-suited to occasional medical use, the same does not apply to regular, general public applications (neuro-feedback, relaxation) which require dry electrodes that are easy to apply without having to shave the head or be coated with gel. This is the case with the EEG headset developed by CEA. Even more recently, we demonstrated the benefits of working on new and even lower impedance electrode materials for intra-cerebral monitoring measurements or neurostimulation. For many years, CEA has been active in the design of innovative electrode materials with high interfacial capacity and/or intrinsic reactivity, such as electrodes nano-textured with platinum black, or carbon nanotubes [21], iridium oxide (INTENSE project), or PEDOT (European INFORMED project). Owing to its considerable resistance to corrosion and its very high biocompatibility, nanocrystalline boron-doped diamond has also been extensively studied at CEA for the production of neuroprosthetics, notably for application to the artificial retina (European DREAM and NeuroCare projects [22]).

## And tomorrow...

Future developments are at the crossroads between these various research fields, with hybrid delivery systems combining Lipidots® technology and biosourced and bioresorbable biomaterials, or the development of bioresorbable transient biosensors for post-surgical monitoring. These objectives are ambitious ones, but CEA unquestionably has the assets needed to meet the challenges of the interface between micro- nanotechnologies and the living organism. ■

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**Régis Guillemaud** is Deputy Head of the Biology and Health Technologies Department at CEA/Leti.

**ECG**

Electrocardiogram.

**SpO2**

Peripheral oxygen saturation.  
 Measured to estimate the quantity of oxygen in the blood.



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# Connected Devices Working for the Patient

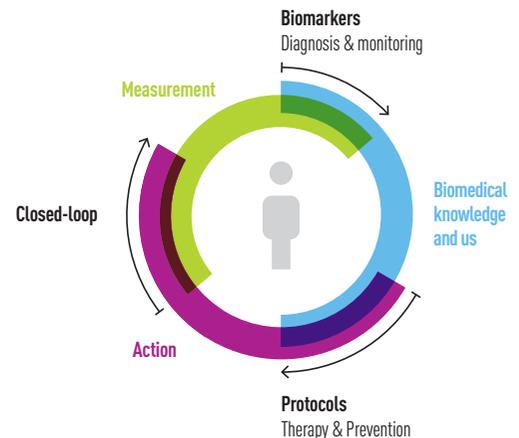
The explosion in the number of connected objects is a feature of our daily lives, with many objects in our environment becoming connected (market up +35% per year for bracelets). This change also mirrors the transformation of approaches to health, with the development of 4P medicine (Preventive, Predictive, Personalised, Participative) and the search for solutions centred on a patient who is constantly more involved.

**W**e are witnessing a two-fold change. On the one hand, connected hardware and software objects, initially developed for sport and well-being, are obtaining Medical Device (MD) classification, such as the recent Apple Watch 4, which measures the **ECG** and proposes a cardiac alert function. The MDs, which used to be analogue, are now digital and are increasingly able to communicate. These MDs, initially connected to a proprietary network and a dedicated platform, now use an internet link enabling the user to directly access the applications and services they propose.

## Digital Markers and Control Loop

The connected MDs are involved along the entire patient health care chain (prevention, diagnostic, therapy, therapeutic follow-up). The first step is the input of information by the patient and/or the medical team, with smartphones and tablets being the first-level data collection platform. To this information can now be added data taken from connected bio-sensors worn by the person or placed in their environment. These devices provide either a measurement of physiological parameters (weight, physical activity, heart rate, blood pressure, **SpO2** measurement, etc.), or a measurement of biological parameters based on a sample (blood, urine, breath, etc.). Processing of this information (in association with biomedical knowledge and knowledge of usages, whether processed locally or not) will automatically (via AI algorithms) produce “digital” markers of use for decision-making and/or therapeutic measures. Information (alert, advice, instruction, prescription, etc.) could then be sent to

the patient with or without intervention by the medical team. A “closed loop” system is thus created, which could potentially be a control loop, for optimised health care. In this feedback loop, the processed information can be used to control connected effectors, worn by the patient or even implanted, such as a pump delivering an active ingredient, or a stimulator [1].



## Expected Benefits

Technological progress (miniaturisation, automation, connectivity, computing power, etc.) is constant, leading to the marketing of less invasive, more secure, smarter and easier to use connected DMs. What are the real benefits to the patient and the care personnel? How do these new tools accompany the transformation of medicine? We will look at three main benefits.

