



CARPEM

CANCER RESEARCH FOR PERSONALIZED MEDICINE

Mid-Term Report 2020



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ITMO Cancer

*Liberté
Égalité
Fraternité*

SIRIC Designation 2018-2022

(Integrated Cancer Research Site)

Mid-term Report (2020)

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MID-TERM REPORT ABSTRACT

1- Global vision of the SIRIC

CARPEM brings together the oncology expertise of Université de Paris, Inserm and Assistance Publique – Hôpitaux de Paris. **We are devoted to cancer research for personalized medicine.** Our vision is that the collaboration within the same organisation of oncologists, hematologists, geneticists, immunologists and epidemiologists creates new knowledge to understand the mechanisms of cell transformation, to better classify tumors, define cancer prognosis and propose new therapeutic targets. Furthermore, to integrate the holistic perception of cancer transformation, we added the dimension of metabolism in our program. To reach our goals we created shared platforms: a translational research platform to integrate the different sources of data generated by the CARPEM clinical and research teams on the same cohort of patients. Information is stored in the CARPEM data warehouse and accessible to the community of CARPEM researchers thanks to the anonymization. We have engaged the creation of a cancer dedicated bioinformatic platform which will accelerate the analyses of large dataset of information generated by the CARPEM programs and provide the tools for speeding translation to clinical practice. Finally, the development of personalized medicine and its acceptance by society places the patients in the center of the CARPEM programs.

2- Integrated research programs

IRP1 explores epidemiological relationships between aberrant metabolism and incidence, molecular subtype, outcome and therapeutic response of cancers. Outstanding achievements are:

New nutritional and metabolic risk factors have been identified, controlling tumor progression.

Metabolic interventions to reduce tumor progression have been designed and successfully tested in preclinical studies, showing that autophagy induced by diets and agents can stimulate anticancer immunosurveillance.

An unprecedented database was created by establishing a genomic and clinically annotated of liver cancers that will help the entire community.

IRP2 consists in understanding the role of tumor heterogeneity in the mechanisms of tumor resistance. The heterogeneity of tumor and immune cells is explored to define its role in the day-to-day management of cancer patients. Outstanding achievements are:

Tertiary lymphocyte structures and B cells have been identified as novel predictive markers for response to immunotherapy in soft tissues sarcoma and extended to other cancers.

Immunoscore™ has been validated in an international study for colon cancer. It also appeared to be a predictive biomarker of the response to chemotherapy. In addition, ctDNA was validated as a marker of recurrence after colon cancer surgery.

Analysis of immune components of preneoplastic stage of lung cancer showed that immunosurveillance is present in the very early stages of neoplasia.

Droplet-based microfluidic approaches were used to detect heterogeneity and minimal residual disease in mantle cell lymphomas in national trials.

IRP3 addresses the legal, ethical, and human barriers encountered in modern translational research, named 'ethical vigilance'. Its main objective was to explore the acceptance and the feasibility of the implementation of the concept of dynamic consent for the purpose of translational research in the "real life" context of CARPEM.

3- Dissemination of knowledge and good practices

200 reviews were published in the last 2 years to diffuse the knowledge acquired by CARPEM. Several members of the CARPEM participate in establishing recommendations of good practices in different cancers and spreading the implication of genomics, immunology and metabolism disorders in the occurrence of cancers. We organize several meetings to upgrade knowledge of oncologists and pathologists, medical residents and fellows in the field of immunotherapy and targeted therapy. Furthermore we have developed animated supports for explaining to patients the SIRIC CARPEM programs and the new therapeutic practices.

SYNTHESE DU RAPPORT À MI-PARCOURS

1- Vision globale du SIRIC

Le CARPEM regroupe l'expertise oncologique de l'Université de Paris, de l'Inserm et de l'APHP. Il vise au développement de la médecine personnalisée en oncologie. La collaboration en son sein d'oncologues, d'hématologues, de généticiens, d'immunologistes et d'épidémiologistes crée de nouvelles synergies pour comprendre la survenue des cancers, mieux les classer et définir leur pronostic et proposer de nouvelles cibles thérapeutiques. Pour intégrer une vision plus holistique de la transformation tumorale, nous avons ajouté une dimension métabolique au projet. Pour atteindre nos objectifs, nous avons créé une plateforme de recherche translationnelle partagée, pour intégrer les données générées sur les mêmes cohortes de patients. Celles-ci anonymisées, stockées, sont accessibles aux chercheurs du CARPEM. Nous allons créer une plateforme de bioinformatique qui accélérera l'analyse des données et fournira les outils nécessaires afin de faciliter le transfert vers la clinique. Enfin, le développement de la médecine personnalisée et son acceptation par la société placent les patients au cœur des programmes du CARPEM.

2- Programmes de recherche intégrés

L'IRP1 étudie les relations entre les anomalies du métabolisme, l'incidence, le sous-type moléculaire et la réponse thérapeutique des cancers. Les résultats les plus remarquables sont:

L'identification de nouveaux facteurs de risque nutritionnels et métaboliques permettant de contrôler la progression tumorale.

L'identification d'interventions métaboliques pour réduire la progression tumorale et leur validation préclinique, montrant par exemple que l'autophagie induite par des régimes ou des traitements peut stimuler l'immunosurveillance anticancéreuse.

La création d'une base de données associant annotations génomiques et cliniques des cancers du foie qui aidera la communauté scientifique.

L'IRP2 étudie le rôle de l'hétérogénéité tumorale dans les mécanismes de résistance. L'hétérogénéité des cellules tumorales et immunitaires est explorée afin de définir son rôle dans la prise en charge des patients. Nos réalisations les plus remarquables sont :

L'identification des structures lymphocytaires tertiaires et des lymphocytes B comme de nouveaux marqueurs prédictifs de réponse à l'immunothérapie dans les sarcomes des tissus mous. Ces travaux ont été étendus à d'autres cancers.

La validation de l'Immunoscore™ dans une étude internationale sur le cancer du côlon. En outre, il semble être un biomarqueur prédictif de la réponse à la chimiothérapie.

La validation de l'ADNtc comme un marqueur de la récurrence après chirurgie du cancer du côlon.

La démonstration via l'analyse des composants immunitaires au stade préneoplasique du cancer du poumon que l'immunosurveillance est présente dès ces premiers stades.

L'étude de l'hétérogénéité et de la maladie résiduelle minimale dans les lymphomes des cellules du manteau lors d'essais nationaux par des approches microfluidiques.

L'IRP3 aborde les obstacles juridiques, éthiques et humains rencontrés dans la recherche translationnelle moderne, appelés "vigilance éthique". Son objectif est d'explorer l'acceptation et la faisabilité de la mise en œuvre du concept de consentement dynamique pour la recherche dans le contexte de « vraie vie » du CARPEM.

3- Diffusion des connaissances et des bonnes pratiques

200 revues ont été publiées au cours des 2 dernières années pour diffuser les connaissances acquises. Plusieurs membres du CARPEM ont participé à l'établissement de recommandations de bonnes pratiques dans les cancers et à la diffusion de l'implication de la génomique, de l'immunologie et des troubles du métabolisme dans la tumorigenèse. Nous avons organisé des réunions afin d'améliorer les connaissances des oncologues, des pathologistes, des médecins en formation en immunothérapie et thérapies ciblées. De plus, nous avons créé des supports animés pour expliquer aux patients les programmes du CARPEM et les nouvelles pratiques thérapeutiques.

MID-TERM REPORT

INTRODUCTION

CARPEM (for Cancer Research and Personalized Medicine) was created in 2012 and was initially unique among the eight SIRICs labeled by the French National Cancer Institute (INCa). Indeed, it was the only SIRIC not originating from an existing comprehensive cancer centre. Renewed in 2018, CARPEM shares now this characteristic with the newly labeled SIRIC CURAMUS.

CARPEM brings together the oncology expertise of Université de Paris (a new joined university between university of Paris Descartes and Paris Diderot), Inserm research teams and *Assistance Publique – Hôpitaux de Paris* (AP-HP) medical teams, thereby addressing the political objective of INCa to establish new conditions for optimization and better integration of translational research in cancer. A new agreement between these partners has been signed the 20/12/2019.

Our original work plan had to be slightly amended as we suffered a delay in the set up of fundings which prevented us from launching the recruitments on the planned schedule or call for projects before May 2018.

1 ORGANISATION AND MANAGEMENT OF THE SIRIC

The first two years of SIRIC CARPEM have been rich in merger and restructuring events of both hospitals and universities participating in SIRIC CARPEM.

•**A/As of July 3, 2019, the Assistance Publique - Hôpitaux de Paris led by Martin Hirsch has set up a new umbrella organization. It allows the newly created university hospital groups to strengthen their links with Universities, territories and partners and thus enhance the quality of care and research for all patients. From this new politics 4 clusters have been created. The SIRIC CARPEM had before the hour prefigured the grouping of Oncology of the hospitals Georges Pompidou, Cochin and Necker-Enfants Malades, those three hospitals being now integrated in a unique university hospital named AP-HP. Centre – Université de Paris** under the direction of Serge Morel. At the same time, the Paris Descartes University merged with Paris Diderot University and the Institut de Physique du Globe de Paris (IPGP) into **the newly created Université de Paris**. This new entity is now the largest medical school in Europe with 13000 students, 800 teachers, 10 research centres among which 5 participated in the SIRIC CARPEM (Cochin, Cordeliers, Imagine, INEM, PARCC).

•**B/A new consortium agreement** has been concluded between the reorganised partners following the above-mentioned mergers. The agreement lays down, inter alia, the rules for the appropriation of the results of the research carried out within CARPEM and their valorization.

•**C/All these restructurations created the opportunity to structure and improve clinical activities, research and teaching in the field of oncology and forster the integration between research and clinics for better care of cancer patients. Under the auspice of APHP.Centre – Université de Paris hospital, we created the Paris Cancer Institute CARPEM led by P. Laurent-Puig. The Institute's first challenge is to obtain European accreditation as a "Comprehensive Cancer Center".** The objectives of this new organization are:

- a) To structure the offer of cancer care within APHP.Centre-Université de Paris
- b) To increase the quality of care, research and care/research interactions
- c) To improve our national and international visibility in a competitive field
- d) To participate in a European network and be able to apply as a Centre, to calls for tenders.
- e) 28 programs in oncology have been defined in which the clinical part, the research part (CARPEM), and teaching side are integrated. These 28 thematic programs define the scope of the Paris Cancer Institute CARPEM. <http://carpem.fr/en/paris-cancer-institute-carpem-3/>

This new institute will reinforce links between clinics and research in the SIRIC CARPEM

•**D/Two new teams have joined the SIRIC CARPEM in 2018 one led by Pr E. Pasmant named “Genomics and epigenetics of rare tumors”** The main research project of this team is dedicated to the study of rare tumor-predisposition syndromes. The team is interested in (1) the genetic and cellular mechanisms involved in the development of these pathologies and their variable expressiveness (study of genotype-phenotype correlations, and identification of modifier genes), and (2) the genomics of the associated benign and malignant tumors and their therapeutic targeting. The team participates in the integrated research program 2 (IRP2). **The second team led par Pr M. Vidal is named Medicinal chemistry and translational research.** This team carries out a translational research on the drugs used in the treatment of solid and liquid tumors. According to an approach of personalized medicine, the team aims to optimize the balance efficacy/safety and therefore to identify the best active and safe dosing schedule for individual patients to maximize therapeutic benefit. For this purpose, they are seeking the pharmacokinetic and pharmacodynamic factors which contribute to the inter- and intra-individual variability in clinical outcomes (efficacy, toxicity) for anticancer agents and immunotherapy. This team integrates IRP2.

•**E/Our Scientific Advisory Board (SAB)** has been partly renewed and is composed of nine international leading experts in cancer who offer their scientific expertise, critical opinion and strategic research advice, as well as their international recognition. The first meeting was hold on February 20-21, 2020. More detailed description is provided in paragraph 1.2.

•**F/The secretary general was trained to fundraising** and we built a partnership with Foundation AP-HP to collect donations. CARPEM can now receive donation from private people including former patients and families or firms. Information is available on our website or at the hospitals where leaflets are distributed. We already collected 50 K€.

•**H/The CARPEM website (www.carpem.fr) was completely redesign in order to present our new project and meet with our communication needs.**

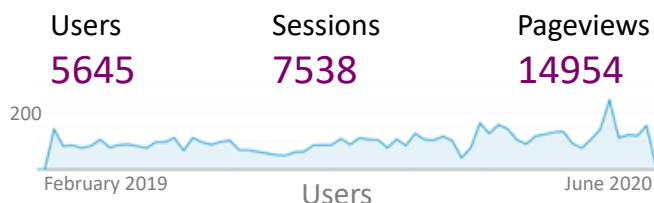
This new website provides:

A presentation of CARPEM within the network of the eight labeled French SIRICs, our national and international collaborations, our 3 new IRPs, our 11 clinical and 23 research teams, our 8 platforms, our educative videos...

New online features: donation through our fundraising partnership with Foundation AP-HP, calls for project, job offers...

Hands on publication: we are able to create our own pages showing our future projects (e.g. The Paris Cancer Institute: CARPEM). This allows us to interact quickly with our partners, promote our events in a broader way, and gives more visibility to the SIRIC actions.

Since February 2019, the key performance indicators for our website are:



Number of sessions per user
1.34

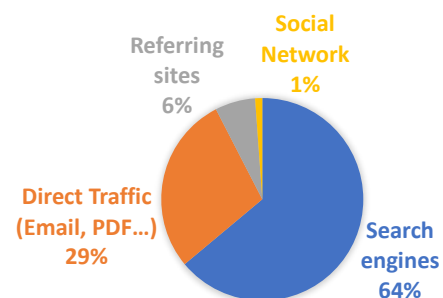
Pages/session
2

Average session duration
00:01:52

Returning visitors



Traffic sources

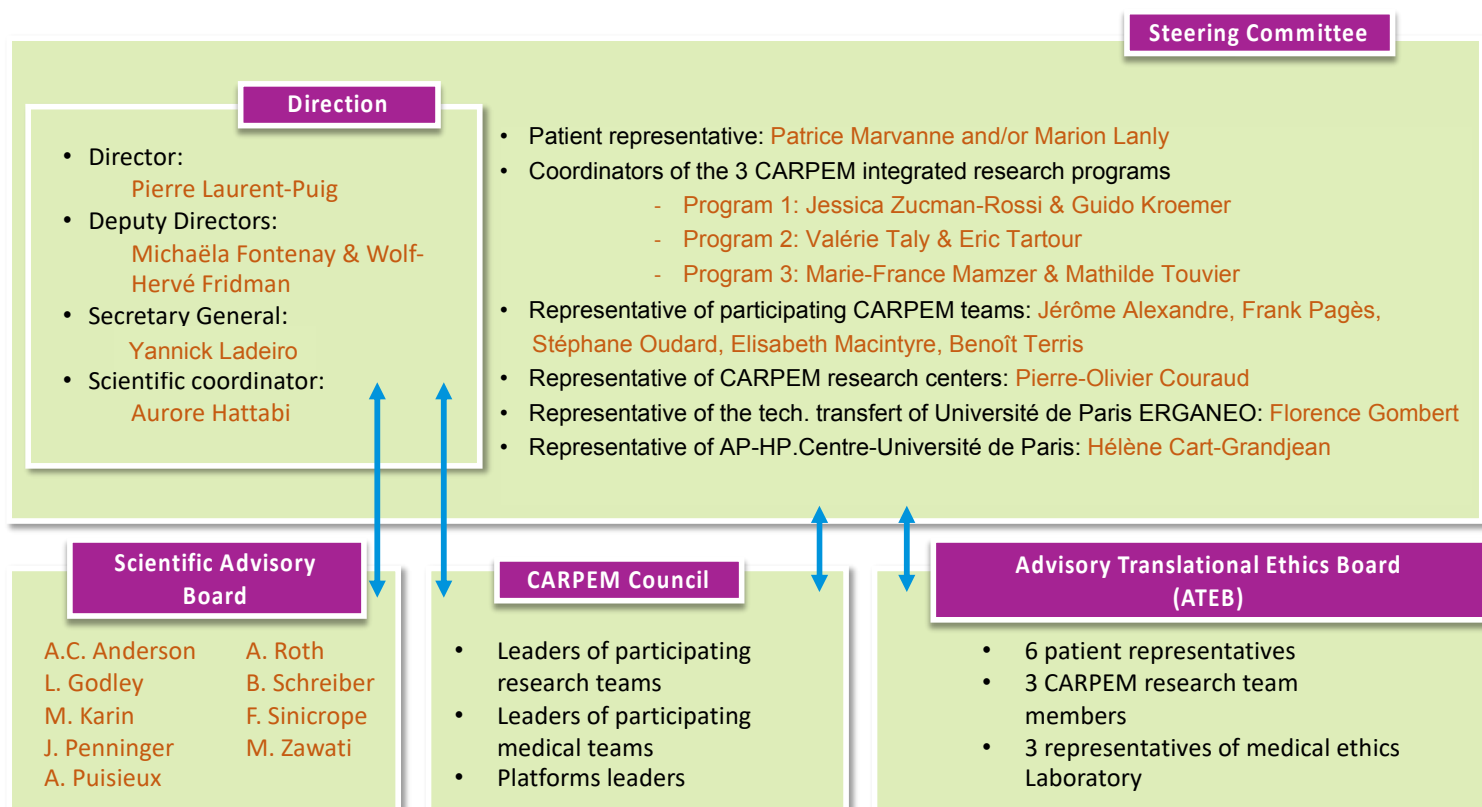


These figures have been reached in a relatively stable manner since the start of data integration (February 2019) as it can be seen on the user curve.

1.1 Governance and managerial organisation

The gender equality is the rule among CARPEM structures. Michaëla Fontenay (MD, PhD) joined the Directorate in 2018 as co-deputy director with Wolf-Hervé Fridman. She is full professor in Hematology at Université de Paris. She is head manager of the laboratory of Hematology and of the Unit of clinical haemostasis of Cochin hospital, APHP.Centre and co-director of PhD school Hematology Oncogenesis Biotherapies, Université de Paris. She is director of the INSERM Team Normal and pathological hematopoiesis at Institut Cochin INSERM U1016. Her main research topics are erythropoiesis and myelodysplastic syndromes. Her publication track records showed 141 original publications in peer reviewed journals such as Cell, Cell Reports, Sci Trans Med, N Engl J Med, Lancet Haematology, Blood, Leukemia, an H-index at 40, and a sum of citation at 6,793.

The steering committee is composed of **10 women and 10 men**.



1.1 Scientific organisation

1.1.1 Steering Committee

The Director and Deputy Directors together with the Secretary General and the Scientific Coordinator manage the Steering Committee. It meets every 2 months and defines the scientific strategy, the financial management of the CARPEM as well as all the items that might have an incidence on the management of the CARPEM.

Structure of the Committee :

- One **patient representative**: Patrice Marvanne and/or Marion Lanly
- **Coordinators of the 3 integrated research programs (IRP)** of the CARPEM
 - Program 1: Metabolism, Genetics, Immunity & Environment (Jessica Zucman-Rossi, Guido Kroemer)

- Program 2: Cancer heterogeneity related to tumor and host diversity for patient management (Valerie Taly, Eric Tartour)
- Program 3: Dynamic consent and health democracy (Marie-France Mamzer, Mathilde Touvier)
- **Representatives of participating CARPEM teams** (Jérôme Alexandre, Frank Pagès, Stéphane Oudard, Elisabeth Macintyre, Benoit Terris)
- **Representative of CARPEM research centers** (Pierre-Olivier Couraud)
- **Representative of the Tech Transfert of Université de Paris ERGANEO** (Florence Gombert)
- **Representative of AP-HP.Centre-Université de Paris** (Hélène Cart-Grandjean)

During our steering committees, various decisions were taken, such as the orientations of the calls for projects, SAB organization, the integration of new teams within SIRIC CARPEM, the recruitment of staff for the platforms.

Since 2018, 14 Steering Committee meetings have been held. 2018 (26 Jan, 26 Mar, 22 May, 10 Jul, 17 Sep, 14 Dec); 2019 (22 Feb, 10 May, 10 Jul, 28 Nov); 2020 (04 Feb, 04 Mar, 03 Jun, 8 Jul).

1.1.2 CARPEM Council

The CARPEM Council, composed of the leaders of the clinical teams and research teams and platforms. It is chaired by the Director and is informed of all key events in the life of the CARPEM. The Director presents and discusses the CARPEM budget, changes in structures and personnel, new participating research teams and changes in the scientific CARPEM strategy. The CARPEM Council can make recommendations as to any subject that has been brought to debate. A general assembly was planned in 2020 but had to be post-poned because of the COVID pandemic.

1.1.3 Scientific Advisory Board

The Scientific Advisory Board (SAB), it is composed of:

Pr. Ana C. Anderson, Associate Professor of Neurology at Harvard Medical School and Brigham and Women's Hospital. Core faculty member of the Evergrande Center for Immunologic Diseases.

Pr. Lucy Godley, Hematology and Oncology (Cancer), Hospira Foundation Professor of Medicine and Human Genetics, UChicago Medicine.

Pr. Michael Karin, Professor of Pharmacology and Pathology at the University of California San Diego School of Medicine, UC San Diego.

Pr. Josef Penninger, Scientific director of the Institute of Molecular Biotechnology Vienna Biocenter.

Pr. Alain Puisieux, Director of the Research Center of the Institut Curie.

Pr. Arnaud Roth, Associate Professor in the Department of Medicine at the Faculty of Medicine of the University of Geneva. Physician in charge of the Onco-surgery Unit, University Hospitals Geneva

Pr. Robert Schreiber, AM Bursky & JM Bursky Distinguished Professor, Departement of Pathology & Immunology, Washington University School of Medicine.

Dr. Frank A. Sinicrope, M.D., Departments: Gastroenterology and Hepatology, Oncology (Medical), Cancer Center, Mayo Clinic Rochester

Dr. Ma'n H. Zawati. Adjunct Professor at McGill University, Executive Director of the Centre of Genomics and Policy in the Department of Human Genetics

As mentioned, the first SAB meeting took place on February 20/21, 2020. The achievements and scientific plans of CARPEM were submitted to the SAB assessment. Overall, the members of the SAB were very satisfied; stressing the excellence of individually presented scientific programs and qualifying our consortium as one of the world-wide leaders in the fields of cancer and cancer immunotherapy. **They particularly appreciated the potential for synergies in the area of cancer genomics and immunotherapy and the data warehouse activities. Regarding the ethical/social issues program, the SAB members acknowledged that it**

is a particularly innovative, forward-thinking & important project. Finally, they appreciated the depth and breadth of the activities performed.

