Developing and researching new approaches to treatment in oncology using immunotherapies

Professor Frédérique Penault-Llorca, director of the Centre Jean Perrin in Clermont-Ferrand and president of the Unicancer Immuno-Oncology Group (IO Group).

For many years, immunotherapy has been considered one of the most promising ways forward in the fight against cancer. A number of molecules, such as anti-PD-1, have recently appeared on the market to treat melanomas and lung cancers. In 2016, having taken note of the challenges posed by these new treatment strategies, Unicancer created the Immuno-Oncology Group (IO Group), which aims to conduct research into these new approaches. This cross-disciplinary group, made up of pathologists, biologists, bioinformaticians and clinicians, brings its expertise in tumour groups to Unicancer, which studies different treatment strategies in order to better understand the predictive factors of response to immunotherapies, as well as those that are seen in resistance to these treatments. The group can therefore be called upon to propose ancillary studies on biological samples and promote translational research programmes.

Among the clinical studies supported by the IO Group are the “AcSé Nivolumab” and “AcSé Pembrolizumab” coordinated trials. In 2017, these two studies broadened the AcSé programme for accessing innovative treatments, conducted under the aegis of the French National Cancer Institute (INCa), which enables patients suffering from certain rare cancers to access new treatments, namely anti-PD-1. This is a pioneering programme on an international scale that aims to evaluate the effectiveness and tolerance of these two molecules on the cancers targeted. The first results are expected this year.

Lastly, at the start of 2018, Unicancer developed the Check’Up prospective cohort study, the goal of which is to evaluate predictive factors of response to immunotherapies (PD-1 and PD-L1 antagonists) and to identify predictive biomarkers of their effectiveness.

However, despite the vast progress made in this field over recent years, predicting the factors involved in the individual response to these treatments is still complicated. This is a challenge on which the IO Group is now working.

AcSéCible: a new programme to identify patients who do not respond to immunotherapies

The AcSé “Immunotherapy and rare cancers” projects, conducted under the aegis of the French National Cancer Institute (INCa), aim to provide access to anti-PD-1 monoclonal antibodies, namely nivolumab and pembrolizumab, outside of MA to patients with rare cancers, the characteristics of which give reason to think that they may respond to these treatments. In fact, it has been demonstrated that blocking the link between the receptor at the surface of lymphocytes T and ligand PD-L1 created on the surface of cancerous cells using monoclonal anti-PD-1 antibodies destroys the mechanism by which tumours avoid the organism’s natural immune response.

Thanks to these trials, the indications for prescribing these two medications have been extended to 11 cohorts of patients suffering from rare cancers by basing the treatment strategy on the biological profile of the tumours and not just on the organ concerned originally, as has been the case until the present.

The number of patients who respond to immunotherapies is only around 20%. For the others, the disease either progresses or remains stable. Among these patients, some avoid any early beneficial effect of the treatment. By taking an interest in the predictive factors of early failure in immunotherapies, the AcSéCible translational research programme takes the opposing view of current research strategies that are more often based on the evaluation of developments in the disease and on interpreting the predictive biomarkers of the treatment’s effectiveness. For this reason, the AcSéCible programme, which is not aimed at the same targets as patients (patients for whom the effectiveness of the treatments has not yet been established), complements the Check’Up programme.

The research is based on an ancillary analysis of biological samples, meaning tumoral tissue and blood samples collected from approximately 500 patients treated with anti-PD-1, in order to identify a biomarker or a combination of biomarkers that would make it possible to predict the ineffectiveness of an immunotherapy and avoid administering a treatment that is costly and useless for the patient, on the basis of a clinical-biological characterisation of the patient and his/her tumour.

Thanks to funding from the La Ligue contre le Cancer organisation, it has been possible to take a preliminary step by taking stock of the tumour. The phase of analysing genome and transcriptome samples can soon be launched.

*Marketing authorisation
Microbiota and immunological response: new challenges for the future

A predictive factor of positive effects in treatments for cancer, the bacterial composition of gut microbiota could have an impact on the development and prognosis of some cancers. This is a new area of research that is currently being explored by 17 European teams in the Oncobiome consortium.

Research carried out over the last few years has shown that the microbiota of a person suffering from cancer plays an important role in his/her resistance or susceptibility to chemotherapy or immunotherapy treatment, particularly the anti-CTLA-4 and anti-PD-1 involved in the treatment for melanoma, bronchial cancer and kidney cancer. Some bacteria in the gastrointestinal tract, mobilised during treatments by increasing intestinal permeability, actually stimulate the activation of lymphocytes that are able to recognise the tumoral cells and eliminate them.

Interceding at the microbiota level to increase the chances of successful treatment

A discovery that opens up two major scientific prospects:

• The development of diagnostic tools to identify patients whose microbiota, due to taking antibiotics, co-morbidities, co-medications, etc., are lacking in diversity and are no longer able to activate the immune system (also referred to as “dysbiosis”)

• The restoration of some bacterial strains in patients who were lacking them

To respond to these challenges, three significant approaches have attracted the interest of scientists:

• Faecal microbiota transplant, taken from a healthy volunteer donor or a donor who has responded to the treatment

• The reintroduction of immunogenic bacteria specific to patients who were lacking them, through a capsule

• Intake of nutritional substances rich in probiotics that are able to increase and propagate immunogenic bacteria

Only the first approach is being explored at the moment for Clostridioides difficile infection, as we know that the disease is eradicated by the transfer of gut microbiota.