© Avalun



The LabPad® pocket laboratory from Avalun

## ← LABPAD®

LabPad® from Avalun is a pocket laboratory which enables various biological measurements to be taken in the home, health centre or by a health professional. Measurement of blood coagulation time for monitoring chronic patients taking anticoagulants has received CE approval and is being marketed.

A drop of blood from the patient's finger is enough to obtain the result in just seconds. Together with the biological analysis laboratories and health professionals, the patient's treatment is thus precisely and immediately adapted, reducing the risk of haemorrhage.

The principle of the LabPad® is based on an advanced optical microscope technology using a CMOS sensor, which captures light diffraction patterns. CEA/Leti developed a first demonstrator for monitoring cell dynamics and thus measure the coagulation time. The blood sample is collected in a small volume single-use plastic device (less than five microliters), through microfluidic channels, and containing an appropriate reagent. The single-use device is then placed in front of the optical sensor for the measurement. Clinical validation was carried out with the CHU Grenoble Alpes.



## ← CHILDSPLAY

Bacteremia is the main cause of child mortality in Sub-Saharan Africa. CEA/Leti has developed an automated, portable laboratory capable of rapidly (< 2 hours) identifying a bacterial infection, allowing diagnosis in areas remote from medical analysis centres. This device comprises a microfluidic cartridge containing the biological protocol and a reader.

The biological protocol was developed by the Pasteur Institute and the sample collector by 'Doctors without Borders' (MSF). Automated analyses of blood samples collected in hospitals in Africa were carried out on a number of bacteria of interest. By extracting DNA from 1 ml of blood, plus LAMP type isothermal amplification, the validation campaign carried out at the Pasteur Institute demonstrated that the system was working satisfactorily. The next step is to optimise the biological protocol for detection on real samples.

### Greater Accessibility to Information, Faster Diagnosis

The ability to take physiological measurements on the person during the course of their daily life and carry out remote biological analyses (patient's bedside, at home, in the field) by means of worn or wearable, connected MDs, improves access to pertinent medical measurement data and thus the quality of the medical response. Connected MDs are contributing to the development of ambulatory medicine, from the hospital to the home. They are participating in the health response for medical deserts and in emerging countries, which are under-equipped in terms of health infrastructure. Thanks to a rapid diagnosis, made possible in the field, they make for safer emergency medicine.

### Improved Acceptability, Improved Observance

The lack of observance (patient actually taking the proposed treatment) is the main cause of therapeutic failure (30 to 50% of patients do not follow the prescribed treatment). The availability of connected MDs, which are easier to use thanks to optimised ergonomics, makes for easier observance. MD miniaturisation, whether worn or implanted, made possible by developments in micro-technologies and microelectronics, is improving patient acceptance and comfort. There are many examples of this trend, such as pacemakers, the transition from the Holter monitor to the cardiac patch, automated wrist measurement of blood pressure and so on.

#### Bacteremia

Presence of bacteria in the bloodstream.

#### LAMP

Loop-mediated isothermal AMplification. DNA amplification technique.

#### Bacteremia

Portable device continuously recording an electrocardiogram for at least 24 hours.

[1] "Utilisation des objets connectés en recherche clinique", *Thérapie* (2018) 73, 41-51

## APNEABAND



The Apneaband demonstrator



© Fotolia

APNEAband is a device worn on the wrist which detects sleep apnoea. Gone are the days of spending the night with a battery of sensors attached to the body! Sensors embedded in the bracelet monitor various physiological parameters such as the heart rate or oxygen saturation of the blood. Combining these indicators by means of automatic processing enables the physician to establish a diagnosis. In collaboration with the Grenoble Alpes University Hospital and the Hospital Clinic of Barcelona, CEA/Leti is working on creating a database, the precondition for developing the treatment software. This portable, non-invasive device, in association with an advanced automatic signal processing algorithm, will facilitate access to a sleep apnoea diagnosis and monitoring of the effectiveness of the medical treatment.

### CERITD

Centre for study and research on the improvement of diabetes treatment.