The complete SAB report is available on our website:

<http://carpem.fr/wp-content/uploads/2020/07/Carpem-Integrated-summary.pdf>

1.1.4 Advisory Translational Ethics Board (ATEB)

The **ATEB** gathers patients, patients' representatives and professionals together with ethicists. It is an advisory board overseeing the ethical and cultural dimensions of all CARPEM projects. It identifies ethical issues that might potentially emerge during the process of translational research. Its role is to advise the steering committee in any actions needed to improve the project in terms of ethics, information, and returned results to the patients. It allows scientists to understand challenges that they are facing in their research projects and to provide better understanding to patients. It is also the witness of the appropriation of CARPEM project by the patients.

1.2 Managerial organisation for platforms and specific infrastructures

The existing platforms already have their own managerial organization as they are not exclusively dedicated to CARPEM projects and are managed by Université de Paris.

CARPEM supports the existing platforms from both an organizational and financial point of view. The platforms' financial support is based on the development and improvements of their services for cancer research. An annual report is submitted to the Steering Committee for evaluation and validation of their activities. Support can take the form of grants or additional specialized staff.

Up to now, there is one specific CARPEM platform, the CARPEM's Translational Research Platform which is managed by Prof. A. Burgun with the support of a former postdoctoral fellow financed by CARPEM who obtained a tenure position as associate professor in 2018 and two bioinformatics engineers. This team reports directly to the CARPEM Steering Committee, which approves and oversees the deployment plans of this platform in order to maximize its progress.

1.3 Administrative and financial management

The CARPEM funding is housed at the HEGP. The CARPEM Secretary General is in charge of the administrative management, including the budget follow-up, purchasing and human resources. The HEGP Human Resources, Administrative and Purchasing Departments facilitate those actions. The Scientific and Communication Coordinator works in close collaboration with the Secretary General to enable efficient administrative and financial management.

1.4 Role and contribution of patient representatives/advocates in the SIRIC governance

The CARPEM program integrates ethical expertise in its governance and develops ongoing empirical-ethical research to identify, support and fuel the debate about ethical issues encountered in real-life practice. Patients and patients' representatives are included during the entire process, giving them the "floor" to express their vision and expectations and engage them in constructing an appropriate normative/ethical framework. As a result of the patient engagement in CARPEM projects, one of them is included in the CARPEM Steering Committee. Moreover, patients and their representatives acquired the knowledge and skills to animate the public debate on precision medicine which is the aim of the Advisory Translational Ethics Board. Meanwhile, professionals get to improve their understanding of **patients' perspective**.

The recent creation of the Paris Cancer Institute CARPEM by the APHP.Centre – Université de Paris hospital-university group and SIRIC CARPEM, is a great opportunity for the CARPEM program dedicated to patient experience and ethics to not only reinforce the partnering with patients within the real life context all along their care pathway but also make sure patient experience improvement is taken into account in major

decisions and priorities. In this context, we have decided to increase the scope of the third axis program “dynamic consent and health democracy” to reinforce the place of patients and representatives by systematizing the “patient experience” approach. Several issues were raised from the debate with patient’s representatives and open-up avenues for improving care and participation in research. We decided (i) the creation of patient’s educational program that aims to improve patients' understanding of their disease, on research undertaken and how to manage the different social aspects of their disease; (ii) to support this educational program, we will extend an information and support centre based on the “patient’s house” already existing in HEGP accessible to cancer patients, family members, care givers and researchers, in order to better display and organize relevant information according to specific needs (audience typology, cancer types, patient’s journeys); (iii) organizing public events to discuss advances in cancer research.

1.5 Conclusion

The main strength of CARPEM is its research and clinical excellence. Indeed, the founders of CARPEM constituted a unique combination of key leaders in oncology, hematology, genomics and immunology. During this second period of CARPEM, we fostered the integration between researchers, physicians and patients thanks to the project of an european accreditation by OEI of a comprehensive cancer institute the Cancer institute of Paris CARPEM. We developed a program dedicated to patient’s experience. We pushed our effort of developing excellence of translational research in immunology, genetics and metabolism by creating bridges between teams from different research fields and hospitals, encouraging systematic collaborations by funding post-doc and emerging projects. A focus was made on the introduction of high-throughput genetic and immunological characterization of tumors in day-to-day clinical care of cancer patients. CARPEM fosters large research projects involving academic and industrial partners in genomics, immunology and AI which will reinforce its national and international visibility. To this end, we have established a common and unique data warehouse in order to generate new integrated knowledge. This strategy has positioned CARPEM as an **effective translational research booster**. The main difficulty is to obtain sufficient financial support to conduct the research as planned. The weaknesses of the CARPEM are (i) the location of clinical and research teams on different sites which we compensate by strongly pushing and supporting multisite shared research projects and by creating a unique data warehouse as mentioned above, (ii) the difficulties of CARPEM funding since we have to compete with other medical priorities of the CARPEM’s stakeholders.

2 GLOBAL TRANSVERSAL ACTIONS SERVING ALL THE INTEGRATED RESEARCH PROGRAMMES

To carry out integrated research programs as planned, CARPEM's policy has been to strengthen existing university or hospital platforms if possible or to create new ones if they did not exist.

2.1 Transversal platforms

CARPEM currently supports 4 platforms and has created its own translational research platform:

2.1.1 Translational research platform

We have continued the effort initiated during the first CARPEM period. This platform has been funded with 130 000 € including 1 post-doc who obtained a tenured position by APHP and Université de Paris as Associated Professor and a bioinformatics engineer. The Translational Research Platform (TRP) is a tool and sets of resources developed to integrate in a unique warehouse all the data (clinical, research, -omics, existence of samples, etc.) from CARPEM patients. This information is stored in a CARPEM datawarehouse which, thanks to the anonymization, is accessible to the community of researchers. This information can be exploited using different tools.

This TRP is **the flagship platform of CARPEM** because it is an essential transversal tool for all CARPEM members. The majority of CARPEM researchers and clinicians are involved in the warehouse and in the development of data exploring tools. **The TRP trains 120 clinicians and researchers a year** (one training per month with an average 10 trainees each session) for the use of REDCap, an electronic data capture software. There are **340 users, mainly but not exclusively CARPEM members showing the general interest of the developed tools.**

TRP explores two additional directions: first, on adding geographical data in order to be able to link clinical and omics data with social determinants and exposome information available as open data. The initial targets are social determinants and air pollution. The work has begun in November 2019 and is ongoing. The second direction aims at providing CARPEM's clinicians and researchers with semi-automated dynamic prospective cohorts. Using data integration, Natural Language Processing and Artificial Intelligence methods, TRP populate databases (hosted in REDCap) every week. The first automated prospective cohort focuses on patients treated by immunotherapy.

Among the new developments of this platform, CARPEM has been largely involved in the OSIRIS national working group animated by French National Cancer Institute: INCa. This group aims at proposing a list of 130 clinical and omics items, the "Set OSIRIS", constituting a minimum data set for sharing clinical-biological data in oncology. This list is based on a conceptual and temporal model of cancer disease that has been agreed upon by the group. CARPEM was co-leader of a work-package dedicated to the implementation of a proof-of-concept enabling a national network of data warehouses dedicated to cancer.

CARPEM is consolidating its data warehouse by adopting the OSIRIS standard in prospective cohorts. The standardized itemsets are also now being used in an Artificial Intelligence challenge, organized by the IT future of Cancer Treatment consortium (a European consortium) coming up in 2021 which aims at predicting the response to treatment of patients suffering from Triple Negative Breast Cancer. The database constituted for the challenge relies on this standard.

2.1.2 Genomics Platform

CARPEM's genomics platform is based on the genomics facilities of the Cochin Institute (GenomIC) and that of the Georges Pompidou European Hospital and has been supported by 104 000€ including 1 bioinformatic engineer. It provides expertise and core genomics technologies such as quantitative and digital PCR, DNA chips and next generation sequencing (NGS) to university research laboratories. It is involved in cancer projects through the implementation of Next Generation Sequencing (NGS) in clinical patient's care and through the research projects of CARPEM teams. The leverage effect of the platform has allowed funding for

additional equipment and research projects. This platform served as a model for the Ile-de-France region platform (SeqOIA) associating (APHP, Gustave Roussy and Curie institutes) and recently funded by the French government (€ 180 millions) for sequencing cancer patient (8000 eq genome / year). **CARPEM members are strongly involved in SeqOIA and are co leaders of some national indications for genome sequencing in cancer** (AP Gimenez-Roqueplo for rare cancers, P. Laurent-Puig for patients in therapeutic failure).

The genomics facility proposes new tools and technological improvements to fit the research team requirements. For example, single cell transcriptomic analysis has been implemented through the 10X technology: 10 scRNA-seq projects have been realized in 2019.

Labelled as Université de Paris (UP) platform, it shares regular relationships with the bioinformatic facility of UP and its involvement in cancer projects studies conducted by research teams of the CARPEM represents around 40% of the total activity of this platform.

The projects of genomics platform with a major involvement of SIRIC CARPEM are listed below with the related publications in bold:

Project 1: Circulating tumor DNA (ctDNA) as a part of new composite biomarkers of cancer (team P. Laurent-Puig/V. Taly)

The characterization of ctDNA represents one of the successes of this platform and its transfer to the clinic is now a reality with more than 263 tests performed in 2018 and 405 tests re-run in 2019. The use of ctDNA in colon cancer as a surrogate marker of the tumor tissues for the detection of *KRAS* and *BRAF* mutation has been validated based on a prospective cohort of 425 patients (**Bachet JB et al. Ann Oncol 2018; Mas L et al. Cancer 2019**). The presence of ctDNA after surgery in a large series of 1450 patients included in IDEA trial was associated with recurrence (**Taieb et al. submitted; oral presentation at ESMO 2019**). The same group confirms the prognostic value of the presence of ctDNA in metastatic pancreatic adenocarcinomas (**Pietrasz et al. submitted**) and in collaboration with **Biotech ERYTECH** the role of ctDNA for predicting the efficacy of eryaspase (L-asparaginase encapsulated) in metastatic pancreatic adenocarcinoma (**Bachet et al. Clin Cancer Res 2020**).

Project 2: Molecular classification of rare endocrine tumors (team J. Bertherat/G. Assie)

An integrated multi omics analysis (exome-seq, RNA-seq, mir-seq and methylation analysis) of a large cohort of 134 pituitary neuroendocrine tumors has generated a large pangenomic classification that challenges the current histological classification of these tumors. (**Neou et al Cancer Cell. 2020**). In adrenocortical cancer, molecular classification yielded independent prognostic factors. The prognostic value of molecular classification was confirmed using targeted molecular measurements (RT-qPCR, MS-MLPA, targeted NGS) in a large european cohort. (**Assie et al JAMA Oncol. 2019**). The integration of such markers in clinical routine practices needs to start from paraffin samples. The platform has indeed successfully evaluated a new library protocol based on 3'RNA-sequencing of highly degraded RNA, thus able to distinguish the two transcriptome profiles previously identified from the same frozen samples **Abstract ECE2020 (Jouinot et al)**. The next challenge is to develop the study of the heterogeneity of these tumors. The aim of this project is to perform the first mapping of adrenocortical cancer heterogeneity at the cell level, by analyzing single-nucleus transcriptome using 10X technology.

Project 3: Transcriptional signature associated with clinical response to immune checkpoints inhibitors (team I Cremer CRC, collaboration with E Tartour PARCC and P Laurent-Puig CRC teams)

A collaboration with Nanostring company was set-up to analyze the transcriptional signature associated with clinical benefit of anti-PD1 in the CERTIM cohort, a prospective cohort which includes patients receiving immune checkpoint inhibitors. RNA extracted from 58 archival formalin fixed paraffin embedded tumor blocks (including 38 lung cancers, 5 melanomas, 10 renal carcinomas, 4 urothelial carcinomas and 1 colon carcinoma) was hybridized to a beta version of the NanoString® PanCancer IO360™ CodeSet. The Tumor inflammation scores (TIS) were significantly associated with complete or partial response to anti-PD-1 treatment and overall survival in the whole cohort well as in the NSCLC population (**Damotte et al J Transl Med. 2019**). The predictive value of these transcriptional signatures and of the TIS score will be further assessed and compared to other pertinent biomarkers (ie T-resident memory cell infiltration, Tumor

mutational load, TCR clonality) in a series of pts treated with anti-PD1 i, as part of the **SIGN'IT project "Tracking preexisting anti-tumor CD8+T cells to predict clinical response to the blocking of PD-1/PD-L1 axis"**, funded by ARC in 2018 and coordinated by Pr E. Tartour.

Project 4: Molecular characterization of lung adenocarcinomas based on NF1 NGS sequencing (Team Pasmant)

The tumor suppressor gene neurofibromin 1 (NF1) is a major regulator of the RAS-MAPK pathway. *NF1* mutations occur in lung cancer but were not extensively explored. *NF1*-mutated tumors could define a specific population with a distinct clinical and molecular profile. *NF1* was screened for mutation by NGS in 154 lung adenocarcinoma surgical specimens with known *KRAS*, *EGFR*, *TP53*, *BRAF*, *HER2*, and *PIK3CA* status, to evaluate the molecular and clinical specificities of *NF1*-mutated lung cancers. Our results confirmed that *NF1* is frequently mutated and represents a distinct molecular and clinical subtype of lung adenocarcinoma. (Tlemsani et al, *Cancer Med.* 2019).

Project 5: Genomic characterization of endometrial carcinomas (team P Laurent-Puig, CRC; team I Cremer CRC)

To get further insights into the genomic profile of endometrial carcinomas and its relationship with clinical outcome, an ancillary study has been set-up within UTOLA study (NCT03745950) **sponsored by ARCAGY-GINECO**. This study is a phase IIB, national, randomized, double-blinded, comparative, multi-center study, assessing the efficacy of Olaparib, a PARP inhibitor, as maintenance after a platinum based chemotherapy in patients with advanced or metastatic endometrial cancer. Capture-based Illumina sequencing of a panel of 144 genes is performed for each of the 150 patients included in this study.

Project 6: Classification and clinical management of patient with low risk myelodysplastic syndromes H2020 MDS-RIGHT project (team M. Fontenay, O. Kosmider)

The Platform has contributed to the H2020-funded European consortium MDS-RIGHT (Providing the right care to the right patient with MyeloDysplastic Syndrome at the right time) effort by performing RNA-seq of 150 MDS bone marrow mononuclear cell samples of the French cohort MDS-04 collected in Cochin hospital by the team of Michaela Fontenay. Methylome (Illumina 850K) and DNA sequencing data are integrated to the profiles of differentially expressed genes. The consequences on gene expression of the deregulation of a set of differentially methylated regions at diagnosis predictive of rapid AML transformation are analyzed (manuscript in preparation). Using the available 10X technology, a description of the bone marrow architecture by sc RNAseq analysis have been performed in MDS samples at diagnosis and in serial samples before and after treatment by hypomethylated agents (**Dussiau et al, manuscript in preparation**). More recently this technology was adapted to the analysis of myeloid cell populations in unfractionated peripheral blood. This allows us to demonstrate the immunosuppressive nature of monocytes and neutrophils related to the elevated production of S100A8/A9 heterodimer calprotectin in patients affected by severe COVID-19 with or without a cancer background (**Silvin et al, Cell 2020**).

2.1.3 Centre of Histology, Cell Imaging and Flow Cytometry Platform (CHIC)

This group of platforms was recently renewed and upgraded to host a complete and automated immunohistochemistry and immunohistology facility. The CHIC platform is a member of the labelled IBiSA LUMIC network of Sorbonne Université (SU) and is a reference in multiplexing analysis using Flow Cytometry, ELISA-multiplex, Immunohistology and Cell Imaging. Among them we detail the Tumor Microenvironment Immunohistochemistry Platform.

This very strategic transversal platform is among CARPEM's key achievements and is funded by 107 000€ including an engineer. The activity of the Tumor Microenvironment Platform is devoted to the analysis of the composition, cell types, cell densities and cell organization in the microenvironment of human primary tumors and metastases on tumor sections. The leverage effect of the platform has allowed funding for additional equipment (automated slide scanner, 2 autostainers, 4 tissue imaging systems including Mantra and Vectra 3.0) that boosted the development of multispectral imaging technology for the simultaneous detection of 7 proteins in cancer tissue. Altogether, 6 CARPEM teams benefitted from data produced using the platform on projects approved by the Ethics and Human Investigation Committees.

The projects with a major involvement of SIRIC CARPEM are listed below with the related publications in bold:

Project 1: International validation of the immunoscore (Team Galon): The Integrative Cancer Immunology Team, headed by Jerome Galon, has developed a consensus Immunoscore assay. Briefly, the Immunoscore is an immunohistochemistry and digital pathology-based assay that is quantifying two lymphocyte populations CD3+ and CD8+ T cells in the tumor core and its invasive margin. The Immunoscore was shown to be a prognostic marker for colorectal cancer. To allow the introduction of the Immunoscore into clinical practice, an international consortium led by the Society for Immunotherapy of Cancer (SITC) evaluated globally its prognostic value in stage I-III colon cancer patients in routine clinical settings. The results showed that patients with a High Immunoscore had the lowest risk of recurrence and the longest overall survival and disease-free survival. This study demonstrated that this consensus Immunoscore can predict the risk of relapse in patients with stage I-III colon cancer (**Pagès, Lancet 2018**). The Immunoscore analysis is now also performed on various solid cancer tissues, using the tumor microenvironment immunohistochemistry platform. Additionally, several multi-plex fluorescent panels have been developed to better characterize the TME, notably in collaboration with **Akoya Biosciences** for some of them. A collaboration with **Ultivue** is also ongoing to explore the TME of colorectal cancer with 6 multiplex panels currently developed by the company.

Project 2: Immune evasion in early lung carcinogenesis (Team Galon).

The role of the TME in precancerous lesions was investigated for lung cancer using a dataset of 9 morphological stages of the development of lung squamous cell carcinoma. Gene-expression profiling and multispectral imaging were performed. These analyses revealed that: (1) immune sensing and immune unleashing are induced at the earliest step of transformation; (2) continual cell proliferation fosters the accumulation of somatic mutations, mounting an anti-tumour immune response; and (3) inherent immune-suppression mechanisms are triggered in high-grade pre-cancerous lesions. These data show that both immune activation and immune suppression occur at pre-invasive stages of cancer development, which supports the hypothesis of immune surveillance in precancerous lesions (**Mascaux, Nature 2019**). Work is ongoing on precancerous lung, cervical and colon lesions.

Project 3: Link between TME in metastases and survival in CRC (Team Galon).

A better understanding of the mechanisms contributing to the development of metastases is needed. The Team of Galon analyzed a set of 441 lung and liver metastases resected from 153 colorectal cancer patients. The Immunoscore assay was performed for all metastases and revealed an intra- and inter-metastatic heterogeneity of the immune infiltrate within a patient and between all patients. The Immunoscore of the least infiltrated metastasis was the most significantly associated with prolonged survival (**Mlecnik JNCI 2018**). A complementary study demonstrated that the predictive accuracy of the Immunoscore quantification from a biopsy was superior to the one of the PD-L1 evaluation (**Van Den Eynde, Cancer Cell 2018**). The Immunoscore can predict survival of metastatic colorectal patients and therefore represents a useful stratifying tool.

Another study was performed using a longitudinal dataset of 31 metastases resected across more than 10 years from two stage IV colorectal patients and validated on 132 tumors. The Immunoscore and immunoediting were the two best predictive factors of metastasis recurrence. Non-recurrent clones from metastases were immunoedited, in contrast to progressive tumor clones which were immune-privileged. This study revealed a parallel immune selection-based model of cancer evolution and dissemination (**Angelova, Cell 2018**).

Project 4: Prognostic and predictive value of tumor-associated B cells and Tertiary Lymphoid Structures in human cancers (Team Sautès-Fridman)

Tertiary lymphoid structures (TLS) are ectopic lymphoid organs that develop at sites of chronic inflammation and in tumors, driving context-dependent effects. Soft-tissue sarcomas (STS) represent a heterogeneous group of tumors with variable clinical behaviors and response to immune checkpoint blockade (ICB). We established an immune-based transcriptomic classification identifying five distinct phenotypes (sarcoma immune (SIC) classes A to E). Quantitative IHC staining for CD3 (T cells), CD8 (CD8⁺ T cells), CD20 (B cells), DC-Lamp

(activated dendritic cells), CD34 (endothelial cells) and PD-L1 were performed to validate the TME profiles of the “Immune desert” SIC A and of the “Immune and TLS high” SIC E. The “vascularised” SIC C exhibited a moderate infiltration by immune cells and high density of CD34⁺ endothelial cells. TLS defined as a CD20⁺ B cells follicle juxtaposed to a CD3⁺ T cells aggregate containing at least one DC-Lamp⁺ mature dendritic cell were identified in SIC-E. The immune/TLS-high E group of patients demonstrated improved survival and is associated with response to PD-1 blockade by pembrolizumab in a phase 2 clinical trial (**Petitprez, Nature 2020, Helmink Nature 2020, Sautès-Fridman, Nature Rev Cancer 2019**). Hepatocellular carcinoma represents a prototype of inflammation-driven cancer characterized by cirrhotic nodules where abundant TLS contribute to a pro-tumoral, inflammatory state. In collaboration with **Team J Zucman Rossi**, we showed that the density of intra-tumoral TLS, but not that of TLS present at distance in the liver, is predictive of a decreased risk of early relapse by univariate and multivariate analyses, suggesting that they truly reflect an ongoing, effective anti-tumor immunity in HCC (**Calderaro, J Hepatol, 2019**).