Two clinical trials that involve transferring microbiota from patients who respond to the treatment to those who do not and are anti-PD-1-resistant are currently ongoing in Israel and the USA for metastatic melanoma.

Gut microbiota: a causal factor of cancer?

Oncobiome relies on data generated by clinical trials promoted by Unicancer to validate the research hypotheses on the impact of dysbiosis on responses to treatment and on the toxicity of treatments for four types of cancer: melanoma, colon, breast and lung.

“The added value of the project’s European aspect”, explains Laurence Zitvogel, clinical oncologist, director of Oncobiome and the Tumour immunology and immunotherapy INSERM research unit at the Gustave Roussy Institute, “is the validation of features of dysbiosis in the prognosis of these four cancers and freedom from the geo-positioning parameter for patients. We are therefore able to put into perspective the impact of genetic and nutritional variables that are difficult to control on the expected result.”

Improving the prescription of immunotherapies

Currently, more than 50% of patients do not respond to immunotherapies, which means that it is essential to identify predictive biomarkers of response to these treatments. The goal of the Check’Up study, promoted by Unicancer and funded by the Fondation ARC, is therefore to identify the predictive factors of response to immunotherapies, namely PD-1 and PD-L1 antagonists.

Launched in 2018 for a duration of seven years, this project is unique in terms of the number and variety of actors mobilised at a national level, notably FCCCs, university hospitals and clinics, as well as the extent of the research being conducted. On one hand, it therefore plans to collect clinical data and data on the response to treatment over a period of five years and, on the other hand, to collect biological samples over one year to carry out immunohistochemical analyses. The objective is to include molecular, immunological and clinical parameters to identify a multi-parameter response signature and to characterise mechanisms of resistance to treatments.

This study includes patients treated with immunotherapy as part of the marketing authorisation. One of the objectives is to find a signature for each organ disease. Today, two patient categories are included in Check’Up: patients suffering from ENT cancers in squamous cells and those suffering from non-small-cell lung cancers.

In short, this study is responding to a major public health challenge, which is to better understand why some patients respond to immunotherapies, while others do not. This will then make it possible to make better decisions regarding which drugs to prescribe.
The Fondation ARC is involved in all areas of research for fighting cancer, in addition to maintaining its level of excellence. It provides financial support to projects and also invests in training and supporting young researchers, in addition to attracting new scientific talent to our country. In order to carry out its mission, it develops collaborations with French and international actors in research, including Unicancer. Nancy Abou Zeid, scientific director of the Fondation ARC, has been involved at every stage.

How did the partnership between the Fondation ARC and Unicancer come about?
In 2012, supporting the development of clinical trials in personalised and precision medicine was identified as a priority field by the Fondation ARC’s Board of Directors. Many initiatives were appearing around the world, so we needed to move quickly. Unicancer proved to be the ideal partner. This strategic choice was the start of a lasting partnership: six programmes have been financed since, totalling almost €13 million, and other projects are in the discussion stages.

What projects has the Fondation supported?
We were the first and only charitable partner of AcSé crizotinib and vemurafenib, led by the French National Cancer Institute (INCa), for patients carrying a genome change targeted by one of these molecules. We supported the SAFIR02 lung and breast trials, which evaluated the genome as a tool for making decisions on treatments, and the EXPRESS study, to understand why some patients respond in the long-term to a targeted treatment. With Check’Up, the last study to date, the research effort opens up a field that strengthens our strategic direction towards precision medicine – immunotherapy.

What was the driving force behind your commitment to this study?
For our foundation, Check’Up was the opportunity to be present in a structured and unified manner when the topic of immunotherapies emerged at the forefront. Our scientific and financial commitment to this project – €3.6 million for the first phase and the intention of supporting the entire programme – is proof of the faith that we have in this unprecedented study, which will have major impacts on treatments. Our strategy for supporting research into immunotherapies is now structured around Check’Up; we are here as part of a system of co-construction.

MyPeBS
This unique project, launched in 2018 by Unicancer, brings together 26 international partners in five “recruiting” countries (France, Italy, Israel, Belgium and the United Kingdom). Its objective is to evaluate a new strategy for breast cancer screening that is based on each woman’s personal risk of developing the illness. Overall, MyPeBS aims at recruiting 85,000 female volunteers aged between 40 and 70 years old and who never had breast cancer.
You can find all relevant information on the website at: www.mypebs.eu

CHECK’UP ELDERLY
Inclusion of the first patient in the geriatric sub-study of the CHECK’UP flagship program: CHECK’UP Elderly. The main objective of this study is to determine the relationship between geriatric parameters and response to immunotherapy treatment (anti-PD-1 or anti-PD-L1) in patients 70 years of age and older in 2 indications: non-small cell lung cancer (NSCLC) and squamous cell carcinoma ENT (SVC).