### ACKNOWLEDGEMENTS

#### FOR THEIR CONTRIBUTION TO THIS ARTICLE

Prof. Stephan Chabardès (Grenoble University Hospital, Clinatéc) ■ Vincent Poher (Avalun) ■ Erik Huneker (Diabeloop) ■ Sandra Barbier, Patrice Caillat, Pierre Jallon, Laurent Gerfault, Fabrice Navarro, Remco Den Dulk and Elodie Lenuzza (CEA/Leti)

### Continuous Analysis for Improved Therapeutic Effectiveness

For some indications, the possibility of monitoring a physiological or biological parameter continuously, or at least at a sampling frequency far higher than that allowed by monitoring in the hospital or at the physician, is a real change in the quality of diagnosis, treatment effectiveness and the reliability of

therapeutic follow-up. The “Grail” is to be able to automatically regulate the treatment, continuously, with a therapeutic delivery device linked to the measurement (embedded and interpreted) of one or more parameters.

This is notably the case with the Diabeloop®, the first connected and autonomous artificial pancreas which continuously regulates the blood sugar levels of type 1 diabetics (see also page 27).

## Preconditions for Deployment and Future Trends

The successful deployment of these new health solutions will entail the creation of a true infrastructure for sharing and exchanging medical data, to which the digital connected MDs and data analysis tools can connect. This infrastructure will also be essential for a new way of practicing medicine, with a coordinated health pathway, built around the patient.

### To prepare for the future, R&D into connected MDs is being developed in three main directions:

■ Technological developments. New biomaterials are becoming available for the production of flexible devices, stuck to the skin (patches) or applied like a tattoo, or even digestible or integrated into textiles. Particular attention is also being paid to the question

of energy (low-consumption devices, remote-power supply, biocompatible batteries, etc.) and that of the security (hardware and software) of information and how it is exchanged;

■ Patient modelling (digital avatar). This is integrated into the heart of the MD for analysis of data and optimises the personalisation of the diagnosis and treatment while helping with therapeutic education, for more effective, precision medicine;

■ Integration of multiple data, taken from physiological and/or biological sensors, along with environmental sensors (air quality, etc.), to measure the exposome, in association with the patient’s “omic” data. This should open the door to more reliable preventive medicine. ■

## DIABELOOP®

Diabeloop is the first connected, autonomous artificial pancreas. It continuously regulates blood sugar levels and significantly improves the quality of life for type 1 diabetics.

It consists of a continuous blood sugar sensor and a miniature patch pump. Both are connected by Bluetooth to a dedicated smartphone whose algorithms calculate the insulin dose to be injected and transmit the information to the pump, with no intervention on the part of the patient. At the same time, the data are transmitted to the monitoring medical service. Blood sugar levels are far better controlled.

A number of clinical studies have confirmed the effectiveness of the artificial pancreas. The patients undergo a radical change as they previously had to check their blood sugar levels themselves and they now have far less to worry about. They simply need to notify the system of their meals and any sports activities. The device was developed by the CERITD, with a dozen or so university hospitals, in collaboration with CEA/Leti, and is going to be marketed by Diabeloop SAS (see p. 27).



A hand-held artificial pancreas, Diabeloop associates a continuous blood sugar sensor, an insulin pump and a smartphone with a personalised algorithm.

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# Preparing **Very High Confidence Systems**

The global digital transformation currently under way is opening up immense prospects for the creation of socio-economic values in the field of health. In this context, the trust placed in digital systems and their role in the protection of information, environments and individuals, have become a core issue.

**A**ttacks on digital health systems have become increasingly frequent, as illustrated by a number of recent examples: The infection of British hospitals by the WannaCry ransomware, the stealing of 160,000 medical files in Singapore, flaws in the Raven II remote-operation robot or, more recently, vulnerabilities in the Medtronic heart stimulators. The threat is now widespread and increasingly sophisticated, exploiting software vulnerabilities and complex networks. The “attackers” show advanced knowledge of the target systems, including their proprietary components, historically protected by industrial secrecy. These attacks can be for a variety of reasons (to steal data, shutdown facilities or take control of sensitive systems) but they all have significant consequences for the patients, physicians, hospitals, equipment suppliers and governments.

In return, the “defenders” must now regain the initiative to ensure in-depth protection, counter lateral movements and maintain control of their

computer perimeters, or even their digital sovereignty.

The CEA cybersecurity teams are conducting innovation and technology transfer programmes across the spectrum of IT systems, with the aim of assisting the development of the industrial ecosystem in the field of cybersecurity and providing French industry with the technical means of ensuring its cyber-protection. They incorporate advances from academic research with the goal of creating innovative technological platforms, providing concrete, operational solutions.