Project 5: Context dependent roles of complement in cancer (Team Sautès-Fridman/Team Roumenina)

Complement is a key factor in tissue inflammation favoring cancer progression through the production of C5a. By data mining, these groups identified clear cell renal cell cancer (ccRCC) as the cancer type expressing concomitantly high levels of the components of the classical complement pathway. To understand how complement cascade is activated in ccRCC and impacts patient’s clinical outcome, primary tumors from 3 patient cohorts (n=106, 154, and 43), ccRCC cell lines and tumor models in complement-deficient mice were used. Detection of complement components by IHC in tumor sections has been developed on the platform. They showed that high densities of cells producing classical complement pathway components C1q and C4 and the presence of C4 activation fragment deposits in primary tumors correlated with poor prognosis. The *in situ* orchestrated production of C1q by tumor-associated macrophages (TAMs) and C1r, C1s, C4 and C3 by tumor cells, associated with IgG deposits, led to C1 complex assembly and complement activation (**Daugan, Cancer Immunol Res, 2019**). Therefore, classical complement pathway is a novel inflammatory mechanism activated by cooperation between tumor cells and TAMs in tumors, favoring cancer progression. These results lay the ground for therapeutic new avenues in ccRCC, by targeting complement components (**Roumenina, Nature Rev Cancer 2019**).

Project 6: The phase 2 BIOMarker driven trial with Nivolumab and Ipilimumab or VEGFR tKi in naïve metastatic Kidney cancer (m-ccRCC) patients (pts): the BIONIKK trial.

BIONIKK is an open-label, French multicenter prospective and randomized phase 2 trial evaluating the efficacy of Nivolumab (N) ± Ipilimumab (I) or a TKI in frontline m-ccRCC according to molecular group, determined by RT-qPCR from frozen tumor tissue. According to molecular subtypes patients were randomized to receive N vs N-I and N-I vs TKI (Sorafenib or pazopanib) respectively. The primary endpoint was the objective response rate (ORR) of each treatment arm and group, evaluated by RECIST 1.1. From June 2017 to July 2019, 202 pts have been randomized. The *in situ* composition of the immune infiltrate (CD3/CD20, CD8/PD-1, CD4/Foxp3, CD163, PD-L1, CD66b), the presence of TLS, and angiogenesis (VEGF) are currently investigated on the platform. Data from IHC will be analyzed together with the gene expression signatures obtained using 3’ RNAseq technology, as well as their impact on outcomes (**Vano et al. Abstract ESMO 2020 submitted**).

Project 7: Impact of Influenza virus infection on tumor progression and anti-tumoral immune responses (Team I. Cremer)

The effects of Influenza A virus infection that could influence the progression of lung adenocarcinomas and the immune response in the tumor were determined using a 7-colour multi-labelled immunofluorescence protocol. Anti-HA (viral hemagglutinin) antibody was used to detect the presence of Influenza A virus, a pan-cytokeratin to allow the visualization of lung carcinomas, and markers of the immune response and immune checkpoints such as CD45n CD3, CD20, CD8, CTLA4, PD-1, PD-L1 were investigated. They identified the presence of HA both in tumor epithelial and in immune cells, and that viral infection correlates with increased expression of PD-1, PD-L1 and CTLA-4 expression on T cells. Quantifications are currently performed using Halo software (manuscript in preparation).

Project 8: Inhibitory functions of Intratumoral NK cells (Team I. Cremer)

They identified a unique gene signature of NK cell dysfunction in NSCLC and demonstrated novel molecular cues associated with NK cell inhibitory functions, associated with CTLA-4 expression. In a large cohort of NSCLC patients, they quantified the density of NKp46+ cells by immunohistochemistry and demonstrated that it negatively impacts the positive prognostic value of CD8+T cells. **(Russick et al. in revision)**

Aucune entrée d'index n'a été trouvée. **Strategy to implement this platform with a new instrument**

Within SIRIC CARPEM programs 2012-2017 and 2018-2022, the study of tumour heterogeneity has led to the establishment of new prognostic molecular classifications. **CARPEM now aims to delve deeper into the characterization of tumor heterogeneity using single cell analysis technologies and multiparametric approaches.**

CARPEM's research teams, have the objective to integrate cutting-edge technologies into the routine methodology for the characterization of tumor immune infiltrates. So, **after the advice of the international scientific advisory board, the COPIL approved the acquisition of GeoMx DSP** which appears to be part of this techno-integrative approach. Nanostring's GeoMx DSP is a platform that allows multiplex, high-throughput analysis of the spatial profile of proteins or RNA from a single FFPE section. The DSP combines standard immunofluorescence techniques with nCounter® optical barcode technology, which allows the simultaneous detection of up to 96 proteins and over 1000 RNA targets in selected regions of interest. Depending on the choice of regions of interest, this analysis can thus be performed on single cells. **To acquire this novel instrument we decided to apply to a call of canceropole Ile-de-France with the SIRIC CURAMUS.**

2.1.4 Pathological and Immunomonitoring Platform

The Immunomonitoring Platform is located at HEGP and facilitates various oncology activities and projects. This platform works in close collaboration with the Tumor Microenvironment Immunohistochemistry Platform. This platform is engaged in quality control and process standardization to ensure reproducibility and transfer to clinical practice. One main exemple is the validation of Immunoscore™. This platform also monitors tumor antigen specific T cell response in cancer vaccine protocols. Some of its tests (Elispot) are already accredited by the Cofrac.

The various activities of this platform are:

- A) Translational Digital pathology with dedicated image analysis softwares for the assessment of immune cells in the tumor microenvironment** (Prof. F. Pages). The translation of *in situ* imaging data from basic research developed in this platform and the associated INSERM unit has enabled to create a test in digital pathology for prognostic purpose in colorectal cancer "Immunoscore".
- B) Immunofluorescence *in situ* analysis for multiparametric analysis at the cellular levels and novel methods of HPV determination** (Profs. C. Badoual and E. Tartour). This structure includes conventional fluorescent microscopy and a multispectral microscope (Vectra/ Polaris) with high throughput based on Leica Bond equipment. Most of the tests performed on this platform involve oncology activities and projects. It is linked with the departments of pathology and immunology of HEGP.
- C) Analysis of specific anti-tumor T cells and immunosuppressive cells in the blood** (Prof. E Tartour). This section works in close collaboration with the CIC Cochin-Pasteur (O. Launay). It is dedicated to the monitoring of vaccines (cancer and other fields) and to the monitoring of immunotherapy and anti-angiogenic protocols in oncology. More than 70% of its activities involve oncology research projects.

The following projects have been developed on this platform:

A) Translational Digital pathology (F Pagès)

Project 1: We analyzed the prognostic and predictive value of the ImmunoScore (IS) in the IDEA France cohort study investigating 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy (FOLFOX) in stage III CC patients. The IS prognostic value for DFS was confirmed in patients with stage III CC treated with

FOLFOX. Additionally, a predictive effect of IS is observed, patients with Low IS do not benefit from longer treatment on the contrary of patients presenting High or Int IS. It supports IS use for guiding the choice of adjuvant treatment duration (**Pagès F, Annals of Oncology 2020**).

Project 2: We developed a Biopsy-adapted Immunoscore (ISB) performed on rectal cancer biopsy samples, as an adaptation of the standardized IS performed on the surgical specimen in colon cancer. We showed that ISB provides a strong and independent prognostic factor for disease free survival of rectal cancer patients. Secondly, ISB predicts the response to neoadjuvant radiochemotherapy (nCRT). Lastly, ISB combined with imaging post-nCRT discriminates the group of patients with a complete histological response to nCRT (no residual tumor) that should benefit from less invasive therapeutic strategies (ie. Watch-and-Wait or minimally invasive surgery), avoiding a disabling and useless rectal amputation surgery (**El Sissy Clin Cancer Res, 2020**).

B) Immunofluorescence in situ analysis platform and innovative methods for HPV determination (Cecile Badoual et Eric Tartour).

Project 1: In collaboration with the group of R. Spisek (Department of Immunology, Hospital Motol, Prague, Czech Republic), we have participated in a work following our previous results in renal cancer showing that the co-expression of PD-1 and Tim-3 on intratumoral CD8⁺T cells is associated with a bad prognosis. In this study, it was shown that in high grade serous ovarian carcinoma PD-1⁺TIM-3⁺CD8⁺ T cells presented all features of functional exhaustion and correlated with poor disease outcome. PD-L1 levels and tumor infiltration by TIM-3⁺ cells improved patient stratification based on the intratumoral abundance of CD8⁺ T cells (**Fucikova J et al Clin Cancer Res 2019**). The co-expression of PD-1+Tim-3+ on CD8⁺T cells thus appears as a robust composite biomarker

Project 2: It is now established that human papillomavirus (HPV) plays a role in the development of a subset of head and neck squamous cell carcinomas (SCCs), notably oropharyngeal (OP) SCCs. However, it is not clear which test one should use to detect HPV in OP and non-OP SCCs. In this study, using 348 head and neck SCCs (126 OP SCCs and 222 non-OP SCCs), we evaluated diagnostic performances of different HPV tests in OP and non-OP SCCs: polymerase chain reaction, p16 immunostaining, in situ hybridization targeting DNA (DNA-CISH) and RNA (RNA-CISH), combined p16 + DNA-CISH, and combined p16 + RNA-CISH. As a stand-alone test, RNA-CISH is the most performant assay to detect HPV in OP SCCs, and combined p16 + RNA-CISH test slightly improves its performances. However, RNA-CISH has the advantage of being one single test. Like p16 and DNA-CISH, RNA-CISH performances are poor in non-OP SCCs to detect HPV, and combining tests does not improve performances (**Augustin, J Hum Pathol 2018**).

Project 3: HPV-related and HPV-unrelated oropharyngeal squamous cell carcinomas are two distinct entities according to the Union for International Cancer Control, with a better prognosis conferred to HPV-related oropharyngeal squamous cell carcinomas. However, variable outcomes are observed among patients with p16 positive oropharyngeal squamous cell carcinoma, which is a surrogate marker of HPV infection.

We aimed to investigate the prognostic value of RNA CISH against E6 and E7 transcripts (HPV RNA CISH) to predict such variability. HPV RNA CISH staining was assessed semi-quantitatively to define two scores: RNA CISH "low" and RNA CISH "high". Clinical and pathologic baseline characteristics were similar between the two groups. RNA CISH high staining was associated with a better overall survival in both univariate and multivariate analyses. In conclusion, HPV RNA CISH might be an independent prognostic marker in p16 positive oropharyngeal squamous cell carcinomas and might help guide therapeutics (**Augustin J, Mod Pathol 2018**).

C) Analysis of specific anti-tumor T cells and immunosuppressive cells in the blood (Eric Tartour)

Project 1: In a collaborative work with the **Vaxeal company**, we have identified novel long peptides derived from the survivin (SVX) antigen expressed by both tumor cells and endothelial cells making it an attractive antigen. This SVX vaccine is composed of three long synthetic peptides containing several CD4⁺ and CD8⁺ T-cell epitopes, which bind to various HLA class II and class I molecules. High frequencies of spontaneous T-cell precursors specific to SVX peptides were also detected in the blood of various cancer patients, demonstrating the absence of tolerance against these peptides. We then demonstrated SVX vaccine's high therapeutic efficacy against four different established murine tumor models, associated with its capacity to generate both specific cytotoxic CD8⁺ and multifunctional Th1 CD4⁺ T-cell responses. When tumors were eradicated,

generated memory T-cell responses protected against rechallenge allowing long-term protection against relapses. These results highlight that this long peptide-based SVX vaccine appears as a promising cancer vaccine and warrants its further clinical development (**Onodi, Front Oncol 2018**).

Project 2: In collaboration with the **Invectys company**, we participate in the immunomonitoring of a DNA vaccine encoding telomerase. Twenty patients with refractory/progressive tumors were enrolled and treated at three escalating doses of 100 µg, 400 µg and 800 µg. 12 pts experienced stable disease according to RECIST. For 10 of them, the treatment was extended up to nine months. INVAC-1 was well tolerated with no dose-limiting toxicities. No significant biological signs of autoimmunity were observed. A majority of pts had high levels of inflammatory plasma cytokines at inclusion, but no significant modification was observed after INVAC-1 administration. IFN-γ polarized anti-hTERT CD4/CD8 immune responses were detected in 55% of pts, following INVAC-1 injections. INVAC-1 triggered de novo anti-hTERT response or enhanced pre-existing natural anti-hTERT immunity. The majority of pts mounted anti-hTERT T cell responses following the second- or third vaccination. These results indicate that INVAC-1 was well tolerated and immunogenic at the doses and schedule tested (**Medioni J, Ann Oncol 29 Suppl 8, 2018**).

Project 3: In collaboration with the group of V Quillien at Rennes (Centre Eugene Marquis) we have participated in a prospective clinical trial with 29 recurrent glioblastomas patients treated with Bevacizumab alone with a longitudinal follow-up of different circulating immune cells [complete blood count, myeloid-derived suppressor cells (MDSCs), classical, intermediate, non-classical and Tie2 monocytes, VEGFR1+ and regulatory T cells (Treg)]. We observed a significant increase of leucocytes, neutrophils, eosinophils and classical monocytes and a decrease for the fraction of Treg during the treatment. The best prognostic values for survival under Bevacizumab were obtained for basal neutrophils and Treg. The predictive value of neutrophils on survival under Bevacizumab was lost in patients treated with corticosteroids, when steroid-free patients with a low neutrophil count had a particularly long median survival (**Quillien V et al Cancer Immunol Immunother 2019**).

2.1.5 Animal housing facilities

Since several research projects involve animal models, CARPEM is supporting two animal housing facilities: the animal core facilities of the Cordeliers Research Center and Cochin Institute. **These 2 animal facilities have been funded with 36 000€ for equipment.**

Animal housing facilities are certified ISO900 since 2015, IBISA labelled and is a member of "Phenotyping Network of the small animal (RPPA)" from Sorbonne Université and the "Anima 75 Network" as well as "PIV, Network of living imaging" from Université de Paris. Numerous multidisciplinary projects among the CARPEM teams involve mice phenotyping to assess metabolic, pathophysiological and behavioural parameters. The development of automated phenotyping systems makes, now, possible to consider an accurate level of parameter measurements. **Recently CARPEM decided to participate in the acquisition of "metabolic" mouse cages.** The project is sustained by SIRIC CARPEM, Sorbonne University and LabexImmunoOnco (Université de Paris). These cages will allow the automated and parallel evaluation of metabolic, behavioural and physiological mice parameters: the food and water intake, the movements and spontaneous activity, weight, temperature, consumption of oxygen and production of carbon dioxide. These cages will contribute to the optimization of the experiments, according to the principles of replacement, reduction and refinement. In fact, these cages will also lead to improve animal welfare because the monitoring and testing will be carried out in an adapted environment with a minimal interface with the experimenter. **This equipment will therefore strengthen the SIRIC CARPEM teams.**

2.2 Biobanks/cohorts

The biobank supported by CARPEM (187 000€ including 3 engineers) is dedicated to clinical diagnosis and research. Human bio-specimens are prospectively collected and stored in accordance with the applicable legislation. Informed consent, de-identification of samples and approval by the local scientific committee are performed for all research programs. This biobank groups together three sites, Necker Biobank (Biological Resources Platform), Georges Pompidou Biobank (Biological Resources Platform) and Cochin Biobank

(Biological Resources Centre). The 3 sites were certified by the AFNOR regarding quality management system (NF S96-900). Three types of human biological samples are stored:

- Biological fluid samples (plasma, serum, faeces, urine, DNA and RNA,...)
- Cells (lymphoblastoid cell lines, EBV-transformed, peripheral blood and bone marrow mononuclear cells, DMSO conserved and cell pellets and others, Peripheral Blood Mononuclear and Bone Marrow cells)
- Tissue samples, originating from clinical and surgical activities (digestive, urological, thoracic, hematological)

Samples are cryopreserved at -80°C, -20°C or at -196°C in liquid nitrogen. Every freezer and cryogenic storage have temperature monitoring as an essential part of quality assurance. To date, 55 storage equipments are available, spread over the three hospitals.

In addition, the pathology departments of the three sites collect and store routinely a great amount of paraffin-embedded tissues, which are available for researchers to perform genomics/proteomics projects, morphometric studies and in situ validation.

The following table gives an overview of the compilation of CARPEM SIRIC's biobank activities

	2018			2019		
	HEGP	Necker	Cochin	HEGP	Necker	Cochin
Sample collected events*	1566	5529	1033	1589	5550	3672
Stored samples for the year ≤ 4°C**	11531	6299	5369	13082	6524	9044
Transferred samples for research	3429	5141	3095	3835	4621	2237
Total stored samples ≤ 4°C	64767	111930	40176	71619	126259	65916

*Number of sample collection events; **Number of stored samples and derivatives (DNA, RNA, aliquot and so on.)

Patient consent: To improve the quality of the collection and the number of samples that can be used for research purposes, **the CARPEM Management Team implemented a new consent form for all cancer patients in the 3 hospitals.** This informed consent process has been discussed by the CARPEM Patients' Committee and it has been approved by the CPP (Person Protection Committee) Ile-de-France 2. It allows the conservation of samples for future research in the field of cancer. This facilitates ethical, retrospective research based on the stored tumor samples. Each new project using these samples must have authorization from a CPP. To better organize and improve the systematic collection and processing of patients consents, 3 biomedical engineers were recruited. They are working with the local clinical teams in HEGP, Cochin and Necker hospitals to improve the circulation of patient's information and the collection of consent agreements. For this purpose, they produced various media supports (leaflets, poster and the movie called "We are all actors for the Cancer research"), which are disseminated in the waiting rooms of the medical and clinical departments.

All these actions at different levels have permitted to increase by 3 folds the number of biospecimens associated with consent form reaching more than 50% of samples in some sub-specialties. For example, in lung pathology, 96% of the tumors are frozen and associated with a consent.

Biological Sample Request: Researchers can request biological samples through the Biological Sample Request Form, where they must indicate, the type and number of samples required, a research summary and proof of ethics approval for the project. Once the biobank manager has reviewed the application, he submits it to the local Research Scientific Committee, and approves it, all researchers involved in the project and their institution must sign a material transfer agreement.

In brief, in 2018, 10 811 events of sample collection for the biobank were performed resulting in 28650 stored samples. 10 693 samples were used for research purpose. To date, close to 264000 samples are stored in SIRIC CARPEM biobank.

Engineer staff: One engineer in HEGP who was hired during the first CARPEM term has got a tenured position at AP-HP. A new engineer has been hired at the beginning of the second term in Cochin and a half-time engineer has been hired for the hematology department in Necker hospital. All three engineers in charge of biobank regulations are working together and with local medical coordinators within the AP-HP group of biobanks.

2.3 Databases

The translational research platform of CARPEM was designed and built to facilitate the storage, manipulation and exploration of the data produced by the different groups (clinical or research). In a nutshell, the translational research platform deployed solutions to collect, store, integrate data and to assist clinicians, biologists and researchers with the exploration and analysis of their data. While the platform was originally designed to integrate user-produced dataset, the activity progressively evolved toward the production of data using Electronic Health Records and data-warehouses and leveraging natural language processing and artificial intelligence methods.

Data collection and integration

We explored different solutions and deployed in 2014 the REDCap data collection tools. REDCap is a free, open software and used by thousands of research centers in the world.

Data collection: Researchers and clinicians of CARPEM have widely adopted REDCap for their studies. REDCap is currently used for 65 CARPEM related studies. The database holds more than 40000 patient records. These data are collected in addition to data already collected through local data warehouses. All data are automatically exportable to the environment of the platform (RStudio server, i2b2...).

Structured and unstructured data sources: While a large amount of information is already present in structured data (lab results, diagnostic codes...), a large quantity of information remains available only in unstructured-text. We have developed and deployed a pipeline to simplify the extraction and queries of free-text data.

Integrating open and private datasets, focus on geodata: In the context of a Canceropôle Ile-de-France working group on open data, we developed an approach to be able to link public and private datasets. We focused our work on geographical data, allowing CARPEM researchers to explore environmental and social determinants of cancer. We added to the CARPEM platform the ability to geolocalize CARPEM patients using a pipeline fully embarked within the hospital. Precise geolocalizations are then identified using the French IRIS level (sub-city paving produced by INSEE).

Bioinformatics: The translational research platform was involved in the management of bioinformatics and sequencing results. We deployed a Galaxy platform now used routinely. The platform also contributed to the development of an automated method to identify insertion site of the HPV virus in the genome of patients. A patent protecting this development is being processed.

Data sharing: The translational research platform has been involved (as WP-leader) in the OSIRIS working group and proof-of-concept project aiming at connecting data warehouses across different French hospitals. We leveraged the open source i2b2/SHRINE software. While the i2b2/SHRINE project is developed by the Harvard School of Medicine, CARPEM worked at simplifying the installation and maintenance process of these tools. Documents and resources are freely available on CARPEM's github repository. CARPEM was also involved in previous steps of the project.

The OSIRIS project includes two minimal datasets (a clinical and an omics dataset), associated recommendations and tools to interconnect local data-warehouses.