The DIALOG Intergroup is organizing its fourth scientific day on Wednesday, December 4, 2019 at the Cité Internationale Universitaire de Paris, on the theme «Cognition and Clinical Research in Oncogeriatrics».
Intended for medical oncologist clinicians, geriatricians, as well as all stakeholders involved in oncogeriatrics, its objectives are to inform, promote and discuss themes/projects led by the intergroup’s working groups.
To register: dialog-oncogeriatrice@unicancer.fr
In our network

Centre François Baclesse: working towards the treatments of the future

With its reorganised services, the modernisation of its medicotechnical centre and the development of close collaborations with local research organisations, the Centre François Baclesse (CFB) in Caen is at the forefront of innovation in the field of cancer.

With ISO 9001 certification and renewal of the CLIP² (INCa Early-stage clinical trial centre – Centre Labellisé INCa de Phase Précocé) label, the CFB’s research activity is focused on coordinating research in Normandy and developing projects with a high level of added value.

A major player in the regional organisation of clinical research in oncology

The new CLIP2 label made it possible to strengthen its collaborations by combining with the oncohaematology unit at the Centre Henri Becquerel in Rouen. The Clinical Research and Innovation Delegation is participating in the launch of regional clinical research within the Interregional Group for Clinical Research and Innovation (GIRCI – Groupe Interrégional de Recherche Clinique et d’Innovation). It also supports several pioneering projects in human sciences, as well as preclinical research.

Strategies adapted to individuals and their environment

At the centre of translational research, the cross-disciplinary research unit for the prevention and treatment of cancers (“ANTICIPE” – l’unité de recherche interdisciplinaire pour la prévention et le traitement des cancers) (U1086 INSERM- University of Caen Normandy) structures its work around two areas of research:
- “Cancers and Preventions” is focused on researching prevention strategies depending on the individuals and their environment, especially agricultural, and on cognitive problems caused by cancer.
- “BioTICLA” (Biology and Innovative Therapies for Locally Aggressive Cancers – Biologie et Thérapies Innovantes des Cancers Localement Agressifs) coordinates cross-disciplinary work on ovarian cancer and resistance to treatments. Recent developments explore, in particular, the approach with apoptosis and ex vivo (or organoids) cultures in collaboration with the centre’s biopathology laboratory and the “Genomic and Personalised Medicine in Cancer and Neurological disorders” research unit (UMR 1245), which is made up of researchers in the genetics of cancer, making it possible to ensure a research continuum between biology and the clinic.

Soon, a research centre unique in the world

The implementation of the ARCHADE (Advanced Resource Centre for HADrontherapy in Europe) programme, which aims to develop therapeutic applications from particle physics in an approach that is developing quickly around the world, is one of the CFB’s most ambitious projects.

As the third site in France (after the Institut Curie in Orsay and the Centre Antoine Lacassagne in Nice) to be equipped with proton therapy facilities, the CFB has been welcoming patients treated since July 2018.

In future, the design of a new particle accelerator for the production of carbon ions will make it possible to develop hadrontherapy research projects with the potential – unique in France and the rest of the world – for new treatments for tumours that are resistant to radiotherapy and/or that require a high level of precision due to their position.

This project, which is structured around treatment, education and research in radiobiology and nuclear physics in particular, is based on collaborations with several research units certified within the Caen agglomeration, including the CYCERON biomedical imaging platform and the National Large Heavy Ion Accelerator (GANIL).

“...This dynamic of developing research is one of the elements that is strongly involved in the Centre’s medico-scientific programme for 2018-2022...” explains Prof Marc-André Mahé, the director of CFB; its goal is to propel Caen onto the international rankings in the fight against cancer.

Key Figures for the CFB

Diseases distribution

1,000 doctors, nurses, researchers, technicians and administrative workers

Approximately 6,500 new patients per year, 99% of whom are from the Normandy region.
Patient's geographic origin

- Calvados (58%)
- Manche (22%)
- Orne (12%)
- Seine-Maritime / Eure (7%)
- Autres (1%)

Clinical investigation research activity

166 open trials, 20 of which are promoted by the centre

534 included in 2018

Proton therapy

NUMBER OF SPECIFICALLY DEDICATED
3 university professors/hospital practitioners (PU-PH),
1 assistant clinic director (CCA),
2 assistant specialists,
7 technicians,
1 health executive working between proton therapy and phototherapy,
3 medical doctors working full-time on proton therapy and a dosimetrist.

CLINICAL TRIALS BEING ROLLED OUT
Adults: benign tumours in the central nervous system, low-grade sarcomas at the base of the skull, ENT and sinus tumours
Children: benign and malignant tumours in the central nervous system, tumours in very young children

PATIENTS TREATED
51
9 of whom were children, since 31 July 2018

Quantitative
gradual increase over three years to reach 300 patients per year

Extension of indications
- Irradiation des très jeunes enfants sous anesthésie générale
- Extension of indications: extracranial localisation in paediatrics; re-irradiation, thoracic tumours in adults