## **An Internationally Recognised Expertise**

Our teams are producing highly innovative developments concerning key elements of the software security chain, from data protection up to protection of software, networks and their operators. Examples are the awarding of the European ICT-2015 prize for the USEMP semantic analysis demonstrator for privacy protection [1],

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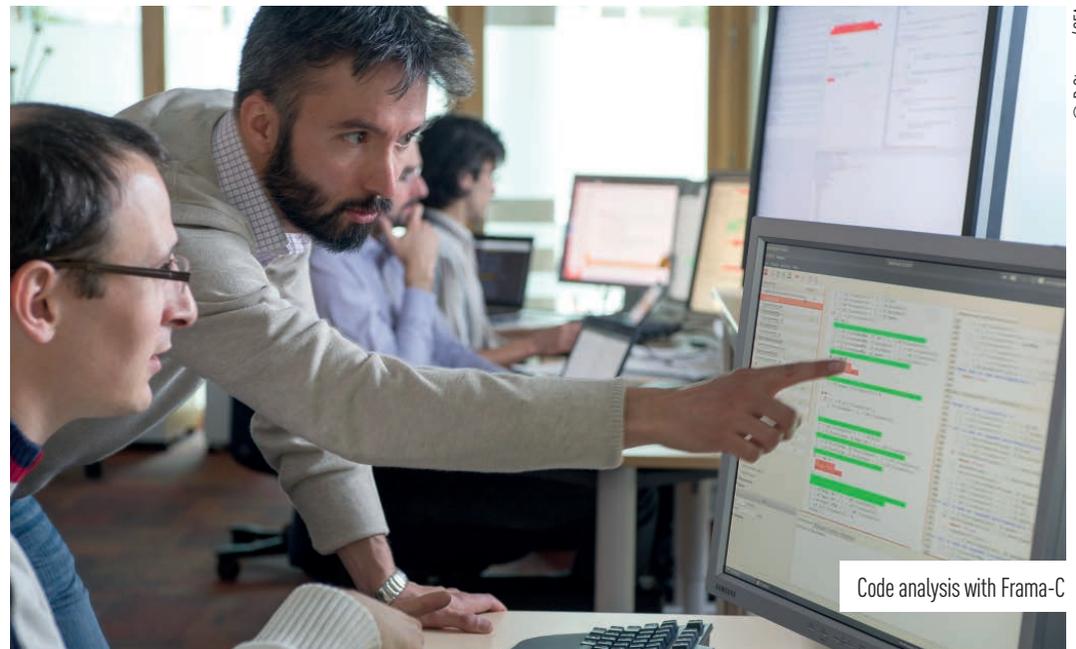


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## **Ransomware**

Malicious software which ransoms personal data.

“The CEA teams are coordinating around structured actions, based on strategic investments, aiming to produce concrete, decisive results.”



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the victory of the Frama-C formal code analysis platform in the SATE V challenge organised by the National Institute of Standards and Technology (NIST) in cybersecurity [2] or the excellent 2nd place of the homomorphic encryption and Cingulata compilation chain teams [3] at the “Genomic Data Privacy and Security Protection Competition” iDASH-2017 (see box) ahead of their competitors from KU Leuven, the EPFL and Microsoft Research [4].

Identification, analysis and the pursuit of disruptive opportunities, as well as building on technological platforms are CEA’s strengths. The CEA teams are coordinating around structured actions, based on strategic investments, aiming to produce concrete, decisive results – such as the use

of advanced analysis techniques to automate the security evaluation of software, the implementation of artificial intelligence to enhance the response capability of network operators, or the use of distributed ledgers and smart contracts to guarantee the integrity of critical data. CEA is building on these technical assets in the form of integration platforms that are unique in France and more particularly made available to the transverse “Global Security” programme.

On the basis of these results, the CEA teams are preparing for the emergence tomorrow of very high confidence digital medical systems, from instruments up to systems, capable of guaranteeing the security of patients, physicians and health data. ■

[1] [www-list.cea.fr/en/media/news/2016/308-november-4-2016-social-media-savvy-users-are-safe-users](http://www-list.cea.fr/en/media/news/2016/308-november-4-2016-social-media-savvy-users-are-safe-users)

[2] [www.nist.gov/publications/sate-v-report-ten-years-static-analysis-tool-expositions](http://www.nist.gov/publications/sate-v-report-ten-years-static-analysis-tool-expositions)

[3] <https://github.com/CEA-LIST/Cingulata>

[4] [www.humangenomeprivacy.org/2017/index.html](http://www.humangenomeprivacy.org/2017/index.html)