Projects with implication of the translational research platform

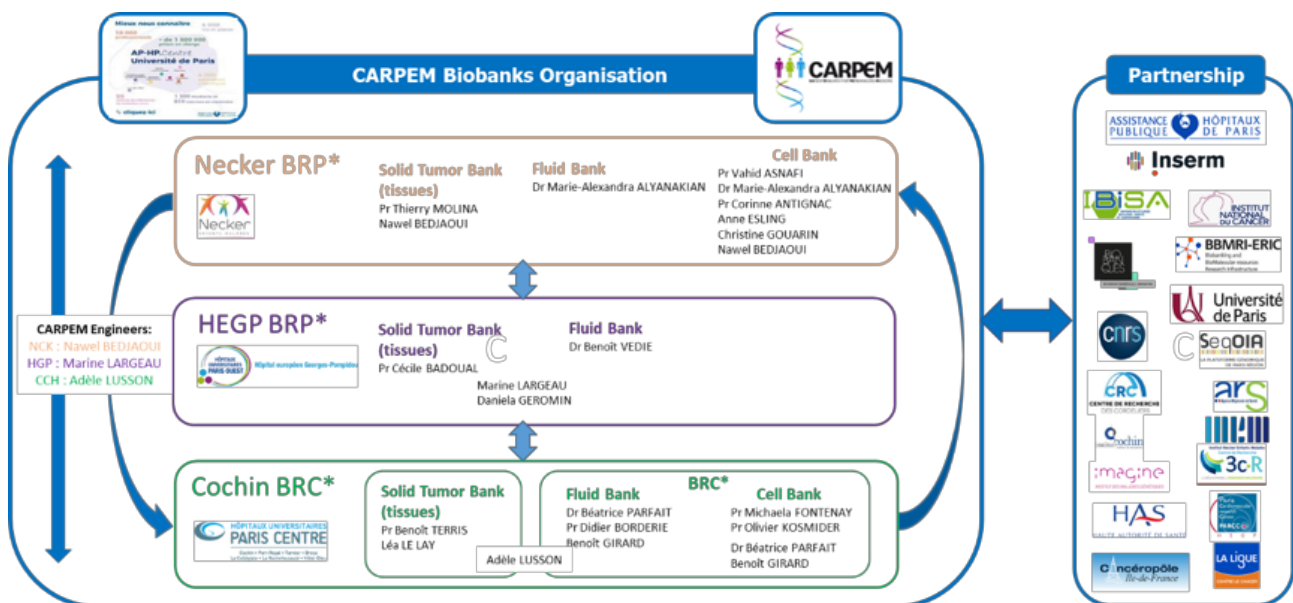
The translational research platform has been involved in several projects:

- RIHDO project (Radiomics and Integration of Heterogenous Data in Oncology) – funded by the Fonds Unique Interministériel-Régions. A large public / private project aiming at improving the care of lung and renal carcinoma using radiomics.
- QualiHealth ANR project – funded by the Agence Nationale de la Recherche. This project involves computer science partners and hospitals and aim at proposing tools to identify and manage quality issues in large biomedical data warehouses.
- ITfoC (IT future of Cancer Treatment) – a Flagship ERA European Project. This project involves a large consortium of European research group focusing on improving the knowledge and treatment option and choice for triple negative breast cancer.

A large part of the team of the translational research platform was implicated in the COVID-19 AP-HP data task force, sharing its expertise on data extraction, Natural Language Processing and geodata.

GeoCANCER was launched in 2018 and made possible through funding by Canceropôle-Ile de France with the ambition of integrating environmental data with patient cancer data. Cancer can be triggered by exposure to toxic agents. The concentrations of such agents display geographical variations, making spatial context important for cancer research. The system combines Geographic Information Systems (GIS) analysis and big data technologies. The first task consisted in enriching cancer data sets with spatial information.

The epidemic of COVID-19 in early 2020 has led to a rapidly increasing number of infections and deaths in the Greater Paris. GeoCANCER system was adapted and transformed into GeoCOV to integrate COVID patient data with spatial information. GeoCOV has played an important role in many aspects, including the rapid aggregation of multi-source big data, rapid visualization of epidemic information, spatial tracking of confirmed cases, prediction of regional transmission, and spatial segmentation of the epidemic risk. GeoCOV provides fundamental spatial information to advise decision-making, measures formulation, and effectiveness assessment of COVID-19 prevention and control. GeoCOV was developed quickly and adapted to COVID epidemic context, thanks to the GeoCANCER experience. GeoCOV provides a pipeline for data preparation, platform construction, model construction, and map production. Clustering is one of the major data mining methods that has been applied to the COVID spatial database at AP-HP to analyze the



*BRP: Biological Ressources Platform
 *BRC: Biological Ressources Centre

microclusters and drive COVISAN interventions in Ile-de-France region.

Ongoing developments

Technologies: The translational research platform relies on modern technologies (docker, kubernetes). Orchestration of the architecture is performed using the open source software Rancher.

We recently added a layer enabling fine automation of sets of tasks. We adopted the open source software AirFlow. This software enabled us to feed weekly dedicated databases (see next section) from different sources. We also leverage the open source workflow management system NextFlow to manage bioinformatics and text processes.

Tumor dedicated databases: Leveraging the developments done on the platform, we have deployed the first CARPEM tumor dedicated databases with a semi-automatic data feeding leveraging the data warehouses. Data are pushed to REDCap databases accessible to clinicians and researchers of the CARPEM. Two databases have been deployed:

- A database for Triple Negative Breast Cancer in the context of the ITfoC European Project
- A dynamic prospective cancer cohort, focusing on cancers treated by immunotherapy

2.4 Teams with specific expertises

2.4.1 Translational bioinformatics and data integration team (Anita Burgun)

The team provides methodological research based on a multidisciplinary approach that synthesizes biomedical statistics and bioinformatics. Their overall expertise includes biomedical ontology, data warehouses, bioinformatics, dose finding methods, hospital information systems, biostatistics and genetic epidemiology.

TEAM 20 expertise has led to **major international collaborations** that will enable three objectives to be reached:

- Develop innovative methods in biomedical informatics, including phenotype algorithms, automatic evaluation of outcomes and methodologies for phenotype/genotype association studies.
- Investigate statistical methods such as bridging studies which can minimize duplication of clinical trials and facilitate the extrapolation of clinical data to a different geographical region.
- Analyze how population variability, either genetic or not, influences disease characteristics, therapeutic decisions and responses to treatment.

2.4.2 Medical Ethics (Marie-France Mamzer)

The team ETREs (EThics, REsearch, translations) is part of the Centre de Recherche des Cordeliers (UMRS 1138). It includes ethicists, sociologists, anthropologists, philosophers, lawyers, and physicians linking Medicine to Human/Social Sciences. This multidisciplinary team has three main areas of cooperation with CARPEM:

- To help CARPEM teams maintain a patient-centered approach and to identify and address ethical issues within the current legal framework in both areas: research and care pathway.
- To develop a specific research program dedicated to ethical issues that may emerge with new practices in personalized medicine.
- To facilitate greater patient's involvement and engagement in CARPEM projects in patient-centered and personalized medicine.

Using a pragmatic approach, members of this team develop empirical research actions making the connection between patients, patient's representatives and society on one hand and health professionals on the other hand. They focus on research practices and health democracy in the field of translational research for cancer, and they address ethical issues emerging in "real life" in CARPEM research. They identified that the most important issues for patients in the CARPEM context were information and consent practices, research results return, data and samples sharing, data linkage for the purpose of translational research and personalized medicine.

2.4.3 Centre essai phase précoce - Early Phase Trial Center (CEPEC)

The CEPEC is the platform for early clinical trials attached to the SIRIC "CARPEM". Created in 2012, the CEPEC is a hospital unit attached to the Medical Oncology Department, directed by Dr. J. Medioni under the responsibility of Pr. S. Oudard. This unit is composed of two beds. The CEPEC has 3 main missions:

- To be a referral treatment centre for cancer patients by offering promising treatments that are still in the experimental stage. The CEPEC conducts clinical trials originating from industry or from academic research.
- Design early stage cancer clinical trials, responding to calls for projects, launched or managed by the French National Cancer Institute (INCa) as well as to industrial or cooperative groups in different cancer areas.
- To train medical residents and fellows in early clinical cancer research. Since 2018 a position has been open at the CEPEC for medical residents who have been specializing in oncology for one year. This position was chosen both times by two residents.

Over the years 2017 and 2018, the CEPEC conducted a total of 19 trials

- 4 Phase I trials with first administration (FIM) in humans; 3 Phase I/II trials; 1 phase II trial; 11 complex Phase III trials. These trials mainly involve patients with cancers of the urological sphere (38 patients) and patients with gynaecological cancer (22 patients) and breast cancer (7 patients). Half of the studies carried out were industrial and half academic. Out of the 8 Phase I, I/II or II trials, 23 patients were included out of the 7 Phase I and I/II trials 11 patients were included. Of the 11 complex Phase III trials, 48 patients were included in total, the CEPEC included an average of 18 patients per bed over 2 years, including complex Phase III trials this led to 8 publications including NEJM and Lancet Oncology.

In 2019, the CEPEC conducted a total of 23 trials: 4 Phase I trials with first administration in humans; 5 Phase I/II trials; 10 phase II trial; 4 complex Phase III trials.

These trials involve patients with cancers of the urological sphere (38 patients), patients with gynaecological cancer or breast cancer (16 patients) and patients with other tumors types (lung, digestive, thyroid and medulo-adrenal cancer (11 patients).

Fourteen of the studies carried out were industrial and eleven academics.

Out of the 19 FIM, Phase I, I/II or II trials, 58 patients were included. Of the 4 complex Phase III trials, 7 patients were included

This led for 2019 to 4 publications including Lancet or Clinical Cancer Research.

An audit was performed in 2019 conducted by the director of SIRIC CARPEM, P. Laurent-Puig and Helene Cart-Grandjean administrative director of SIRIC CARPEM to define the financial sustainability of the CEPEC and how the clinical activity could be increased. **The conclusion of the audit was in favor of the sustainability of the CEPEC with a surplus of 60 000 €. It also concluded that in order to increase the number of patients included in early phase, the CEPEC needed to hire a new nurse. The APHP.Centre steering committee approved the conclusion and budgeted a position for a supplementary nurse for CEPEC-CARPEM increasing the contribution of our institution in the SIRIC CARPEM.**

Furthermore the CEPEC works in narrow collaboration with the department of hematology of Necker and the Oncology department of Cochin which conducted trials in 2018 and 2019 that have included more than 100 patients in Phase II trials during the last 2 years.

2.4.4 Nutritional Epidemiology Research Team (Mathilde Touvier)

The objective of the Nutritional Epidemiology research team (EREN) is to investigate the relationships between nutrition and health, the mechanisms underlying these relationships and the determinants of dietary behaviours. The ultimate purpose of our research is to provide health authorities and government agencies with scientific evidence to guide public health nutrition policymaking. "Nutrition" includes not only diet in its various dimensions (food, beverages, bioactive compounds, environmental exposure), but also physical activity, sedentary behaviour, and nutritional status (bio- and clinical markers). We also explore non-nutritional dimensions of the diet (e.g. food additives, food processing, mode of production, contaminants, etc.). We investigate a large spectrum of nutrition-related pathological and functional health outcomes, such as chronic diseases (cardiometabolic disorders, cancers, skin diseases, etc.), obesity, mental and cognitive

health, mortality, and (healthy) ageing. EREN is the only French team fully dedicated to the epidemiology of nutrition and health, in all its dimensions, and one of the few at the international level. Our overarching goals are to elucidate the complex relationships between nutrition and health, to understand the mechanisms underlying these relationships, and to carefully investigate the full spectrum of determinants of dietary behaviors. To reach these objectives the team has developed, implemented and coordinated randomized controlled trials, several large scale epidemiological studies including the NutriNet-Santé prospective web-based cohort study. **EREN team has a long-lasting experience, extended track record in the field nutritional epidemiology applied to primary cancer prevention and is also recognized as a pioneer at an international level in the field of e-epidemiology.**

2.5 Actions supporting emergence

Total financial support: 420 000 €

CARPEM organizes two calls for tenders for ‘Emerging and Innovative project’ per year for projects strictly within the scope of CARPEM research programmes 1 and 2.

The projects must be emerging, innovative and collaborative, involving at least two CARPEM teams or at least 1 CARPEM team and 1 labelled platform within the framework of a CARPEM technological development. Transdisciplinary projects are prioritized. The funding is 40 000 € maximum for one year and not renewable. This support should allow access to other sources of funding and lead to new collaborative projects. This approach has been adopted by CARPEM teams and is an ongoing success.

32 projects were submitted until 02/2020 and 11 have been funded so far, for a planned total of 420 000 € (3 in 2018, 5 in 2019 and 3 in 2020). 14 out of 23 teams have taken part in emerging projects, as well as 5 clinical teams.

The calls for tenders are not open for program 3 “Dynamic consent and health democracy” because CARPEM members decided to fund this program according to their staffing needs, as the requirements are not the same than for other programs.

AAP	PI	Collaborative teams	Project title	IRP / WP
2018	F. Goldwasser	G. Kroemer / J. Le Naour	Study of the role of energy metabolism in the efficacy of immunotherapies and the mechanism of hypermetabolism.	IRP1 / WP1
2018	L. Roumenina	C. Fridman/ I. Cremer/ Oudard/ Alifano	S. Complement factor H as a prognostic marker and M. tumor growth driver in lung and renal cancer	IRP2 / WP4
2018	B. Tavitian	J. Favier / A.P. Giménez-Roqueplo	Comparative Multimodal Imaging Evaluation of the Preclinical Efficacy of Sunitinib and HIF2a Inhibitors in SDH-dependent Paraganglioma	IRP2 / WP5
2019	M. Castedo	G. Kroemer / P. Laurent-Puig	Modulation of intestinal permeability, autophagy and cancer: development of an in vitro screening system	IRP1 / WP1
2019	B. Romagnolo	E. Donadieu	Modulating T cell responses and DNA repair via autophagy in intestinal stem cell and cancer cells	IRP2 / WP4

2019	C. Desdouets	J. Zucman-Rossi / C. Maiuri	Ploidy spectrum: a new marker of HCC tumor classification?	IRP2 / WP3
2019	N. Burnichon	V. Taly	Evaluation of hypermethylated circulating tumor DNA as a universal predictive marker of recurrence and response to treatment in metastatic renal cancer	IRP2 / WP3
2019	S. Mouillet-Richard	C. Badoual	The cellular prion protein and the mesenchymal subgroup of colorectal cancer: investigation of the tumour-environment interaction	IRP1 and 2 / WP2, WP3
2020	S. Oudard / A. Simonaggio / F. Goldwasser	C. Sautés-Fridman / S. Czernichow / M.A. Dragon-Durey / C. Badoual	Study of immuno-metabolic relationships in patients treated with Immune Checkpoint Inhibitors (ICIs) in metastatic cancer in the Medical Oncology Departments of HEGP and Cochin Hospital: RIMEC project (Relation Immuno-Métabolique hEgp Cochin).	IRP1 / WP1
2020	F. Pagès	P. Laurent-Puig	Personalized Medicine and Organ Preservation in Early Stage Colon Cancer	IRP2 / WP5
2020	O. Kosmider	V. Asnafi	Preclinical Models and Precision Medicine: Application to Patients with Acute Leukemia	IRP2 / WP4

We launched our second 2020 call in May and received 8 candidate project 3 will be selected mid-september.

2.6 Actions supporting training

2.6.1 PhDs and Master 2

Total financial support: 663 000€

To promote training through research, CARPEM organizes a call of proposal in the form of a thesis or Master 2. To promote translational research, CARPEM funds PhDs (2 calls per years) and Master 2 (one call in 2018). Candidates must be MDs, PharmDs or biological, biomedical or informatics engineers intending to complete their training with a PhD. To date, **CARPEM has received 13 applications and funded 4 PhDs, (1 started in 2018 for 3 years she has a MD and the 3 others are funded for one year in 2019, they are specialized in cancer immunology, cancer hematology and cancer endocrinology) and 2 Master students (2 MD, one of them with a radiology background and one with a cancer pediatric background).** Due to the lack of visibility of the cancer plan beyond 2020, CARPEM cannot commit to fund full doctoral fellowships, so we decided to help in setting up funding for a doctoral student allowing to co-finance one year of scientific thesis in order to complete a research year, a medal year (AP-HP) or to finance a 4th year of thesis for example. The demand being more important for thesis years, we have decided to prioritize thesis year funding rather than Master 2. Our second 2020 call in May received 3 candidate files 1 will be selected mid-september

*3 PhD students responded to the AAPs of the first labellisation in 2015. The last year of these PhDs were financed in 2018 by SIRIC CARPEM second labellisation.

PhDs:

AAP	Name	Team	Project title	IRP / WP
*2015	A. Grenier	P. Mayeux/D.Bouscary	Study of the mechanisms of cytotoxicity induced in response to AMP-Activated Protein Kinase (AMPK) in acute myeloid leukaemia: involvement of the PERK kinase	
*2015	C. Granier	E. Tartour	Co-expression of inhibitory co-stimulation molecules (ICMs) on infiltrating T lymphocytes (TILs) in kidney tumours: biological and clinical significance.	IRP2 / WP3
*2015	F. Petitprez	C. Sautès-Fridman	Pan-cancer immune classification: prognostic and theranostic value	IRP2 / WP3
2018	M.E. Dourthe	E. Macintyre / V. Asnafi	Molecular Dissection of the Latent Cell Death Pathway Activated by TCR Triggering in T-ALL	IRP2 / WP5
2019	C. El Sissy	F. Pagès	Study of immune infiltration in locally advanced CRCs	IRP2 / WP5
2019	E. Grignano	M. Fontenay / D. Bouscary	Targeting the Glutathione Metabolic Pathway in Acute Myeloid Leukemia and Protective Mechanisms by the Medullary Stroma: Relationship to the p53 Pathway	IRP1 / WP1
2019	L. Bouys	J. Bertherat	Genetics of bilateral adrenal cortical tumours responsible for cushing syndrome: identification of new causal genes and phenotype-modifying genes.	IRP1 / WP1

Master 2:

AAP	Name	Team	Project title	IRP / WP
2018	S. Haguiri	E. Donnadieu	Influence of extracellular matrix on the antitumour activity of CAR T cells in solid tumours	IRP2 / WP3
2018	T. Léger	M.P. Revel	Prediction of tumor response to immunotherapy in advanced non-small cell lung cancer: contribution of radiomics and deep learning	IRP2 / WP3

2.6.2 Post-doctoral research fellowships

Total financial support: 428 000 €

In line with the strategy to promote intensive team collaboration and training, CARPEM funds post-doctoral researchers for one year. This call for projects was organized to allow applicants to initiate a project while awaiting further funding and/or pending tenure. The chosen projects must be within CARPEM's scope. CARPEM has so far received 19 submissions and funded 7 post-doctoral researchers and one was renewed for an extra-year.

AAP	Name	Team	Project title	IRP / WP
2018	G. Kerdivel	V. Boeva	Characterization of the role of DNA methylation in adrenocortical carcinomas	IRP2 / WP3
2018	W. Xiao	V. Taly	Study of chemo therapy - induced exosomes in tumor heterogeneity and drug resistance using a biomimetic 3D model	IRP2 / WP3
2019	R.N. Ramos	J. Galon	Study of the role of the immune system in the spatio-temporal evolution of metastases	IRP2 / WP3
2019	J. Pol	G. Kroemer	What if autoimmunity holds the key for cancer immunotherapy? – The case of primary biliary cholangitis and cholangiocarcinoma	IRP2 / WP4
2020	T. Hirsch	J. Zucman-Rossi	Integrated genomic analysis of pediatric liver tumors	IRP1 / WP2
2020	M. Pérez-Liva	B. Tavitian	Simultaneous multimodal imaging of metabolic and functional parameters of tumours: tumour heterogeneity and influence of precision medicine treatments	IRP1 / WP1
2020	L. Paolini	E. Tartour	Phenotypic and functional characterization of memory resident CD8+ T cell sub-populations and their prognostic value in lung cancer patients	IRP2 / WP3

2.6.3 The inter-university diploma “Molecular Medecine in Cancer”

This inter university diploma (UID) co-organized by the SIRICs of Île-de-France: SOCRATE, CURIE and CARPEM in partnership with the Universities of Paris Descartes and Paris Sud, under the aegis of the Cancéropôle Ile-de-France, is a success since 2015. This IUD, set up in 2015 and continued in 2018, 2019, is open to oncology specialists from both the public and private sectors. This IUD aims to present recent developments in oncology and to meet the new needs of all specialists involved in this discipline, to acquire a solid biological and technological basis for the implementation of Molecular Medicine in Oncology, but it is also a training course on the ethical and industrial challenges of oncology. The number of participants was **27 in 2018 and 29 in 2019.**

3 INTEGRATED RESEARCH PROGRAMS

A. INTEGRATED RESEARCH PROGRAM 1: METABOLISM, GENETICS, IMMUNITY & ENVIRONMENT

3.1 Initial action plan

Workpackages Tasks and Deliverables of Integrated Research program IRP1	Expected year of rendering
Workpackage 1: Role of metabolism in cellular transformation and therapeutic intervention	
<i>Task: 1.1.1: Clinical connections between oncometabolism and immunosurveillance</i>	
D.1.1 Clinical correlations between metabolic and immunological features of major cancers.	3
D.1.2 Mechanistic comprehension of the immunometabolic crosstalk in cancer	4
<i>Task 1.1.2: Experimental and clinical connections between whole-body metabolism and immunosurveillance</i>	
D1.3 Impact of whole-body metabolism on anticancer immuno-surveillance	3
D1.4 Crosstalk between whole-body metabolism and tumor-intrinsic immuno-metabolism	3
<i>Task 1.1.3: From epidemiological associations between metabolism and cancer to clinical trials</i>	
D1.5 Epidemiological associations between metabolism and cancer using "big data"	2
D1.6 Pilot trials to modulate metabolism in the context of cancer treatment	5
Workpackage 2: Metabolism, Genetics, Immunity & Environment interactions in digestive cancers	
<i>Task 2.1: Liver tumors: from physiopathology to metabolic interaction in patients</i>	
<i>Task 2.1.1: How metabolic syndrome modulates the risk occurrence and molecular subtype of liver tumors</i>	
D2.1.a Identification and validation of genetic markers predisposing to hepatocellular adenoma and carcinoma	2
D2.1.b Identification of cooperative interactions between exposure, metabolic defect and genetic predisposition in liver tumor occurrence	5
<i>Task 2.1.2: Role of the WNT/β-catenin activation in metabolic program and hepatocarcinogenesis</i>	
D2.2.a Assessment of the role of the metabolic partners of the WNT/ β -catenin in murine liver carcinogenesis	4
D2.2.b Validation in Human HCC of the WNT/ β -catenin metabolic partners, cooperative effects and translation in biomarkers	5
<i>Task 2.1.3: Role of metabolic syndrome and diabetes in liver cancer development</i>	
D2.3.a Interaction of polyploidy and immune response in NASH and HCC development	3
D2.3.b Role of sphingolipid metabolism and mineralocorticoid receptor inhibitor in NASH/HCC transition	5
<i>Task 2.2: Metabolism and Colon cancer</i>	
<i>Task 2.2.1: Interaction between metabolic features and molecular subclasses of colon cancer in patients</i>	
D2.4.a Interaction between metabolic features and molecular subclasses of colon cancer in patients based on PETACC08	1
D2.4.b Models of Immune response and molecular metabolic alteration in malignant colon cells and patients	5
<i>Task 2.2.2: Role of the WNT/β-catenin activation interacting with gut microbiota and immune response in intestine carcinogenesis</i>	
D2.5 Modeling microbiota and high fat diet interaction in murine intestine carcinogenesis	5

The IRP1 explores epidemiological relationships between aberrant metabolism (overweight, obesity, vitamin deficiencies, metabolic syndrome, diabetes...) and incidence, molecular subtype, outcome and therapeutic response of several major cancers like breast carcinoma, colorectal cancer, non-small-cell lung cancer and hepatocellular carcinoma. Epidemiological links are hypothesis-generating to investigate the possible cause-effect relationship between metabolic alterations at the whole-body level and cancer development in mouse models and to perform interventional clinical trials on cancer patients. Beyond whole-body metabolism, IRP1 investigates the metabolic alterations affecting isolated cancer and immune cells as well as the entire tumor micro-ecosystem with the ultimate goal to identify new biomarkers for risk stratification and novel therapeutic targets for cancer treatment. This program is coordinated by two leaders in their field, Pr. G. Kroemer and J. Zucman-Rossi. IRP1 is subdivided in two work packages (WP). WP1 deals with the clinical connections between oncometabolism and immunosurveillance, by looking for associations between major cancer cell-intrinsic alterations of metabolism and the local immune infiltrate on clinical samples and by demonstrating cause-effect relationships between such parameters in relevant model systems. WP1 also explores the connections between whole-body metabolism and immunosurveillance both in experimental mouse models and, more importantly, by means of

novel technologies like immuno-oncology chip (that allow to study the interaction between patient-derived malignant and immune cells) and “in vitro technologies” (freshly generated oligocellular tumor suspensions for testing the effects of metabolites, conventional drugs and immuno-oncology agents). WP1 also deals with strictly epidemiological/clinical observations aiming at determining new associations between metabolic and oncological parameters by “big data” analyses and by performing clinical trials in which nutrition and/or physical activity will be targeted with the scope of ameliorating the treatment of major cancers. WP2 focuses on the clinical connections between cancer cell genetics, immunity, metabolism and environment in digestive cancers (mostly hepatocellular carcinoma and colorectal but also to some extent in pancreatic cancer). WP2 deals with the important question as to whether metabolic syndrome, diabetes, obesity and non-alcoholic steatohepatitis (NASH) affect the risk of developing liver cancer of specific molecular subtypes, and how WNT/ β -catenin activation can affect the metabolic zonation in the liver, thereby favoring the development of malignant disease. In colorectal cancer, WP2 will address the question as to whether obesity and/or metabolic syndrome will affect the mutational pattern, specific molecular subtype and the “immunoscore” and how such novel links may be explained in mechanistic terms. To address these questions, last-generation technologies including mass spectrometric metabolomics, genomic and transcriptomic deep sequencing and microbial metagenomics will be used.

3.2 Achievements

Major achievements were obtained by the close collaboration of the experimental (G.Kroemer and J. Zucman-Rossi coordinators, Colnot, C.Desdouets, F. Fougelle, J. Galon, P. Laurent-Puig, B. Romagnolo) with the clinical (J. Taeib, F. Goldwasser, S. Czernichow) research CARPEM teams. Below are summarized the major achievements reported mostly by WP and the corresponding deliverables are reported in red.

WP 1: Role of metabolism in cellular transformation and therapeutic intervention

Nutrition and cancer. Low quality of the food consumed, especially ultra-processed food, was associated with a higher risk of cancer (*Fiolet T et al. BMJ 2018*; *Lavalette C et al. Cancer Res 2018*; *Deschasaux M et al. Plos Med 2018*), while a plant-based diet protects against cancer (*Kane-Diallo et al. Int J Cancer 2018*). The prospective Nutrinet-Santé study with 107,377 participants revealed that low dietary fibre consumption predisposes to mortality from cancer, particularly in breast and colorectal cancer (*Partula et al. Am J Clin Nutr. 2020*). The consumption of sugary drinks was significantly associated with the risk of overall cancer (n=2193 cases, subdistribution hazard ratio for a 100mL/d increase 1.18, 95% confidence interval 1.10 to 1.27, P<0.0001) and breast cancer (693, 1.22, 1.07 to 1.39, P=0.004) (*Chazelas et al. BMJ 2019*). High spermidine uptake with nutrition was found to reduce overall cancer risk in two independent prospective studies (*Kiechl et al. Am J Clin Nutr 2018*), perhaps reflecting an immunostimulatory effect of this polyamine that was revealed in preclinical studies (*Levesque et al. Oncolmmunology 2019*). **D1.5**

Plasma metabolome and cancer risk. A lower plasma level of O-succinyl-homoserine and higher plasma levels of valine/norvaline, glutamine/isoglutamine, 5-aminovaleric acid, phenylalanine, tryptophan, γ -glutamyl-threonine, , and pregnene-triol sulfate were associated with an increased risk of developing breast cancer during follow-up (*Lécuyer et al. Cancer Epidemiol Biomarkers Prev 2019*). Metabolomic plasma analyses revealed that a lower level of piperine (a compound from pepper) and higher levels of acetyltributylcitrate (an alternative plasticizer to phthalates), pregnene-triol sulfate (a steroid sulfate), and 2-amino-4-cyano butanoic acid (a metabolite linked to microbiota metabolism) were observed in plasma from women who subsequently developed breast cancer (*Lécuyer et al. Cancer Epidemiol Biomarkers Prev. 2020*). **D1.5**

Obesity and cancer. Although obesity is one of the most important risk factor for cancer, some cancer types have a paradoxically better prognosis in obesity, as true for metastatic colon cancer¹. Obesity is linked to higher plasma levels of circulating acyl coenzyme A binding protein (ACBP), while anorexia is associated with low ACBP levels. ACBP turned out be the most ancient, phylogenetically conserved stimulator of appetite in multiple model species (yeast, nematodes, mice), acting through GABAA receptors to stimulate food intake and lipo-anabolic reactions. Accordingly, neutralization of ACBP had anti-obesity effects in mouse models

¹ Aparicio et al. Eur J Cancer 2018

and then might constitute a strategy for treating obesity and these co-morbidities (*Bravo San Pedro JM et al. Cell Metabolism 2019; Charmpilas et al. Cell Death Dis 2019*). D1.1, D1.2 & D1.5 Among them non-alcoholic fatty liver disease can be counteracted by multiple new strategies in animal models including the treatment with anti-ACBP antibodies (*Bravo San Pedro JM et al. Cell Metabolism 2019*), treatment with the SAT1 activator triethylene tetramine (*Castoldi F et al. Cell Death Dis 2020*) or treatment with RIPA-56, a specific inhibitor of receptor-interacting protein kinase 1 (*Majdi et al. J Hepatol, 2020*). There are also data suggesting that the microbiota plays an important role in this disease (*Hoyles et al. Nat Med 2018*). D2.1 & D2.5

Autophagy and cancer. Autophagy plays a major role in the suppression of oncogenesis. Thus, knockout of ATG7 is oncogenic when combined with that of TP53, supporting the notion that autophagy is a tumor suppressive mechanism (see IRP2 Trenteseaux et al. PNAS 2020). In glycogen storage disease type Ia, high fat diet great accelerates oncogenesis as a result of metabolic stress and suppressed autophagy (*Gjorgjieva M et al., J Hepatol 2018*). Conversely, stimulation of autophagy by starvation, spermidine, hydroxycitrate, thiostreptone or 3,4 dimethoxychalcone can sensitize cancers to treatment with immunogenic chemotherapy or PD-1 targeting immunotherapy, as shown in multiple models (*Lesveque S et al. 2019 Oncolmmunology; Chen G et al. EMBO Mol Med 2019; Wang Y et al. J Immunother Cancer 2020*). D1.3 & D1.4

A dialogue between cancer cell metabolism and anticancer immune responses. It appears that aldehyde dehydrogenase 7 family, member A1 (ALDH7A1) and lipase C, hepatic type (LIPC), which have prognostic impact on non-small cell lung cancer also affect the composition and density of the immune infiltrate (*Stoll G et al. Oncolmmunology 2019*). D1.3

Hypermetabolism as a negative prognostic factor. Metastatic non-small cell lung cancer (NSCLC) patients with an increased ratio of the resting energy expenditure (mREE) over the expected resting energy expenditure (pREE) have poor prognosis, and this parameter (mREE/pREE) emerged as an independent prognostic factor (*Jouinot A et al. Clin Nutr 2019*). Accordingly, in preclinical models, starvation, which reduces resting energy expenditure can reduce tumor growth while sensitizing to chemotherapy (*Obrist F et al. EMBO J 2018*). D1.6

Oxidative phosphorylation and cancer. We found that inhibition of oxidative phosphorylation by the knockout of AIFM1, a gene required for the biogenesis of respiratory chain complexes, can reduce tumor growth in vivo, in mouse models (*Rao S et al., Cell Res 2019*). Accordingly, inhibition of respiratory chain complex I can be used to inhibit tumor growth in preclinical experiments (*Sica V et al., Cell Rep 2019*). Inhibition of the mitochondrial calcium uniporter also has anticancer effects (*Marchi S et al. EMBO J 2019*). Moreover, beta-catenin-induced liver cancers are addicted to fatty acid oxidation in mitochondria (*Senni N et al. Gut 2019*). D1.2 & D2.2

Protein synthesis and endoplasmic reticulum stress in cancer. Several studies point to the importance of transcription/translation for oncogenesis and tumor control. Thus, inhibition of ribosome biogenesis inhibition efficiently reduces cancer cell proliferation in the intestinal epithelium driven by APC defects (*Raveux et al. Cell Death Dis 2020*). Similarly, it appears that immunogenic cell death inducers including chemotherapeutics systematically inhibit transcription and subsequent translational stress with phosphorylation of eIF2alpha (*Gomes-da Silva LC et al. EMBO J 2018; Bezu L et al. 2018 Cell Death Dis; Humeau J et al. EMBO Mol Med 2020*). For endoplasmic reticulum stress, it appears that urinary elevation of the prion protein PrPC is an accurate biomarker (*Bignon Y et al. Cell Death Dis 2020*). Intriguingly, PrPC also predict survival in colorectal cancer (*Le Corre D et al. eBiomedicine 2019*). D1.3 & D1.4

Stress and cancer. Psychiatric conditions have a major impact on the therapeutically relevant cancer-immune crosstalk. Thus, in non-small cell lung cancer and in colorectal cancer, depression and stress cause an increase in the glucocorticoid tonus (both in mice and humans), leading to failure of immunogenic chemotherapy and immunotherapy (*Yang H et al. Nat Med 2019*). Moreover, comedication with psycholeptics were independently associated with pCR in breast cancer patients. Importantly, level 3 hypnotics (N05C) alone were able to reduce tumor growth in BC bearing mice and increased the anti-cancer activity of cyclophosphamide in a T cell-dependent manner (*Hamy AS et al. Oncolmmunology 2019*). It appears that some chemotherapies can sensitize to subsequent immunotherapy as this has been shown for oxaliplatin

(Liu P et al. *Nat Commun* 2019) and cisplatin (Fournel et al. *Cancer Letters* 2019), in part due to the upregulation of PD-L1 on tumor cells. D1.3 & D1.4

Microbiota and cancer. The treatment of non-small cell lung and renal cell carcinomas by immunotherapy is profoundly conditioned by the composition of the gut microbiota, which in turn is influenced by broad-spectrum antibiotics (for both lung and renal cancer) and prior treatment with tyrosine kinase inhibitors (for renal cell carcinoma). This has been shown in retrospective clinical analyses, as well as in a prospective trial (NCT03013335) (Routy B et al., *Science* 2018 & Fluckiger A et al. *Science*, 2020 in press) and European Journal of Urology (DeRosa L et al., *Eur J Urol* 2020). Indeed, it appears that the microbiota has a vast effect on organismal fitness, healthspan and lifespan (Barcena C et al., *Nat Med* 2019) D1.1 & D1.2 & D1.6.

WP 2: Metabolism, Genetics, Immunity & Environment interactions in digestive cancers

Genetic predisposition and liver cancer. In the search of genetic markers predisposing to liver tumor development, we identified a protective impact of a17-beta-hydroxysteroid dehydrogenase 13 (rs72613567 loss of function) variant on hepatocellular carcinoma development in alcoholic liver disease, as shown in a cohort of European patients with HCC (n = 1,109) or without HCC, but with chronic liver disease (n = 2,206) (Yang J et al. *Hepatology* 2019). Furthermore, TM6SF2 and PNPLA3 variants were identified to cooperate to increase the risk of HCC occurrence in particular in patient with alcoholic or non-alcoholic metabolic disorders (Yang J et al. *Int J Cancer* 2019). We also identified that patients with germline APC mutation develop hepatoblastoma characterized by an important immune microenvironment and tertiary lymphoid structures (Morcrette G et al. *Oncoimmunology* 2019). These results illustrate the potential translation of specific germline genetic predisposition in surveillance and therapy. Moreover, it shows the interaction between genetic predisposition and exposure to other risk factors in the development of liver cancer. D2.1 and D1.3

Translating tumor metabolic alterations in PET-CT imaging. Metabolomic analyses in liver tumors showed that both human and mouse β -catenin activated HCC (β cat-HCC) have an increased uptake of choline, visualized through Positron Emission Tomography-Computed Tomography (PET-CT) imaging using Radiolabelled Fluoro-Choline. Dietary choline is a major methyl group donor, and its increased uptake leads to DNA hypermethylation in β -catenin-activated tumors, linking metabolic changes to epigenetic reprogramming. This study brings the dual message that β cat-HCC could be specifically diagnosed through a non-invasive PET-CT imaging approach, and that choline deprivation could be therapeutic for β cat-HCC as it is in mice (Gougelet A et al. *Gastroenterology* 2019). D2.2

Fatty acids fuels β -catenin HCC: metabolic and epigenetic interactions. Using murine model of β -catenin-activated tumors, we have shown that fatty acid oxidation increases, contributing to the absence of steatosis in these HCC. By intercrossing tumor-developing mice with mice unable to oxidize fatty acids, we observed a decreased tumor progression, demonstrating the energetic dependency of β cat-HCC on fatty acids (Senni N et al. *Gut* 2019). We previously showed that the expression of Hnf4 α is often lost in β cat-HCC, and we demonstrated a functional antagonism between β -catenin and Hnf4 α in the transcriptional regulation of gene expression. We intercrossed tumor-developing mice with Hnf4 α -null ones and showed how these two players functionally interact in metabolic alterations and tumorigenesis (Sartor C et al. *Liver Int* 2019). Finally, to assess the role of ARID1A loss on β cat-HCC, a compound inactivation of both Apc and Arid1a has been done. Unexpectedly, it leads to a dramatic accumulation of red blood cells in the liver, due to an aberrant erythropoiesis, linked to a *de novo* intrahepatic transcription of erythropoietin. This brings the first proof that the loss of Arid1a, a chromatin remodeler, is able to reprogram β -catenin transcriptome in the liver (Riou et al, in revision *eLife*). D2.2.

Polyploidy and liver cancer. In order to identify diagnostic and prognostic markers in liver cancer patients implemented the determination of in situ ploidy spectrum on tissue section. The strength of this approach is to localize polyploid contingents accurately within the liver tumor and non-tumor parenchyma. It was shown that nuclear ploidy was sufficient to distinguish between premalignant and malignant liver parenchyma. Interestingly, binucleate polyploid fraction (cellular ploidy) is drastically reduced during human liver tumorigenesis, and conversely, mononucleate polyploid fraction (nuclear ploidy) is specifically amplified in HCCs. In tumors, we showed that the quantification of mononuclear polyploid hepatocytes could be a marker of HCC with poor prognosis (Bou-Nader M et al. *Gut* 2020). Hyperploidy and aneuploidy of cancer cells may

also affect the cancer-immune dialogue because of the preferential capacity of hyperploid cells to stimulate anticancer immune responses, causing them to be selected or "edited" by the immune system (*Aranda F et al. Oncolimmunology 2018* *Tripathi R et al. Oncolimmunology 2019*) (D2.3 & D1.2).

Heterogeneity of liver cancer and therapeutic response. Taking into consideration the molecular heterogeneity in liver tumors, we developed preclinical models based on the genomic characterization of a large collection of human tumor cell lines (n=40) screened with >100 compounds. This strategy enabled the identification of new therapeutic targets associated with biomarkers (*Caruso S et al. Gastroenterology, 2019*). In parallel, new subtypes of HCC have been described associated with specific signaling pathway alterations in HCC with the identification of BAP1 mutations in variant fibrolamellar carcinoma (*Hirsch TZ et al. J Hepatol 2020*), activation of CCNA2 or CCNE1 drive a new subtype of chromosome rearrangement (*Bayard Q et al, Nature Com 2018*), ROS1 translocation in benign inflammatory hepatocellular adenoma (*Bayard Q et al. Gut 2020*). Also, various molecular subclasses of liver tumors are associated with prognosis of disease progression underlining correlation with clinical heterogeneity (*Nault JC et al. Hepatology 2019*). In addition, a close correlation has been identified between transcriptomic and molecular subclasses of HCC with the pathological phenotype for HCC (*Calderaro J et al, Clin Can Res 2019*) or HCA (*Calderaro J et al, NEJM 2018*).

Genomic heterogeneity in mesothelioma. Using the development of new bioinformatic tools, we dissected heterogeneity in mesothelioma through histo-molecular gradient, revisiting the transcriptomic classification of these tumors, that is useful for future innovative clinical care of the patients (*Blum Y et al. Nature Com 2019*). Also, assessment of signaling pathway inhibitors and identification of predictive biomarkers in malignant pleural mesothelioma using drug screening in the largest collection of 80 primary mesothelioma cell lines identified new targets that are relevant for clinical trials (*Tranchant R et al. Lung Cancer 2018*)

Metabolic-molecular tumor subclasses interactions in colon cancer. We explored the impact of body mass index (BMI) in prognosis of colon cancer in relation with molecular subtype in the framework of the clinical trial PETACC8 for which a collection of tumor DNA was prospectively done. We analyzed the prognostic impact of different BMI status (18.5-25, 25-29.9 and ≥ 30 kg/m²) in stage III colon cancer patients (n=1723) included in the PETACC 8 trial according to the CMS classifications of tumors assessed for 1723 patients. The 3 categories of BMI were comparable for the whole in criteria on the oncology plan. The results showed that BMI was not associated with TTR or OS in CMS 1, 2, 4 groups. However, we have found a tendency toward the association between obesity and shorter TTR only in patients with CMS 3 (HR=3.89, 95% CI: 0.99- 15.26). No impact was observed with overall survival in this class (manuscript in preparation) (D2.4)

Autophagy, microbiota and intestinal barrier. Autophagy is required for maintenance of intestinal integrity, meaning that conditional knockout of an essential autophagy gene such as ATG7 compromises barrier function due to disruption of stem cell renewal (see IRP2 Trenteseaux et al. PNAS 2020) and that substitution with bacteria that induce autophagy improves intestinal barrier integrity commensurate with a better immune function (*Daillere et al. submitted*). Also, modulation of the WNT/ β -catenin signaling pathway in the protection of the intestine barrier is currently further investigated integrating the function of microbiota (*Hassan M et al. J Hepatol 2020*). D2.5.

3.3 Amendments to the original work plan

The Integrated Research Program 1: "Metabolism, Genetics, Immunity & Environment" has been executed as planned, meaning that no deviations from the work plan have occurred. For this reason, no specific action plan is required, and the program will be continued without any relevant modifications.

3.4 Outstanding performances and successful developments

The immuno-metabolism-centered integrated research program (IRP1) has led to multiple high-impact factor publications including Science, Nature Medicine, British Medical Journal, Cancer Cell, Cell Metabolism as well as to multiple high-impact factors specialty journals and **directly led to 46 publications during the 2018-2020 designation period with first and/or last authors from CARPEM (annex 1.1). Among them 24 publications were made in journals with an impact factor superior to 10, including 13 in journals with an impact superior**

to 15 and 8 in journals with an impact superior to 20. Furthermore, this IRP1 led to 23 indirect publications (see annex 1.2)

Among the successful developments:

- New nutritional and metabolic risk factors have been identified, while multiple studies indicate the important role played by immune effectors in controlling oncogenesis and tumor progression. This extends to the intestinal microbiota, which conditions anticancer immunosurveillance in patients.
- Metabolic interventions to reduce tumor progression have been designed and have been successfully tested in preclinical studies, showing for example that autophagy inducing diets and agents can stimulate anticancer immunosurveillance and hence be considered as adjunct treatments that can be combined with immunogenic chemotherapies and immune checkpoint inhibitors.
- An unprecedented database was created by establishing a well genomic and clinically annotated liver cancers that will help the entire community as underlined by the SAB in its report.
- The demonstration of a very interesting linkage of BAP1 mutations to PKA upregulation, which may offer new avenues for therapeutic intervention in fibrolamellar carcinoma.

3.5 Quality of the collaboration

3.5.1 IntraSIRIC collaboration

IntraSIRIC collaboration is at the heart of the concerns of the steering committee, which brings together all CARPEM's sensitivities. Indeed, the steering committee brings together clinicians, researchers, epidemiologists, human and social science researchers and patients. In order to encourage interactions between CARPEM teams, the emergence program makes it compulsory for at least two different CARPEM teams to interact. The steering committee is extremely attentive in its project selection to this aspect.

In the framework of IRP1 SIRIC CARPEM funded 7 projects associating at least 2 teams of CARPEM (emergence program) see § 2.5 and 7 projects with a PhD or post-doc financed by the CARPEM involved.

In addition, various projects resulting from IRP1 were developed during the first two years of the CARPEM 1/ based on regular meetings between CARPEM research groups participating to IRP1, Pr. G. Kroemer by fostering the interaction between members of the CARPEM proposed a new program for the renewal of Immunoncology labex (laboratories of excellence). The LABEX project deals with the fact that the micro-metabolism of cancer cells (oncometabolism) and that of immune cells (immunometabolism) is influenced by whole-body metabolism, which determines the efficacy of antitumor immunosurveillance. Lifestyle factors including the quantity and quality of nutrition, physical activity, exposure to pollutants and infectious agents, co-morbidities and co-medications play a major role in oncogenesis, tumor progression and therapeutic response including to immunotherapy. The natural evolution of cancer as well as their response to treatment is profoundly shaped by tissue inflammation, infectious agents and immune responses, suggesting that these processes might be actionable targets for cancer prevention. The Labex program will invest the forthcoming 5 to 6 years into examining these problems and questions. This project was retained by the French Government and involves 6 research teams of the SIRIC CARPEM (G. Kroemer, J. Galon, E. Tartour, I. Cremer, J. Zucman-Rossi, P. Laurent-Puig and one from the SIRIC SOCRATE (L. Zitvoguel).