## Genomic Information Security

A new challenge for genomics is that of automatic, robust and secure use of the emerging massive sequencing technologies for personalised medicine. The promising applications that result from it require the development of genomic data processing infrastructures which are open – owing to the need to integrate various sources of medical information to make the most of the genomic information, reliable – the medical context demands this, and secure – genomic data being inherently very sensitive. The PPGEN project, which is the result of collaboration between List and the CNRGH in Evry, aimed to demonstrate a phenotype prediction capability which is automatic and secure, for an initial selection of biomarkers of immediate clinical interest. In terms of cybersecurity, the goal was to demonstrate that the genomic information could be processed in encrypted form, in other words without being deciphered by the processing platform, using homomorphic cryptography techniques developed at the List [3]. The initial results are conclusive and received an award at iDASH-17 [4].



# Guaranteeing Optimum Protection

Data for personalised medicine raise certain problems that are in principle specific. The fact that they concern human health, or in other words what is most intimate about us, logically implies major confidentiality constraints, but losing this information could also lead to a delayed diagnosis with dramatic consequences for the patient.

**A**lthough personalised medicine is a new subject, the confidentiality requirements concerning these data mirror problems already familiar in high-performance computing (or HPC). Reliable solutions exist and have been developed and proven for some considerable time within the **CEA scientific computing complex**, on the Bruyères-le-Châtel site.

From a computing viewpoint, confidentiality raises the question of data security, leading to a series of situations which are already managed in other contexts, such as protection of Defence Confidential data used by the TERA supercomputer. Preventing data loss and corruption and thus guaranteeing their security, is also a conventional problem that is for example encountered in the TGCC, which manages experimental data that it is impossible to reproduce, such as that produced by genomic research or climatology.

Data security involves methods linked to cryptography and knowledge of a secret giving access to the data. In our case, the patient's file is totally encrypted and only those authorised (the patient, health care personnel, etc.) must be able to read and modify it. Existing algorithms with international "Top Secret" classification certification offer sufficient guarantees for total confidentiality: To "break" them would take years, if not decades, on the world's most powerful supercomputers. Admittedly, computing power is increasing, but these encryption methods are also adapting, so that the best possible protection is guaranteed. Deciphering them involves a "secret" which will for example consist of the physical possession of an electronic device plus a password. Conventional "strong authentication" can be based on a password composed of a fixed part, known to the user, and an ephemeral, single-use part generated by a small device no larger than a flash drive or a credit card.

Security must also cover the physical failures affecting the media containing the sensitive data. A component can break down, one or more machines

can be damaged by a fire or, more simply, when relocating. The media themselves (disks, flash drives, magnetic tapes) can become unknowingly corrupted and affect the nature of the files they contain. The multiplication of the physical media (a computer centre will contain several tens of thousands of disks and as many magnetic tapes) and thus the increased probability of multiple, simultaneous failures, has led to strategies being defined to mitigate the impact. RAID (Redundant Array of Independent Disks) technologies thus associated several physical disks to create virtual disks usable by the applications. The data are replicated, either partially or in full, depending on the degree of protection required. Convolution calculations are performed at each data access and the result is compared with a reference value, with any divergence indicating physical corruption of the medium and triggering mechanisms to retrieve the undamaged version of the files. These mechanisms are in widespread use in all major computing centres and large office automation installations.

In short, these solutions have proven their effectiveness and can now be used for personalised medicine. ■