2/ Thanks to large collection of biological samples of colon and hepatocellular carcinoma patients P. Laurent-Puig and J. Zucman Rossi teams participated in a work of G Kroemer to demonstrate that a TLR3 ligand reestablishes immunogenic chemotherapeutic responses in the context of FPR1 (Formyl peptide receptor 1) deficiency on antigene presenting cells. This work is in revision in Cancer Discovery

3/ Different CARPEM research teams have combined their efforts to apply successfully to different calls:

P. Laurent-Puig/V.Taly and G. Kroemer teams were funded for their COCAHEMSICLE project in 2018 by the single cell call (ITMO cancer)

J. Zucman-Rossi, P. Laurent-Puig/V.Taly and C. Dedouets teams were funded by the PRTK (2018-2021) in the TELOTEP project

C. Dedouets, J. Zuman-Rossi & F. Foufelle teams were funded by an PLBIO projet "Control Points for DNA Damage and Polyploidy: Guardians of Hepatic Cancerogenesis Associated with Metabolic Disorders"

3.5.2 ExtraSIRIC collaboration

ExtraSIRIC collaboration in the framework of IRP1 are described in annex 5 and by the analysis of publications directly and indirectly linked to CARPEM integrated research program 1. This analysis shows a large level of collaborations through the world (Sweden; Usa; China; Spain; Austria; Italy; Belgium; Germany; England; Greece; Canada; Finland; Japan; Netherlands; Norway; Portugal; Switzerland; Australia; Brazil; Czech Republic; Denmark; Israel; Malaysia; Pakistan; Serbia). Indeed, most of the participating teams developed collaborations with national and international partners. More specifically, in the framework of WP2, J Zucman-Rossi developed a national network for hepatocellular carcinomas as well as pediatric liver tumors research. She organized half-day meetings every three months on WP2, open to a national audience, in order to foster collaboration between French liver researchers. These meetings include physicians dedicated to liver cancer patients, specialized pathologists in liver diseases and molecular biologists. This network reinforces the quality of research of the IRP1, most of the results obtained involved several researchers from outside CARPEM which attests the quality of the extraSIRIC collaborations. Furthermore J Zucman-Rossi, with Sergio Roman-Roman (director of SIRIC CURIE), pilots the working group of Cancéropôle Ile-de-france dedicated to platforms. Together, they initiated the new Cancéropôle Ile-de-France call of tenders. Indeed, the Cancéropôle Ile-de-France wishes to unite the research teams in the Paris Region around innovative and open platforms by launching a 2020 call for tenders with the aim of acquiring and making available equipment enabling the use of new technologies for cancer research. The project will have to be carried out by research teams located in the Ile-de-France region and involving at least two Sirics from Ile-de-France. The SIRIC CARPEM and CURAMUS applied together for the buying of a complement of nanostring platform GeoMx® Digital Spatial Profiler. This project has been preselected and the final decision is expected in November.

G. Kroemer team has multiple collaborations (academic and with industrials) in the framework of IRP1 particularly with the SIRIC SOCRATE 2.0 both with L. Zitvogel and thanks to the metabolomic platform. This was highlighted by the SAB in its report.

The team of Chantal Dedouest has developed strong collaborations in the field of inflammation and liver cancer with M. Heikenwalder at German Cancer Research Center (DKFZ), Heidelberg and N. Gueera at Imperial College London.

3.6 Programmes for the dissemination of knowledge and good practices

IRP1 led to 67 original articles resulting directly or benefited from CARPEM structuring actions (annex 1.1 & 1.2). The number of citations of these original articles was 1405 without self citation². The h index of this corpus of document was 13 showing the impact of the scientific production of IRP1.

Furthermore, CARPEM strongly encourages the dissemination of knowledge through reviews writing.

A total of 82 reviews were published in the framework of IRP1 during the second period of CARPEM. Among them 4 were written in French for medical students and general practitioners. Among the 78 reviews in English several are published in high impact journals (Cell, Nat Rev immunol, J Hepatol, Gastroenterology). **Several members of the IRP1 participate to international guidelines, nomenclature and clinical recommendations on immunogenic cell death, autophagy and hepatocellular carcinoma. Furthermore, the most recent research advances in liver carcinogenesis and their implication in clinical practices as well as the interaction between metabolism and cancer are described in didactic reviews.**

As already mentioned in §3.5.2 IRP1 organize in the WP2 regular meetings every 3 months and beside the aim to foster collaboration between researchers, there is an objective to favor the teaching of medical residents and fellows in the liver cancerogenesis. They actively participated in this open meeting which is a true success of CARPEM. Furthermore, the Cordeliers Research Center and SIRIC CARPEM co-organize on weekly basis an open scientific seminar. During the second period of CARPEM, 20 seminars were dedicated

² Data provided by web of Science

to the themes developed in the framework of IRP1. Among them, 8 were presented by young researchers of CARPEM. The other speakers were invited, including 8 from abroad (United States, Germany, Italy, Israel, etc.).

Concerning patients and publics 2 video concerning the IRP1 programs are available on the CARPEM web site the first one is about immunosurveillance of breast cancer <http://carpem.fr/immunosurveillance-du-cancer-du-sein/> the second is a video about microbiote, metabolism and response to immunotherapy about the work of G Kroemer in the framework of IRP1 <http://carpem.fr/avancees-dans-les-traitements-anticancereux/>

3.7 Impact of the SIRIC designation on the integrated research program

The effect of SIRIC designation was to introduce the metabolism in the framework of genomics and immunology and their interactions with environment. IRP1 structured the interactions between epidemiologists, geneticists, immunologists, physicians dedicated to nutrition and oncologists. It allowed potential identification of new targets for therapy which will be implemented in clinics. As mentioned by the SAB, these works seem to be particularly interesting and of potential use in future cancer therapy. Furthermore, the cell biology screening platform created by G. Kroemer is a valuable resource and could be leveraged to benefit research programs of scientists in CARPEM. Specifically, this platform could be adapted to study different cells of interest. Our priority is to ascertain that these resources be made available to CARPEM investigators thank to the CARPEM support. The effect of CARPEM SIRIC's designation can also be assessed by the leverage effect of CARPEM. For the IRP1 program see Annex 4, the leverage effect, so far, is approximately EUR 4.7 million for the second CARPEM SIRIC period.

3.8 Action plan for the 2nd period of the designation

A strong recommendation of the scientific advisory board is the creation of a specific cancer-dedicated bioinformatics platform, which will be led by Aurélien de Reynies recruited as full professor by Université de Paris and APHP in 2021. The Siric CARPEM and the Université de Paris will provide two engineers as initial support. Aurelien de Reynies has already collaborated with several CARPEM teams as a bioinformatician and his contribution to several ongoing IRP2 projects is decisive. His hiring by the Université de Paris and by the APHP testifies of the strong involvement of the 2 institutions in the SIRIC CARPEM. This platform will accelerate the analyses of large dataset of information generated by the CARPEM research programs and provide the tools for speeding translation to clinical practice. Aurelien de Reynies is the scientific director of the very succesfull national program “Carte d’identité des tumeurs” of Ligue contre le cancer. Indeed, in the framework of this program collaborates with the CARPEM. His main publications of the last 5 years with membesr of the SIRIC CARPEM are: Beuselinck B et al. Clin Cancer Res 2015; Guinney J et al. Nature Med 2015 ; Castro-Vega LJ et al. Nature Comm 2015; Becht E, et al. Genome Biol 2016; Becht E et al. Clin Cancer Res 2016; Tranchant R et al. Clin Cancer Res 2017 ; Puleo F et al. Gastroenterology 2018 ; Roumenina et al. Cancer Immunol Res. 2019 ; Blum Y et al. Nat Commun. 2019 ; Le Corre D et al. EBiomedicine 2019 ; Job S Clin Cancer Res 2019 ; Petitprez F et al. Nature 2020.

B. INTEGRATED RESEARCH PROGRAM 2: CANCER HETEROGENEITY: A CHALLENGE FOR PATIENT MANAGEMENT

3.1 Initial action plan

Workpackages Tasks and Deliverables of Integrated Research program IRP2	Expected year of rendering
Workpackage 3: Development and improvement of new technologies to understand cancer heterogeneity	
<i>Task 3.1: Multiparametric analysis based on single cell microfluidic analysis for tumor heterogeneity characterization</i>	
D3.1 Development and validation of scRNA-seq and scATAC-seq (or scChIP-seq) on hematological and solid tumors	4
<i>Task 3.2: Multiparametric analysis based on imaging for tumor heterogeneity characterization</i>	
<i>Task 3.2.1: Multiplex in situ analysis</i>	
D3.2 Validation of a multiplex immunofluorescence analysis on paraffin embedded tissue	3
<i>Task 3.2.2: Multi-parameter probing</i>	
D3.3 Application of the microfluidic probe (MFP) technology to perform multiple testing of solid tumors (IHC) coupled with cell lysis and genetic or epigenetic analysis	4
<i>Task 3.2.3: Novel-imaging tools to monitor interaction between cancer and immune cells</i>	
D3.4 Demonstration that the modulation of tumor microenvironment may improve CAR trafficking	5
<i>Task 3.3: Tracking biomarkers of disease and treatment resistance</i>	
<i>Task 3.3.1: Overcoming genetic heterogeneity using universal markers to track circulating tumor DNA</i>	
D3.5 Development of universal cancer methylation markers as form of signature (detected by a NGS panel) allowing to highlight presence of several cancer types (lung, digestive and gynecologic cancers)	3
<i>Task 3.3.2: Assessment of genetic and immunogenic biomarkers in myeloid and lymphoid malignancies</i>	
D3.6 Optimization of droplet digital PCR to characterize clonal architecture at single cell level and to detect minimal residual disease in myeloid and lymphoid malignancies.	2
<i>Task 3.3.3: Development and validation of genome-wide CRISPR/Cas9 screen to identify new treatment resistance biomarkers</i>	
D3.7 Validation of newly discovered targets in the CRISPR screen and identification of efficient therapeutic tools by using a pharmacological screen	3
<i>Task 3.4: 3D cultures for the characterization of tumor cells in different cancer contexts</i>	
<i>Task 3.4.1: Towards patient derived tumor mimics</i>	
D3.8 Set-up and analysis of heterogeneity of 3D multicellular tissues derived from cell lines and patient colon cancer samples	5
<i>Task 3.4.2: Humanized scaffolds to mimic bone marrow niches and give insight on importance of tumor-inflammation in myeloid malignancies</i>	
D3.9 Use of humanized scaffolds to investigate the relationship between transplantation efficiency and genotype and for in vivo testing of genotype-targeted therapy.	4
Workpackage 4: Preclinical model to address medical and scientific concerns linked to host and tumor heterogeneity	
<i>Task 4.1: How the dialogue between tumor and immune cells dictates the immune landscape heterogeneity and the regulation of tumorigenesis</i>	
<i>Task 4.1.1: Influence of the tumor suppressor gene Math1 on the composition of tumor microenvironment and regulation of tumor growth</i>	
D4.1 Comprehensive analysis of the composition of tumor microenvironment (CD8+T cells) in the presence or absence of Math1	2
<i>Task 4.1.2: Interplay between epigenetic modifiers and the immune response in liver carcinogenesis</i>	
D4.2.a Identification of the immune cell population in contact of β -catenin activated hepatocytes and required for the transcriptomic control of the Dkl1/Dio3 locus involved in tumor formation	4
D4.2.b Identification of the consequence of the loss of ARID1A or ARID2 on the composition of immune cell in the tumor microenvironment as well as of the genetic or pharmacological inactivation of immune players on the oncogenic mutations (β catenin, ARID1A, ARID2) mediated tumor formation	3
<i>Task 4.1.3: Complement and tumor heterogeneity</i>	
D4.3 Comparative analysis of tumor microenvironment in wild type, transgenic or complement deficient mouse strains grafted with wild type tumor cell lines and deciphering of the complement proteins role in	5
<i>Task 4.2: Respiratory viral infections: consequence on lung tumor heterogeneity</i>	
D4.4.a Comparative analysis of lung tumor microenvironment in tumor bearing mice (orthotopic and spontaneous models) infected or not with influenza virus and with RSV and consequences in resistance to therapy	1
D4.4.b Looking for the expression of human virus in the tumor microenvironment of human lung cancer.	5
<i>Task 4.3: Role of the initial site of immune priming and location of tumor on the heterogeneity of cancer vaccine induced immune response</i>	
D4.5 Correlation of the sensitivity and resistance to cancer vaccine and the tumor heterogeneity of the various tumor microenvironment influenced by the site of priming and location of the tumor in mice	3

Workpackages Tasks and Deliverables of Integrated Research program IRP3	Expected year of rendering
Workpackage 5: Composite biomarkers: the new frontier of patient care	
<i>Task 5.1: Validation of composite biomarkers</i>	
<i>Task 5.1.1: Validation of biomarkers of response to treatment in colon cancer</i>	
D5.1.a Characterization of circulating tumor DNA and Immunoscore™ in IDEA & PETAC-8	1
D5.1.b Molecular classification of the 1450 IDEA tumors and characterization of the main genetic and epigenetic alterations and establishment of the nomogram for predicting recurrence	4
<i>Task 5.1.2: Validation of perspective biomarkers of response to immunotherapy in non-small cell lung carcinoma</i>	
D5.2.a Predictive value of the PD-L1 expression, immune contexture and mutational load on immunotherapy clinical response on the COLCHECKPOINT collection and Ionesco trial	2
D5.2.b Integration of the different biomarkers before and after therapy into a common database to produce a reliable composite biomarker to predict response to anti-PD-L1 in lung cancer	4
<i>Task 5.1.3: Validation of biomarkers in non-Hodgkin lymphoma</i>	
D5.3.a Development of MDD measurement in FFPE samples and validation in a selected cohort of lymphoma samples	2
D5.3.b Prognostic value of ctDNA detection in selected lymphoma (prospective cohorts)	4
<i>Task 5.1.4: Validation of biomarkers in malignant paragangliomas</i>	
D5.4.a Diagnostic performances of PPGL molecular signature	1
D5.4.b Diagnostic performances of circulating PPGL biomarkers	5
<i>Task 5.2: Optimisation of biomarkers to speed up clinical translation</i>	
<i>Task 5.2.1: Deciphering the cross talk between immune infiltrating cells in the Clear Cell Renal Carcinoma to improve value of biomarker and guide treatment</i>	
D5.5.a Novel Immune classification in ccRCC which CD8+T cell exhibit a poor prognosis	3
D5.5.b Predictive value of this immune signature on the recurrence in ccRCC and on the response to immunotherapy	5
<i>Task 5.2.2: Optimization of colorectal cancer biomarkers</i>	
D5.6 Validation of an immunoscore like from colon and rectal cancer biopsies	4
<i>Task 5.2.3: Optimization of adenocortical biomarkers</i>	
D5.7.a Developing a routine panel for the molecular classification of ACC	1
D5.7.b Validation of the use of the new panel for ACC patient stratification and set-up of a clinical trial for validating the use of panel stratification for comparing mitotane to mitotane + chemotherapy	4
<i>Task 5.2.4: Development of optimization of biomarkers linked to immunosenescence to predict clinical response to immunotherapy</i>	
D5.8 Predictive value complete geriatric assessment and immunosenescence biomarkers on the clinical response toxicity following immunotherapy	5

The development of personalized or precision medicine requires the integration of different sources of knowledge to identify biomarkers that at the end render precision medicine useful for medical management of patients. **The Integrated research program 2 (IRP2) consists in understanding the role of tumor heterogeneity in the mechanisms of tumor resistance to both targeted therapeutics and immune response modifiers.** It seems essential to understand the relations between the immune cells and the tumor cells in order to develop therapeutic strategies to prevent or delay the phenomena of resistance. IRP2 explores the place of innovative tools allowing the

large-scale study of the heterogeneity of tumor cells and immune cells. It also helps to define the role of tumour heterogeneity in the day-to-day management of cancer patients. IRP2 brings together technological developments to decipher at single-cell level the interactions between tumor cells and immune cells, animal models, cohorts of patients with annotated tumor collections and clinical trials based on biomarkers to choose the adapted treatment. IRP2 has major strengths, a concentration of teams of excellence (8 clinical and 14 research teams) in the field of genomics and immunology research, high-level technical platforms and oncologists, hematologists, surgeons, physicians and radiotherapists capable of caring for patients with the greatest competence and to build clinical research of excellence attested by their publications and their national and international leading positions in cooperative clinical trial groups such as PETACC, EORTC, ARGAGY, FFCD, IFCT, LYSA, FILO, GFM...

IRP2 is coordinated by Pr. E. Tartour and Dr. V. Taly. **It is divided into 3 work packages (WP) WP3 to WP5. WP3 is devoted to the development and improvement of new technologies to understand the heterogeneity of cancers, WP4 is devoted to preclinical models to address scientific concerns related to host and tumor heterogeneity, and WP5 is devoted to the validation of biomarkers.**

3.2 Achievements

The achievements are described according to WPs and tasks to facilitate the follow-up. References before 2018 are reported as footnotes. Only 2018-2020 references are reported in the text. The deliverables associated with the achievement are reported in red

WP 3: Development and improvement of new technologies to understand the heterogeneity of cancers

Task 3.1: Multiparametric analysis based on single-cell (SC) microfluidic analysis for tumor heterogeneity characterization

Thanks to CARPEM funding, droplet-based microfluidic single cell RNA-sequencing (10x genomics) was implemented by several laboratories of the CARPEM including the M. Fontenay/D. Bouscary, E. Tartour and P. Laurent-Puig/ V. Taly teams (D3.1). Pr O. Kosmider in the Fontenay/Bouscary team has in particular used scRNA-seq approaches on age- matched normal and pathological bone marrow samples from patients with a myelodysplastic syndrome (MDS). The heterogeneity of these preleukemic disorders is related to the coexistence of malignant cells at the different stages of differentiation starting from the hematopoietic stem cell at the top of the hierarchy and a leukemic clone emerging at various stages of hematopoietic progenitors. This theme has deciphered the trajectories of differentiation and the gene expression stochasticity before and after disease modifying treatment by hypomethylating agents in elderly patients (*manuscript in preparation, collaboration with O. Gandrillon - P. Sujobert, Lyon*). The Laurent-Puig/Taly team in collaboration with Dr A. de Reynies has applied this technology to explore at the single cell resolution colon cancer intra-tumoral heterogeneity. By using proprietary dedicated deconvolution algorithm (WISP, R-package), they showed the clinical impact of intratumor heterogeneity on a large cohort of patients (n=1779) included in PETACC08 adjuvant trial. They confirmed their results by applying single cell RNA sequencing analysis (10x genomics) to colon cancer cell lines which showed CMS intra-sample heterogeneity by WISP analysis of bulk RNA-sequencing (*Marisa et al. manuscript submitted*).

Task 3.2: Multiparametric analysis based on imaging for tumor heterogeneity characterization

Task 3.2.1: Multiplex in situ analysis

Several tools have been developed. E. Tartour/C. Badoual team has been pioneer in the development of in situ multiparametric immunofluorescence techniques³. One of the limitations of these techniques was the restriction to the use of frozen tissue sections. **The team implemented the OPAL technique for the SIRIC CARPEM**, and validated the transposition of these techniques to paraffin embedded tissue (*Granier C et al. J Vis Exp 2018, Hofman P Cancers 2019*) (D3.2). In addition, they have also introduced the RNAscope technique, which will allow to measure the expression of both mRNA and proteins on the same tissue section

³ Granier C, Cancer Res 2017; Nizard M, Nat Commun 2017

(Augustin J et al. *Mod Pathol* 2018, Outh-Gauer et al. *J Vis Exp* 2019 Outh-Gauer et al. *Head Neck Pathol* 2020).

Moreover, new imaging algorithms (radiomics) and novel in vivo imaging techniques have been introduced to assess tumor heterogeneity. Thus L. Fournier in O. Clement team has developed a theme in radiomics, a technique for extracting a large number of descriptors from radiological images. The tools and softwares necessary for extracting data from images and reducing the dimensionality and selection of relevant parameters are now operational (Lecler A et al. *Sci Rep* 2019, Duron et al. *PLoS One* 2019). The B Tavitian team **has set up the first trimodality preclinical imaging instrument**, PETRUS (Positron-Emission-Tomography Registered Ultrasound). This instrument performs simultaneous 3-dimensional imaging of carbohydrate metabolism (PETscan) and vascularization (ultrasensitive Doppler), two of the main markers of oncogenesis (Provost et al. *Nat Biomed Eng* 2018; Facchin et al. *Theranostics* 2020; Cal-Gonzalez et al. *Mol Imaging Biol* 2018).

Task 3.2.3: Novel-imaging tools to monitor interaction between cancer and immune cells

Until recently, there was some compartmentalization between teams working on tumor cells and those analyzing immune cells in the tumor microenvironment. Thanks to the support of CARPEM first period, new cancer classifications based on the association of immunological and molecular markers have been defined showing the strong interplay between tumor and microenvironment cells⁴. During this new CARPEM project different groups try to better understand the dialogue and interactions between tumour cells and the microenvironment. Using an experimental system of fresh human lung tumor slices combined with dynamic imaging microscopy the E Donnadieu's team showed that T lymphocytes are blocked in their antitumor activities and identified a detrimental impact of tumor-associated macrophages (TAM) on T lymphocyte migration (Peranzoni et al. *Proc Natl Acad Sci U S A* 2018). In addition, the team found that TGFβ limits the production of type I IFNs by TAM, and that this brake could be partially released by TGFβ neutralization (Guerin et al. *Nat Commun* 2019); Based on these findings, they recently proposed different strategies to reprogram TAM in order to increase T cell antitumoral activities CAR-T cell trafficking (Bercovici N, et al. *Front Immunol* 2019 & Kantari-Mimoun et al. *BioRxiv* 2020). (D3.4).