## HPC

High Performance Computing

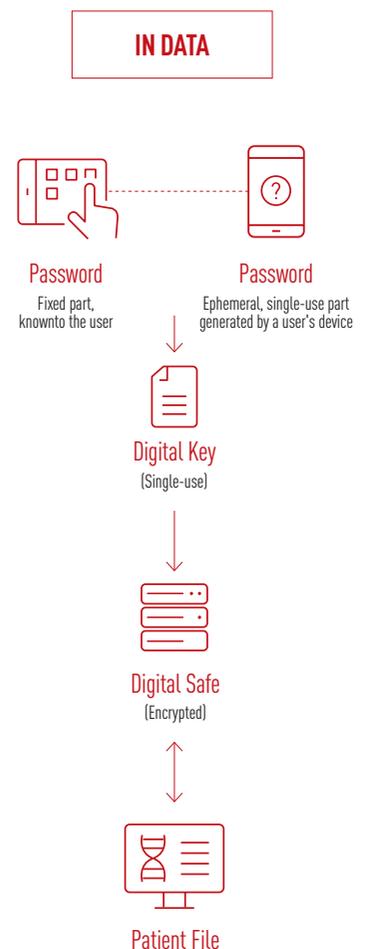
## CEA SCIENTIFIC COMPUTING COMPLEX

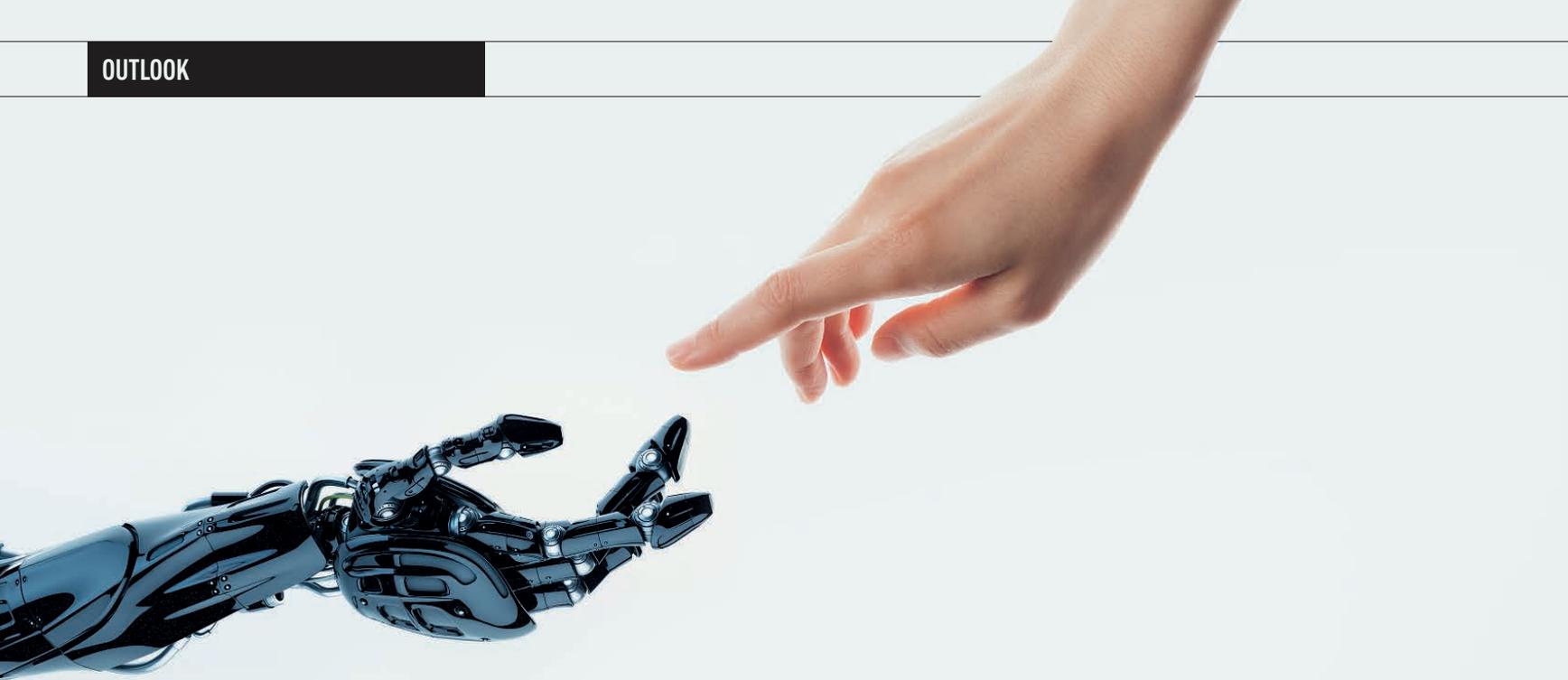
It is located in Bruyères-le-Châtel and includes TERA, an infrastructure dedicated to Defence programmes, as well as the TGCC (CEA's very large computing centre) for academic and industrial research, which houses the CCRT (Research and Technology Computing Centre).

•  
**BY PHILIPPE DENIEL**  
(Military Applications Division)



**Philippe Deniel** is Head of the Storage and Systems Architecture Laboratory (Simulation and Information Sciences Department) at CEA/DAM.





# An Alliance for the Medicine of the Future

Reading this issue offers an extremely complete overview of CEA's activities and confirms the fact that it is today a major technological player, capable of addressing the global challenges of the medicine of the future.

•  
**BY PROF.  
ANDRÉ SYROTA**



**André Syrota** is adviser to the CEA Chairman, Professor Emeritus at Paris Sud University and President of the University Cancer Institute in Toulouse; former President of the Inserm and the Aviesan alliance.

**I**n recent years, we have seen a veritable revolution in the medical sector, owing to the massive accumulation of data, ambulatory surgery, telemedicine and so on. These developments require new technologies (sensors, connected objects, artificial intelligence, high-performance computers, etc.) which favour the emergence of players from sectors other than that of health, with the aim of replacing the traditional drugs, diagnostics and imaging players on the medical scene. These newcomers are, for example, Google (which aims to be a leader in the health arena tomorrow) or industrial firms such as Samsung which is creating the “hospitals of the future” in Korea and around the world.

CEA can and must play an essential role, together with its research partners, with industry and the public authorities, to ensure that France maintains a decisive position and is not simply an importer of health care services. It should be recalled that the French drug industry is a net exporter and that health is considered by economists to be one that will enjoy significant growth in the future. Our country also has major industrial players, be it in drugs (Sanofi), diagnostics (Biomérieux), medical aid (Air Liquide), but also in the digital and software fields (Atos, Dassault Systèmes, Orange Healthcare, Cap Gemini...). And there is a fabric of SMEs, inside and outside the health sector, which hope to take part in the growth of this industry.

CEA has much to offer in positioning itself as a central French player in the medicine of the future. Since its creation it has been involved in biology and health research and has become a recognised player in technological innovations and their integration. CEA has developed exceptional platforms for data acquisition and interpretation; it is also present in the field of 3D cell culture and biological engineering, as well as in the development of cutting-edge digital technologies: Datamining algorithms, modelling, data security and encryption, etc. CEA also has significant storage and computing resources for digital simulation, as well as expertise in the development of specific software architectures and AI for health.

It is also well placed in a number of major national and European programmes such as the European Human Brain Project flagship; it is a key player in the France Genomic Medicine Plan 2025 overseen by Aviesan and a candidate for several other European flagships in the field of health.

CEA can thus legitimately position itself as a major player in the field but it needs to consolidate and boost its academic, hospital and industrial partnerships to enhance the synergies that will enable France to be a key player in the health of tomorrow

## A Deep-rooted Change in the Health Ecosystem

All these new technologies are creating upheavals in medical practice, the role of physicians and health stakeholders and the relationship between the citizens and health, treatment and prevention. Owing notably to the explosion in the volume of data, not only strictly medical, but also environmental, and with information available at all times on the web, medicine is changing from a medicine of disease to a medicine of the patient, at a dizzying speed. The medicine of the future will in particular be the result of the massive integration of technological innovation throughout the care pathway. This is an industrial sector experiencing fundamental change, highly competitive, and displaying considerable economic growth.

The transition to the medicine of the future is underway around the world. The health sector is being transformed with the arrival of new players - more particularly the information and communication technology majors - who, thanks to their strike-power and their tools, will soon be imposing their standards and their products. This is all happening at a pace which is unlike anything traditionally seen in the health sector, historically organised around the time needed to develop a drug (an average of 15 years).

It is essential to fully grasp the profound change to the health ecosystem and to act firmly if France wishes to continue to play a role on the world health industry scene and retain its healthcare independence. At an industrial level, this means being in a position to effect the transformation of our health industry, failing which, we run the risk of being reliant on imported technological solutions produced using standards to which we have contributed nothing.

As pointed out in her foreword by Ms Agnès Buzyn, Minister of Solidarity and Health, the emergence of the medicine of the future also entails a reorganisation of the entire care pathway. This in-depth change to our national system must be backed by a political will and strong oversight, requiring the implementation of dedicated governance.

Over the past two years, several important initiatives have been launched in France by the public authorities, including the France Genomic Medicine 2025 Plan in 2016 [1] and the “Artificial Intelligence” Plan in March 2018 [2]. Recently, at the 8<sup>th</sup> Health Industries Strategy Council meeting [3], the French Prime Minister announced various measures to promote innovation (InnoBio fund) and develop our health industry, with the creation of the “Health Data Hub”. On 18 July last, at the creation of the Innovation Council, which selects the “Major Challenges” receiving 150 million euros in funding per year from the Innovation and Industry Fund, the first selected projects were announced, including one for improving medical diagnoses by means of AI.