Task 3.3: Tracking biomarkers of disease and treatment resistance.

Task 3.3.1: Overcoming genetic heterogeneity using universal markers to track ctDNA

P. Laurent-Puig/V. Taly team has searched for new cancer-specific methylation to include in a universal signature that would cover a large panel of cancer types. During the two last years, methylation markers have thus been discovered and validated on relevant clinical samples thanks to physicians involved in CARPEM and to the CARPEM biobanks. Markers were discovered and validated for gastric cancer (EP19305811.2, *PCT extension submitted*), pancreatic cancer (n° PCT/EP2020/065099, *manuscript in preparation*), lung cancer (*industrial collaboration, patent application under preparation*). The validation is ongoing for ovarian, colorectal, kidney, bladder and cervix cancers and melanoma (collab. Dr M. Arris, Fundación Cáncer, Buenos Aires, Argentine). Some of these markers have been applied in a national colon cancer clinical trial (Circulate NCT04120701 PI Pr. J Taieb member of the CARPEM) and also applied to avoid false negative results when assessing KRAS mutations within DNA extracted from plasma samples (Moati *Int J Cancer* 2020). (D3.5).

Task 3.3.2: Assessment of genetic and immunogenetic biomarkers in myeloid and lymphoid malignancies

The Macintyre/Asnafi team has developed droplet-based microfluidic approaches (droplet-based digital PCR, ddPCR) to understand cancer heterogeneity and detect minimal residual disease in mantle cell lymphomas treated on national trials⁵ (Le Guill S et al. *Lancet Hematology* *accepted*), using clone-specific immunogenetic (IG) and oncogenetic (BCL1-IgH) probes. The team demonstrated that ddPCR provided better discrimination of low-level positivity than the q-PCR gold standard and was also more sensitive than conventionally used flow cytometry (Drandi et al. *Hemasphere* 2020) This approach is also being applied to lymphoblastic lymphoma (Trinquand A. et al., *oral presentation at EHA*) (D3.6).

⁴ Becht E, *Clin Cancer Res* 2016; Becht E, *Oncoimmunology* 2015; Beuselinck B, *Clin Cancer Res* 2015.

⁵Le Guill S, *N Engl J Med* 2017;

The Fontenay/Bouscary team has applied deep RNA-sequencing and a dedicated bioinformatic pipeline to detect RNA splicing aberrancies in MDS with mutations in splicing factor gene SF3B1. Among more than 1,500 abnormalities affecting 5' or 3' splice site, they identified an aberrant splicing in the erythroferrone transcript (ERFE) (*Bondu et al., Sci Transl Med. 2019*). This abnormal transcript is translated into a variant protein which upregulation together with the normal protein, contributes to hepcidin repression and systemic iron overload (Collaboration Pr T Ganz and E Nemeth, UCLA). Therefore, the quantification of the variant transcript in the bone marrow in a large cohort of 256 MDS patients enrolled by the GFM is a biomarker of hyperferritinemia and the risk of secondary hemochromatosis. A quantification assay of the variant protein for patient risk assessment and an antisense oligonucleotide strategy to specifically neutralize the variant transcript are developed (patentPCT/EP2020/050946). Investigations are ongoing to better understand the mechanisms of action of the variant ERFE (collaboration Dr.L. Kautz, IRSL, Toulouse).

Task 3.3.3 development and validation of genome wide CRISPR/Cas9 screen to identify new treatment resistance biomarker

Dr Tamburini in the team of M. Fontenay/D. Bouscary used a crispr KRAB genome wide library to screen new resistance mechanisms to tyrosine kinase inhibitors (TKI) in acute myeloid leukemia. CRISPR-KRAB system allows an inhibition of gene expression by targeting the transcription co-repressor KRAB to genes promoters without cutting DNA in contrast to conventional CRISPR as Cas9 enzyme is inactivated. However, a high variability was observed of the efficacy of CRISPR dependent on the target gene, and this variability was even amplified when combined to TKI treatment. The team thus exploited its baseline screen to uncover acute myeloid leukemia (AML) dependencies and focused on the mitochondrial MARCH5 E3 ubiquitin ligase. In agreement with other dropout screens (such as now available on Depmap portal), MARCH5 was one of the most significant dependency across AML cell lines. The project now focuses on the validation of MARCH5 as a therapeutic target in AML using multi-omics approaches including RNAseq, proteomics and massive pharmacological screens. The team collaborates on this project with Prof. Kimberley Steigmeier (Dana Farber Cancer Institute, Boston, USA) who developed a dTAG approach for MARCH5 invalidation *in vitro* and *in vivo* and expects to submit a manuscript on this project within the next couple of months (D3.7).

Task 3.4: 3D cultures for the characterization of tumor cells in different cancer contexts

Task 3.4.1: Towards patient derived tumor mimics

Laurent-Puig/ V. Taly team has explored several systems to develop relevant 3D cultures in the form of spheroids within microfluidics (*Pitingolo et al. Micromachines 2019; Pitingolo et al., Advanced Engineering Materials 2019; Pitingolo et al. Chemical 2018; 274: 393-401*). The first generation microfluidic platform that has been developed allowed to create relatively small spheroids (200-300 μm) for drug response analysis, but with low-throughput. In a second set of experiments, the team has explored the ability of several colorectal cancer cell lines to organize within multicellular tumor spheroids but also to create larger microtissues. The aim is now to create new systems that will offer quantitative characterizations on the population scale, but also on thousands of cells *in situ* within the spheroids by imaging analysis. Moreover, the continuous flow will enable oxygen and nutrient gradients, inter-spheroid integrations and metabolite recovery. Resistant and sensitive cell populations have been fluorescently tagged in collaboration with G. Kroemer team and the different cell populations are monitored in the spheroids to follow their drug responses and crosstalk *in situ* over time. A collaboration with C. Baroud in Pasteur institute for these aspects has been set-up. The different platforms are under investigations to study intra and inter-tumor heterogeneity as well as related tumor tissues evolution both in presence or absence of treatment. In parallel the team explores different strategies of 3D printing (collab. 3D-Fab, Lyon and Univ. Bristol) allowing to create highly controlled organized microtissues. Such procedures will be used to mimic tumor microenvironment and vasculature (D3.8).

Task 3.4.2. Humanized scaffolds to mimic bone marrow niches in mice and give insight on importance of tumor inflammation in myeloid malignancies Team R11, C7 (M Fontenay, O Kosmider) Deliverable D3.9

In collaboration with the team of Dr. Françoise Pflumio (CEA, Fontenay aux roses), we have established a robust model to study human bone marrow microenvironment (ME) based on the engraftment of human mesenchymal stromal cell (MSC) in NSG mice. We believe that the cotransplantation of MSC with clonal hematopoietic stem progenitor cells (HSPC) may improve the efficiency of human cells engraftment in

immunodeficient mice, especially when injected into humanized scaffolds subcutaneously implanted to mice. We will implement this technology for MDS and AML xenografts.

We have established the reproducible conditions of MSC isolation and expansion to provide the better human ME in mice. Experiments allowing the engraftment of normal and pathological CD34+ cells in mice are on going and preliminary data shown that the human ME in mice help to the engraftment of immature populations. We will use this model to understand the role of the ME in the MDS physiopathology and to screen drugs affecting the interdependency between ME and hematological cells (D3.9).

WP 4: Preclinical models to address medical and scientific concerns linked to host and tumor heterogeneity

Task 4.1: How the dialogue between tumor and immune cells dictates the immune landscape heterogeneity and the regulation of tumorigenesis:

Task 4.1.3: Complement and tumor heterogeneity

The group of L Roumenina and C Sautes-Fridman reported that the cooperation between tumor cells and tumor-associated macrophages (TAMs) stimulates the classical complement pathway and favors tumor progression. Indeed, the in situ orchestrated production of C1q by TAM and C1r, C1s, C4, and C3 by tumor cells associated with IgG deposits, led to C1 complex assembly, and complement activation. In addition, the ccRCC tumors infiltrated with high densities of C1q-producing TAMs exhibited an immunosuppressed microenvironment, characterized by high expression of immune checkpoints (i.e., PD-1, Lag-3, PD-L1, and PD-L2). High densities of cells producing classical complement pathway components C1q and C4 and the presence of C4 activation fragment deposits in primary tumors correlated with poor prognosis. Preclinical models support the deleterious role of complement as mice deficient in C1q, C4, or C3 displayed decreased tumor growth (Roumenina et al. *Cancer Immunol Res* 2019; Roumenina et al. *Nat Rev Cancer* 2019). (D4.3).

Task 4.2: Respiratory viral infections: consequence on lung tumor heterogeneity

The I. Cremer's team previously reported that in non-small cell lung carcinoma (NSCLC), stimulation of toll-like receptor 7 (TLR7), a receptor for single stranded RNA, is linked to tumor progression and resistance to anticancer chemotherapy. However, the mechanism of this effect has been elusive. During this project, using a murine model of lung adenocarcinoma, the team demonstrated a key role for TLR7 expressed by malignant (rather than by stromal and immune) cells, in the recruitment of myeloid derived suppressor cells (MDSCs), induced after TLR7 stimulation, resulting in accelerated tumor growth and metastasis. Since these lung tumors expressing high levels of TLR7 have a phenotype of epithelial mesenchymal transition, the cross-talk between tumor and myeloid cells in this phenotype is being investigated (Dajon M, et al. *Oncoimmunology* 2018). (D4.4.a)

Finally, the team of J Galon provides important data supporting the hypothesis of immune surveillance in precancerous lesions, as both immune activation and immune suppression occur at pre-invasive stages of cancer. Interestingly tumor escape mechanism blocking the immune system predominantly occurs in high-grade pre-cancerous lesions (Mascaux et al. *Nature* 2019).

WP 5: Composite biomarkers: the new frontier of patient care

Task 5.1: Validation of composite biomarkers

Task 5.1.1: Validation of biomarkers of response to treatment in colon cancer

#Validation of Immunoscore as a prognostic biomarker in colorectal cancer

The J Galon/F Pages' team developed a prognostic immune scoring system, termed Immunoscore (IS), that quantitates both CD3+ T cells and CD8+ T-cells in the tumor and its invasive margin. The robustness and the analytic performance of the IS test was recently investigated (Marliot et al. *J Immunother Cancer* 2020) and the prognostic performance of the IS on primary tumors was confirmed in an international validation study (Pages et al. *Lancet* 2018). This has led to new recommendation by World Health Organization (WHO) edition of Digestive Tumor Classification (5th edition) to test the immune response as an essential feature.

In metastatic lesions, the immunoscore of the least infiltrated metastasis was the most significantly associated with prolonged survival (*Mlecnik B, et al. J Natl Cancer Inst 2018*). In a large series of metastatic patients with Stage IV colorectal cancer, the Immunoscore and immunoediting were the two best predictive factors of metastasis recurrence (*Angelova M, et al. Cell 2018*).

#Immunoscore as a predictive biomarker of clinical response to chemotherapy.

The Immunoscore was evaluated in the International Duration Evaluation of Adjuvant Therapy (IDEA) France cohort study investigating 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy in stage III CC patients. We reported that only patients with high-IS may derive a greater benefit from chemotherapy in terms of recurrence-risk. Indeed, patients with IS Low (46.4%) did not significantly benefit from the 6-month mFOLFOX6 versus the 3-month (*Pages F, et al. Ann Oncol 2020*) (D5.1.a).

#Post-operative ctDNA as prognostic and predictive marker in digestive cancer

In a pioneering work carried out by P.Laurent-Puig/V. Taly team, an excellent concordance was observed between RAS status in plasma analyzed on circulating tumor DNA by NGS or methylation digital PCR and in tumor tissue from patients with colorectal cancer and liver metastases, thus validating plasma testing for routine RAS mutation analysis in these patients (*Bachet JB, et al. Ann Oncol 2018*) (D5.1.a). Based on the same test they showed in patients with advanced pancreatic adenocarcinoma, that detectable ctDNA was an independent negative prognostic factor for overall survival. In patients with ctDNA detectable at baseline, eryaspase (L-asparaginase encapsulated in erythrocytes), was associated with better PFS (*Bachet JB, et al. Clin Cancer Res 2020*).

They also applied ctDNA detection in plasma detection of patients from IDEA trial. A total of 877 patients were found ctDNA-negative and 140 ctDNA-positive (13.8%). The 2-year DFS was 68% in ctDNA-positive patients and 82% in ctDNA-negative patients (p=0.014). In multivariate analysis, ctDNA was confirmed as an independent prognostic marker for DFS and OS and the comparison of 3- and 6-months arms suggests that patients with ctDNA should not be treated with 3 months of chemotherapy (*Taieb et al. Submitted*).

The direct comparison of the respective performances of the 2 tests (ie immunoscore and ctDNA) is ongoing in the same IDEA set of patients. Others molecular characteristics which have been shown by CARPEM teams of prognostic significance (*Bruzzi M, et al. Ann Surg Oncol 2019; Taieb J, et al. JAMA Oncol 2018; Gallois C, et al. Clin Cancer Res 2018*) will be also included and compared to set-up a composite biomarker for colon cancer and this project is the basis for a large project implicating several teams (see §1.5; 1.7 section).

#Novel players (B cells and Tertiary lymphoid structure (TLS)) and composite biomarkers predict clinical response to therapy in soft tissue sarcoma and lung cancer

•B cell and TLS in soft tissue sarcoma

Soft-tissue sarcomas represent a heterogeneous group of cancer, with more than 50 histological subtypes. The group of H. Fridman performed an immune-based classification of these tumors on the basis of the composition of the tumour microenvironment and identified five distinct phenotypes: immune-low (A and B), immune-high (D and E), and highly vascularized (C) groups. Class E was characterized by the presence of tertiary lymphoid structures that contain T cells and follicular dendritic cells and are particularly rich in B cells. The presence of B cells was associated with a good prognosis regardless of the level of the T signature. Most importantly, 50% of patients with tumors of the immune class E characterized by the presence of TLS respond to immunotherapy with an anti-PD-1 antibody and have prolonged survival (*Petitprez et al. Nature 2020*). Based on this work one prospective clinical trial is underway in France, coordinated by A. Italiano (Institut Bergonié, Bordeaux) and supported by the French sarcoma group, to validate the presence of structures tertiary lymphoids as a biomarker of response to immunotherapy. Two other publications by independent groups in the same issue of Nature confirm the role of IB and TLS in predicting the response to immunotherapy in melanoma and renal cell carcinoma. Intratumoral TLS was also associated with a low risk of early recurrence of hepatocellular carcinoma (*Calderaro et al. J Hepatol 2019*).

•Composite biomarkers predict response to immunotherapy and radiotherapy in NSCLC

A correlation was found between the mutational profile of these tumors and the immune infiltration within the tumor microenvironment. D Damotte's group showed that distinct combinations of *STK11*, *EGFR*, and

TP53 mutations were major determinants of the tumor immune profile (TIP). The presence of *TP53* mutations without co-occurring *STK11* or *EGFR* alterations (*TP53*-mut/*STK11*-*EGFR*-WT), independently of *KRAS* mutations, identified the group of tumors with the highest CD8 T-cell density and PD-L1 expression. In this tumor subtype, pathways related to T-cell chemotaxis, immune cell cytotoxicity, and antigen processing were upregulated. Finally, a prolonged progression-free survival was observed in anti-PD-1-treated patients harboring *TP53*-mut/*STK11*-*EGFR*-WT tumors (*Biton et al. Clin Cancer Res 2018*). To go beyond the intratumoral CD8+T cell biomarker, the same group recently showed that the CD8+/Foxp3+ double positive T cell densities were the best predictor of stage III N2 NSCLC patient's survival in multivariate analysis and could represent a biomarker of radiotherapy efficacy (*Boulle et al. Eur J Cancer 2020*).

#Novel mechanisms and target may potentially guide therapeutic intervention

The group of B. Romagnolo reports that autophagy, a pathway allowing the lysosomal degradation of intracellular components, plays a crucial role in the maintenance and genetic integrity of intestinal stem cells (ISC) under physiological and stress conditions. Following irradiation, the team showed that intestinal stem cells repair DNA damage more efficiently and that this protection is dependent on an autophagy gene. The stimulation of autophagy on fasting protects against DNA damage and cell death mediated by oxaliplatin and doxorubicin treatments. The team also showed that *Atg7* deletion sensitizes ISC to irradiation and chemotherapy (*Trentesaux et al. Proc Natl Acad Sci U S A 2020*)

S. Oudard and L. Mauge provide evidence that angiogenesis-related parameters that could reflect intratumoral hypoxia seem to be associated with worse outcome in mRCC. Since hypervascularization most often secondary to hypoxia is a predictor of response to anti-angiogenics, circulating angiogenesis profile has a promising place in antiangiogenic therapy guidance (*Mauge et al. Clin Cancer Res 2018*).

To optimize the efficacy of cancer vaccine, C Tanchot (E Tartour's team) identified peptides from the surviving universal antigen and showed that they were effective in causing tumor regression in different preclinical tumor models (*Onodi et al. Front Oncol 2018*). The E Tartour group had previously shown that intratumoral regulatory T lymphocytes (Treg) preferentially expressed the CCR4 chemokine receptor. An inhibitor of the CCR4-CCL17-CCL22 interaction blocked the migration of Treg *in vivo* and improved the efficacy of cancer vaccines⁶. E Tartour's group in collaboration with Adotevi group (Besançon) confirmed this result by showing that rapamycin (an mTor inhibitor)-induced increase in Treg, could be thwarted by the use of a CCR4 inhibitor. This triple therapy (cancer vaccine, mTor and CCR4 inhibitors) improved the efficacy of cancer vaccines in different preclinical models (*Beziaud et al. Int J Cancer 2018*) (D4.5). In human clinical trial, an anti-CCR4 mAb, Mogalizumab has demonstrated its ability to decrease intratumoral Treg supporting our results⁷.

Task 5.1.3: Validation of biomarkers in non-Hodgkin lymphoma (NHL)

The proof of concept Celimmune Phase II trial of anti-IL15 was performed by Prs. C. Cellier and O. Hermine (*Cellier et al. Lancet Gastroenterol Hepatol 2019*) with molecular biomarker assessment of TCR clonality by the Macintyre team. Optimisation of TCRG clonality assessment of gut biopsies with suspected lymphoma was undertaken and published (*Derrieux et al. J. Mol Diagn 2019*) and NKP46 developed as a promising immuno-histological biomarker (*Cheminant et al., Gut 2019*) by the Molina and Hermine teams (D5.3.a)

Moreover, in adult T-acute lymphoblastic leukemia (ALL) Dr. Aurore TOUZART, MD, obtained her CARPEM financed PhD in Nov. 2018 (supervisor V. Asnafi), on epigenetic deregulation in adult T-ALL and is currently a post-doctoral fellow at DFKZ, Heidelberg (C. Plass lab) before hopefully rejoining the Asnafi/Macintyre INSERM and hospital teams in Sept. 2021. During her PhD she used a leukemic 'proof-of-concept' model to delineate the implication of epigenetic modulation in individual patient-related drug response. TLX1+ T-ALL patients expressed low levels of Asparagine Synthetase (ASNS) when compared to TLX3+ and TLX negative patients, due to epigenetic silencing of ASNS by both DNA methylation and a decrease of active histone marks. Promoter methylation of the ASNS gene correlated with L-asparaginase sensitivity in both T-ALL cell lines and Patient Derived Xenografts and ASNS promoter methylation was an independent prognostic factor T-ALL and T-LBL patients. We concluded that ASNS methylation status at diagnosis may allow individual adaptation of L-Asparaginase dose (*Touzart et al. Clin Cancer Res 2019*). She then systematically analyzed

⁶ Pere et al. Blood 2011

⁷ Cohen et al. J Immunother Cancer 2019 ; Zamarin et al. Clin Cancer Res 2020

the whole genome DNA methylation profiles of normal thymic sorted T-cell subpopulations and 143 primary T-ALLs. Results indicated that T-ALL includes 5 epigenetically distinct subtypes (C1-C5), including an unexpected subset of hypermethylated T-ALL associated with poor outcome and primary therapeutic failure. Using mouse xenografts, we showed that these hypermethylated T-ALLs displayed therapeutic response to the DNA hypomethylating agent, 5-Azacitidine, which significantly delayed tumor progression, suggesting epigenetic-based therapies as a novel treatment option in hypermethylated T-ALL ([Touzart et al EHA 2020](#), [Manuscript under revision in Science Translational Medicine](#)).

Task 5.1.4: Validation of biomarkers in malignant paragangliomas

First objective of the AP. Gimenez-Roqueplo team ([D5.4.a](#)) was to establish diagnosis performance of molecular signature of PPGL that relies essentially on mutational profile that the team has previously defined by an integrated genomic approach⁸. The team has now transferred this signature in routine diagnostic by developing a NGS test using a gene panel allowing to identify somatic or constitutive mutations (from paraffin embedded tumor tissues) in 78% of cases of 824 sequenced samples, method that is COFRAC accredited ([Ben Aim et al. J Med Genet 2019](#)). This test will be used in the first trial of personalized medicine developed for metastatic PPGL (JUMMPPP) that should start in 2021. The team has defined several signatures predictive of metastasis emergence including the overexpression of a lncRNA ([Job S et al. J Clin Endocrinol Metab 2020](#)) and telomerase activation ([Job S et al. Clin Cancer Res 2019](#)) discovered thanks to analysis the transcription data from 202 PPGL. Thanks to mirnome analysis, other biomarkers were highlighted such as the combined expression of miR-21-3p/miR-183-5p ([Calsina B et al. Theranostics 2019](#)) and overexpression of miR-483-5p ([Castro-Vega et al, 2020, submitted](#)). The team also observed that some of these biomarkers can be detected in blood using droplet-based digital PCR in collaboration of P. Laurent-Puig/V. Taly team. In order to determine their diagnosis performance, the team performed the dosage of these biomarkers in a series of more than 200 liquid biopsies from the PRTK prospective collection COMETE-TACTIC ([D5.4.b](#)).