Over and above all these actions, against a backdrop of global competition, it is necessary to bring all the stakeholders to the table to share a common strategy and roadmap for research, health and industry. This constitutes a veritable alliance for the medicine of the future bringing together public and private players, administrations and users, from the fields of research, health and industry, for a shared vision of France’s position that will have to be created at the highest level of the State [4]. CEA is clearly situated at the heart of this alliance. ■



“It is essential to fully grasp the profound change to the health ecosystem and to act firmly if France wishes to continue to play a role on the world health industry scene and retain its health independence.”

[1] France Genomic Medicine Plan 2025:  
<http://m.enseignementsup-recherche.gouv.fr/cid132716/8eme-conseil-strategique-des-industries-de-sante-csis.html>

[2] AI Plan :  
[www.enseignementsup-recherche.gouv.fr/cid128618/la-strategie-ia-pour-faire-de-la-france-un-acteur-majeur-de-l-intelligence-artificielle.html](http://www.enseignementsup-recherche.gouv.fr/cid128618/la-strategie-ia-pour-faire-de-la-france-un-acteur-majeur-de-l-intelligence-artificielle.html)

[3] 8<sup>th</sup> Health Industries Strategy Council:  
<http://m.enseignementsup-recherche.gouv.fr/cid132716/8eme-conseil-strategique-des-industries-de-sante-csis.html>

[4] (In French) « 5 propositions pour la médecine du futur - Un enjeu majeur pour la France », Report by Prof. André Syrota and Olivier Charmeil - 26 April 2017 : <https://dg.dk/wp-content/uploads/2017/04/M%C3%A9decine-du-Futur.pdf>

•  
BY  
FRANÇOIS JACQ



François Jacq is CEA Chairman.

“This topic is an inherent part of one of the areas of the CEA development project for the coming years: Digital transition for industry and the medicine of tomorrow, alongside energy transition and support for deterrence.”



## At the Digital/Innovation Crossroads

As illustrated by the articles published in this issue, CEA is fully committed to the development of technologies for the medicine of the future. Contrary to what one might think, chance has nothing to do with it.

**B**acked by its atomic research and, more generally, its research on low-carbon energies, CEA has over the years acquired cutting-edge expertise in electronics and digital systems (for example, for the design, development and manufacture of sensors, control-command systems and so on) as well as in the field of the life sciences, for monitoring occupational health and gaining in-depth knowledge of the impact of ionising radiation. It has also developed a unique capacity for designing, building and managing innovative technological platforms, notably in imaging, genomics, bioenergetics and emerging diseases, for the benefit of the scientific and industrial community as a whole. All of this know-how has also led to the creation of about thirty companies based on technologies developed in the field of health in the broadest sense, representing nearly 10% of the 6,000 active families of patents that CEA today possesses

These assets are at the disposal of the teams in CEA's Fundamental Research Division, Technological Research Division and Military Applications Division, working in the Paris region as well as in Grenoble and Marcoule, on digital convergence in the field of health.

This topic is an inherent part of one of the areas of the CEA development project for the coming years: Digital transition for industry and the medicine of tomorrow, alongside energy transition and support

for deterrence. It must be developed more extensively than it is today and this entails a closer association between the CEA teams and reinforced cooperation with our industrial and research partners such as Inserm, CNRS, or Inria.

We are working on these collaborations because it is clear that developing this medicine of the future requires highly interactive research and innovation: The goal is to ensure a continuum, from the technologies developed at CEA up to medical practices implemented by the health stakeholders. With CEA's expertise in genomic, proteomic, metabolomic analysis, in vivo imaging, but also laboratories on a chip, digital aspects, software architecture and big data, and in collaboration with the other players in the field, the analysis and processing of the data generated in biology and medicine will help expand our understanding of the living world in all its complexity and, eventually, offer health professionals rapid diagnostic tools, innovative therapies but also powerful decision-making aids.

Whether in terms of technology, biology, medicine or digital systems, all of this academic and industrial know-how is needed for the emergence of a sector of excellence in France and Europe, at a time when other states around the world, such as China and United States, are massively investing. ■

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COMING IN MAY

# LATEST NEWS FROM THE OUTER SPACE



## If you want to find out more about the medicine of the future: Follow the on-line masterclass by Jean-François Deleuze!

This masterclass was recorded at the Centre national de recherche en génomique humaine, at Evry, on 29 November 2018 [only in French]

[bit.ly/masterclass-medicine-futur](http://bit.ly/masterclass-medicine-futur)

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