Task 5.2: Optimisation of biomarkers to speed up clinical translation

Task 5.2.2: Optimization of colorectal cancer biomarkers

Recent investigations also proved the capacity of the Immunoscore, applied on biopsies performed for diagnosis purpose, to predict the response to neoadjuvant radiochemotherapy in rectal cancers ([El Sissy C et al, Clin Cancer Res 2020](#)). The IS test makes it possible to consider less aggressive therapeutic strategies (Watch and Wait strategy or minimal surgery) with an organ preservation in subgroups of patients with high IS. The investigations are now extended to patients with very early stage colon cancer (T1) treated by endoscopic resection to determine whether Immunoscore could help to avoid radical colectomy ([D5.6](#)).

Task 5.2.3: Optimization of adrenocortical carcinomas (ACC) biomarkers

The Boeva team has characterized the role of DNA methylation in ACC. In particular, the team studies an ACC subtype associated with a **CpG island methylator phenotype** (CIMP). In order to study the mechanisms implicated in the establishment of this phenotype and the potential reasons for its increase aggressivity, the team re-analyzed data from a previously studied patient cohort and performed a multiomic analysis. They demonstrated that CIMP was associated with an increased expression of DNMT1 and DNMT3A DNA methyltransferases as well as with a decreased abundance of infiltrating immune cells. This last point was confirmed by immunohistochemistry. These data suggest that the treatment of patients with demethylating agents could be envisioned to potentialize the effect of immunotherapy in CIMP ACC ([Kerdivel et al. submitted and Kerivel et al. Methods in Molecular biology accepted](#)). The Bertherat team has developed a test for ACC prognostication based on tumor mRNA to quantify the level of expression of 3 genes, tumor DNA driver gene alterations, methylation and chromosomal alterations ([D5.7.a](#)). They have validated this test on a series of 244 ACC ([Assie G et al. JAMA Oncol 2019](#)). More recently the team has also demonstrated the stability of the DNA marker assessing chromosomal alterations by comparing the primary tumor with distant metastasis or local recurrence of ACC ([Jouinot A et al. Endo Connections 2020](#)). The use of these markers has been implemented for routine analysis in the genetic laboratory of Cochin hospital. In order to offer the possibility to use these markers in patients operated in centers that do not systematically freeze tumor tissue

⁸ Castro-Vega Nat Commun 2015

the teams are in the process of validating the mRNA markers by studying gene expression from paraffin embedded tissues. Based on this test, they developed an international trial comparing in aggressive ACC adjuvant treatment with mitotane alone or in combination with platin-based cytotoxic chemotherapy. The study has been designed and supported at the national level by the PHRC. The study that should start in late 2020 (D5.7.b).

3.3 Amendments to the original work plan.

There is no major deviation from the original work plan. In terms of delay in relation to certain deliverables, we have had recruitment problems for the Colcheckpoint collection (cessation of recruitment during the Covid) but this delay is being made up thanks in particular to specific funding from the Fondation ARC (Sign'it) (WP5: D5.2a). The deliverable WP4 D4.1 has been delayed because the group of B. Romagnolo has identified in the same model a role of autophagy in the protection of intestinal stem cells against the stress that delayed the initial project (*Trentesaux et al. PNAS 2020*). There is no recommendation regarding the IRP2 by the designation scientific committee nor by the SAB.

3.4 Outstanding performances and successful developments

IRP2 directly led to 65 publications during the 2018-2020 designation period (annex 1.1 first and last authors). 20 publications were made in journals with an impact factor superior to 10, including 10 in journals with an impact superior to 15 and 5 in journals with an impact superior to 20. IRP2 indirectly led to 38 publications during this period (annex1.2). IRP2 directly led to 13 patents since 2018.

In the first two years of the CARPEM designation we discovered and validated, in the field of the prognostication and or the prediction of therapeutic efficacy, several biomarkers in different tumor types. Among them we would like to enlighten 4 outstanding performances.

Hervé Fridman's group has identified the role of tertiary lymphocyte structures in predicting response to control check-point inhibitors. To date, biomarker research to predict response to immunotherapy has focused primarily on the expression of PD-L1 in the tumor or stromal cells and infiltration by CD8+T cells or factors associated with this infiltration (mutational load, IFN gamma signature). Hervé Fridman's group shows that infiltration by B lymphocytes and associated tertiary lymphoid structures (TLS) is a marker that is often neglected but may appear dominant in certain tumors (Sarcomas) (Petitprez Nature 2020). This study was directly supported by CARPEM through the funding of the thesis of Florent Petitprez, an engineer from a Grande Ecole (Polytechnic). This also opens the way, on the one hand, to cognitive studies on the mechanism of action behind this result (intrinsic role of B lymphocytes or antibodies produced by these cells or a surrogate of the presence of TLS) and on the other hand to the modification of inclusion criteria of PEMBROSARC trial (Combination of pembrolizumab and Metronomic Cyclophosphamide in Patients With Advanced Sarcomas: Multicentre Phase II - NCT02406781) limiting the pembrolizumab to sarcomas patients with TLS.

Among the biomarkers closest to clinical transfer for patient management, two markers seem to emerge as a result of IRP2. First, Immunoscore™ as an independent prognostic marker in colon cancer, has been validated in an international study Pages (Lancet 2018). More recently, in the IDEA study, the Immunoscore also appeared as a predictive biomarker of the response to chemotherapy. Indeed, patients with a low Immunoscore do not benefit from the extension of the duration of FOLOFX6 chemotherapy to 6 months (Pages Ann Oncol 2020). In addition, much work is underway to validate ctDNA as a marker of recurrence after surgery for colon cancer. We submitted for publication the results of the efficacy of ctDNA detection after surgery for colon cancer in the prediction of recurrence. This was done with thanks to the support of the CARPEM molecular biology platform. It will be the largest series of patients validating the role of ctDNA detection after surgery.

Immunosurveillance present as early as in preneoplastic stage in NSCLC. J Galon's group showed that the activation of the immune system but also the mechanisms of resistance to its action appeared as early as pre-neoplastic lesions in lung cancer. Interestingly, in high-grade pre-neoplastic lesions the escape mechanisms become more predominant (Mascaux Nature 2019).

In the aim of deciphering the heterogeneity of T-ALL, Vahid Asnafi's group identified 5 epigenetically distinct subtypes (C1-C5). Prognostication has been related to the degree of methylation of the genome with a poor prognosis and primary resistance to chemotherapy associated to hypermethylation. Tumor progression in mice engrafted with hypermethylated T-ALL being delayed by 5-Azacytidine, this opens the route for the design of clinical trial (Touzart et al, under revision in Science Translational Medicine).

3.5 Quality of the collaboration

3.5.1 IntraSIRIC collaboration

IntraSIRIC collaboration is at the heart of the concerns of the steering committee, which brings together all CARPEM's sensitivities. This steering committee is composed of clinicians, researchers, epidemiologists, human and social science researchers and patients. In order to encourage interaction within CARPEM teams, the emergence program makes it compulsory for at least two different CARPEM teams to interact with each other. The steering committee is extremely attentive in its project selection to this aspect.

IRP2 led to in 7 projects associating at least 2 teams of CARPEM (program emergence).

Furthermore, CARPEM organized during the 2 first years of CARPEM second period regular meetings inside the integrated research program 2. This led to the will to present an ambitious project around the management of colorectal cancer patients in partnership with industrials in the framework of the response to Investment for Future calls (see § extra-Siric collaboration). These working meetings integrates the following teams: Research teams: A. Burgun, J Galon/F. Pages, P. Laurent-Puig/ V.Taly, J. Zucman-Rossi, Clinical teams : J. Taieb, E. Paillaud, G. Chatellier and the medical ethic laboratory MF Mamzer. Based on clinical observations, the teams of V. Asnafi/E Macintyre and M Fontenay/D Bouscary collectively elaborated in vivo and in vitro preclinical investigations to identify alternative therapeutic strategies in patients with acute leukemia at high risk of primary resistance or precocious relapse. CARPEM supports this project by a funding of the program emergence.

Several CARPEM teams have also responded to national calls for tenders together on themes supported by CARPEM.

E. Tartour I. Cremer, P. Laurent-Puig research teams and the physicians involved in lung cancers (M. Wislez team) were funded by the association for cancer research in the Sign'it call

J. Taieb and P. Laurent-Puig teams were funded by the association for cancer research in clinical research call.

V. Taly and A.S. Bats were funded by ARCAGY-GINECO association for their participation to the trial CHIVA GINECO-OV119

O. Kosmider and the team of F Pflumio (CEA) were funded by the ITMO Cancer program 3R for the development of alternative models of patient-derived xenografts.

3.5.2 ExtraSIRIC collaboration

ExtraSIRIC collaboration in the framework of IRP2 are described in annex 5 and by the analysis of publications directly and indirectly linked to CARPEM integrated research program 2. This analysis showed a large level of collaboration through the world (Usa; Belgium; Italy; United Kingdom; Germany (Fed Rep Ger); England; Netherlands; Switzerland; Spain; Sweden; Canada) by the different IRP2 participating teams. Furthermore the success of the identification of several biomarkers in colon cancers led the different teams to try to foster their collaboration in a large common project in collaboration with industrials. They applied through the coordination of P. Laurent-Puig to the application "investment for future" launched by the French Government. The project was based on the personalization of colon cancer surveillance and has as ultimate aim to provide patients with safe and personalized colon cancer follow-up, to transform patient way-of-care. The project proposes to accurately define the recurrence risk of each patient at diagnosis by combining the prognostication knowledge and recent advances in machine learning for marker assessments and survival predictions. It will lead to a digital colon cancer survivorship companion the PreciCompanion. It will support personalized medical decisions during follow-up of resected colon cancer patients based on precise survival

risk estimation over-time. Specifically, the companion will compute the risk of relapse for a specific patient based on multiple markers proven for their high prognostication value. This project associated 9 research and clinical teams of the SIRIC CARPEM and one research team of the SIRIC CURAMUS, it also associated several industrial partners: Dassault Systems (Dassault Systems is a software publisher specializing in 3D design, 3D digital modeling and product lifecycle management solutions) <http://www.3ds.com/>, BioSerenity (BioSerenity is a French startup founded in 2014 that provides diagnostic and patient monitoring solutions, ranging from data capture via connected medical devices to data analysis via artificial intelligence tools for automatic identification of digital biomarkers and healthcare professionals) www.bioserenity.com/ and Owkin (Owkin is a French-American startup that uses AI and machine learning to augment medical and biology research) www.owkin.com and 2 national collaborative groups in digestive cancer research: FFCD (www.ffcd.fr) and GERCOR (www.gercor.com). The budget of this project was 30 M€. This project was selected among the 60 submitted for discussion in a second round of evaluation but was not retained. It was presented again this year with the same academic and industrial partners to the investment bank for a call for Competitiveness Structuring Projects". The first round of evaluation is ongoing. The budget is about 38M€. This project shows on the one hand the structuring effect of SIRIC CARPEM within these teams, and on the other hand the attractiveness of SIRIC CARPEM to industrialists in the field of artificial intelligence and modelling (Numerical Twins).

The relation between Canceropôle Ile-de-France (directed by P. Laurent-Puig from 2019) and the SIRIC CARPEM are close. Several members of the SIRIC CARPEM are leaders of the working groups of the Canceropôle Ile-de-France. Some of these groups are directly related to the integrated research program 2: data integration lead by A. Burgun, Immunology and cancer lead by C. Sautes-Fridman; Geriatric oncology lead by E. Paillaud and rare cancer lead by Anne Paule Gimenez Roqueplo. These working groups bring together the different research partners of the region Ile-de-France and they define the actions of the canceropôle. For example, the next Emergence call of Canceropôle Ile-de-France will be exclusively dedicated to the theme "Heterogeneity, Plasticity, and Spatial and Temporal Evolution of Cancers" which is completely in line with our integrated research program 2.

IRP2 has made it possible to strengthen national and international collaborations (see Annex 5). These collaborations involve different types of cancers and biomarkers. Regarding colon cancers, Pr J Taieb, P. Laurent-Puig and Dr. J Galon have a strong collaboration with the Mayo Clinic sharing data from 3 large adjuvant trials in colon cancers (NO147, PETACC08 and IDEA) leading to 3 publications in the 2nd CARPEM period to determine the prognostic impact of different biomarkers. Furthermore, in November 2018, a 1st symposium was held in Paris between the CARPEM, Paris Descartes University and the Mayo Clinic to reinforce this collaboration. It consisted of one day of public scientific presentations and half a day of closed-door work. The alternation of the annual holding of the Paris vs USA symposium was agreed. The structuring of the partnership for the training of researchers is in progress. Unfortunately, the 2nd symposium was canceled in March 2020 due to the COVID pandemic situation. Several other collaborations have been set up we can enlighten some of them.

Two collaborations were initiated, thanks to the work of a PhD student (A. Touzart) supported by the CARPEM, between the CARPEM research team (Macintyre/ Asnafi) with A. Gessaint from Pasteur Institute and J. Ghysdael from Curie Institute on the therapeutic potential of inducing T lymphoid cancer cell death via TCR activation and C. Plass from DKZF, Heidelberg, Germany on T-ALL epigenetic signatures. The team of M. Fontenay/D. Bouscary has been involved in an international collaboration between E. Papaemmanuil from the Department of Epidemiology and Biostatistics of the Memorial Sloan Kettering, NYC which demonstrated that *TP53* multi-hits but not single-hit were related to a poor prognosis in MDS (Bernard et al. Nat Med, 2020), in an H2020 MDS-RIGHT consortium with J. Janssen in Nijmegen University hospital and M. Dugas in Muenster University to conduct an integrative analysis of multi-omics (DNAseq, RNAseq and methylome) in low risk MDS (manuscript in preparation) and in a collaboration with S. Kordasti (Guy's hospital and Kings College, London, UK) to validate a computational tool Immunocluster to explore the immune profile and cellular heterogeneity of hematological diseases using liquid and imaging mass, and flow cytometry data (Abs. ASH 2020). A collaboration between the CARPEM research team of J. Bertherat and the Dr MA Habra from the MD Anderson is ongoing on the genetic signature of rare endocrine tumors. A collaboration between Dr. V Ntziachristos (Institute for Biomedical Imaging, Technical University and Helmholtz Center of Munich, Germany) and the CARPEM research team of B. Tavtavian was ongoing on analysis of optoacoustic

measurements and their correlation with PET and ultrasonic measurements in cancer. The CARPEM supports a Post-doc implicated in this collaboration. Finally, the CARPEM team of E. Donnadieu is involved in two European networks (H2020 and IMI) directly related to CARPEM supported projects.

3.6 Programmes for the dissemination of knowledge and good practices

IRP2 led to 85 original articles resulting directly or benefiting from its structuring actions (annex 1.1 & 1.2). The number of citations of these original articles was 1207 without self citation⁹. The h index of this corpus of document was 16 and the average of citation per article was 15.99 showing the impact of the scientific production of IRP2.

Furthermore, CARPEM strongly encourages the dissemination of knowledge through reviews writing.

A total of 94 reviews were published in the framework of IRP2 during the second period of CARPEM. Among them 14 were written in French for medical students and general practitioners. Among the 80 review in English several are published in high impact journals (Immunity, Gastroenterology, Nat Rev Cancer, J Clin Oncol, Ann Oncol). **Several members of the IRP2 participate to international recommendations for the management of cancer patients (colon cancers, Acute T cell leukemia and Lymphoma).**

H. Fridman, O. Hermine (CARPEM members) and A. Eggermont (Gustave Roussy), created in collaboration with different academic partners and industrials a two-day educational meeting dedicated to an up to date knowledge in novel biomarkers or therapeutic approaches in immunotherapy, the JSIC (“Journées Scientifiques Immunité et Cancer”). The academic director of the JSIC is E. Tartour leader of IRP2. These 2 days are becoming the unmissable meeting of the medical community in the field of immuno-oncology, these days are an opportunity to share, discuss and put into perspective the latest advances in cancer immunotherapy. They have been launched in 2017 and become an annual educational meeting with 3 editions in 2018 and 2019 and 2020. Different members of the CARPEM participate to the scientific committee (O. Hermine, WH. Fridman, E. Tartour, J Taieb) or give lectures (P. Laurent-Puig, D. Damotte, M. Wislez, S. Oudard, L. Fournier, WH Fridman, O. Hermine). This allows the CARPEM members to disseminate their last advances in the field of IRP2 program. The next meeting is planned in 2021 <https://www.jsic.fr> under the responsibility of E. Tartour director of IRP2. >In addition C. Sautès-Fridman member of the IRP2 is editor in chief of the journal “Immunité et Cancer” which disseminates knowledge and advances in immunotherapy towards French clinical oncologists and pathologists.

In February 2018, SIRIC CARPEM took part to the 13rd Rare Cancer Annual colloquium organized in Paris by the canceropôle Ile-de-France under the responsibility of AP Gimenez-Roqueplo member of the Siric CARPEM. This symposium was a good occasion for clinicians and scientists to discuss research projects covering different types of rare cancers. Three keynote speakers were invited to talk about rare cancer networks : Thomas Giordano (University of Michigan), Jean-Yves Blay (head of the ERN EuraCan network: Rare cancers), Pierre Fenaux (Head of EuroBloodNet).

In September 2019, W. H. Fridman, C. Sautès-Fridman and A. Dimberg organized the “TLS in the era of cancer immunotherapy” symposium the day before the 5th cancer immunotherapy conference, at the Centre de Recherche des Cordeliers in Paris with the support of SIRIC CARPEM. The symposium gathers top international experts in the developing field of Tertiary Lymphoid Structures (TLS), their clinical impact, their potential use as biomarkers of response and their modulation (<http://carpem.fr/en/tls-in-the-era-of-cancer-therapies-symposium>.)

Late 2019, the SIRIC CARPEM participated to the organization of the 3rd Gilles Thomas Symposium focusing on genetic of cancers. The symposium took place in Lyon in October and was organized by the collaboration of CRCL, Centre Léon Berard and SIRIC Lyrican and SIRIC Curie. Furthermore, the SIRIC CARPEM facilitates the participation to these meetings by grants. Finally, the Cordeliers Research Center and SIRIC CARPEM co-organizes on weekly basis an open scientific seminar. During the second period of CARPEM, 13 seminars were dedicated to the themes developed in the framework of IRP2. Among them, 7 were presented by young researchers or members of the CARPEM platforms (see annex 7).

⁹ Data provided by web of Science

In term of education related to IRP2, Université de Paris proposes a university diploma “DU Therapeutiques Immunologiques” coordinated by F Pages and E Tartour members of the SIRIC CARPEM to better understand the rational of immunotherapy, especially in oncology. Since 2019, Pr. L. Fournier member of the SIRIC CARPEM obtained a chair in medical imaging in the new 3IA PRAIRIE Institute, an institute for interdisciplinary research and education in artificial intelligence founded by 5 academic and 16 industrial partners. <http://prairie-institute.fr>

As last year, the SIRIC CARPEM co-organize the DIU: Molecular medicine in cancerology that will take place next university year. This university diploma organized by Université de Paris and 3 SIRICs from the Paris region: CARPEM, SIRIC Curie and SOCRATE is open for clinicians, pharmacists, biologists, researchers, drug manufacturers and regulatory agency personnel (<http://carpem.fr/diu-medecine-moleculaire-en-cancerologie-2020-2021>).

Dissemination of knowledge toward general public about the notion that we (scientists physicians, patients, ...) are all research actors, was done through short movie, brochure, flyer (see annex A8 and www.carpem.fr). The NutriNet-Santé CARPEM Lynch was promoted since 2019 to general public trough flyers and brochures. In 2020, we are creating didactic videos for general public about immunotherapy and composite biomarkers.

3.7 Impact of the SIRIC designation on the integrated research programme

The SIRIC CARPEM designation fosters the collaboration between the teams with different expertises (Immunology, Genetics, Artificial intelligence). The IRP2 program by sharing collection of patients' samples between the different teams led to an unprecedented accumulation of data in the same patients which will allow the development of new knowledge about prognostication for example in colon cancers. Thanks to the reputation of SIRIC CARPEM, and by promoting meetings and facilitating interaction between teams through the emergence programs, it has enabled the creation of a joint project beyond Integrated Research Program 2 (not yet funded) in collaboration with industrial partners. The designation of the new SIRIC CARPEM allowed the development of common tools for understanding the intra-tumoral heterogeneity of tumors cells and those of microenvironment which allow to better understand the mechanism of resistance to conventional, targeted and immunological therapies. First significant results are obtained in sarcomas and in colon and lung adenocarcinomas. These results have changed ongoing national therapeutic trial in sarcoma (**PEMBROSARC**), and they were used as the basis for a national therapeutic trial in patients with stage II colon cancer funded by the French government (**CIRCULATE** PI J Taieb and P. Laurent-Puig members of SIRIC CARPEM). The designation of the new SIRIC CARPEM also allows the selection of the better PhD Students by allowing gratification superior to that obtained from the government based on previous salaries for medical student (resident and fellowship). Aurelie Touzard and Florent Petitprez are examples. The interaction between the different platforms and CARPEM teams is strengthened and facilitated by the financial contribution of CARPEM SIRIC. Particularly, Tumor Microenvironment Immunohistochemistry Platform has made it possible to facilitate a large number of studies within the framework of IRP2 by promoting the dissemination of techniques through the different CARPEM teams and the high quality of the results obtained. Finally, the IRP2 program fostered the leverage effect of the CARPEM. The various teams participating in IRP2 have received 7.7 million euros to finance their research through the response to calls for tenders.

3.8 Action plan for the 2nd period of the designation

The IRP2 evaluation reveals exciting data showing the remarkable success we have had in combining various well-established imaging platforms to assess changes in tumor and immune cells applied to various forms of cancer and during the administration of drugs. We think that the data presented here are very interesting for the scientific community and took advantage of the merging between scientists with various forms of expertise. The big question at this point for the IRP2 is which of the new technologies that provide high dimensional profiling on a single cell basis while preserving the three-dimensional structures of the tumor microenvironment should be recruited into the program. The four most likely systems are Hyperion, CODEX, Nanostring and 10X Spatial Transcriptomics. There are pluses and minuses of each system and we are well-aware of them. At the current time, Nanostring, CODEX and the 10X systems appear to be the most cost effective of the four approaches and several high-profile papers have begun to appear demonstrating their

flexibility and sensitivity. We plan to implement at least 2 of these platforms in the next year. We are in the process of filing a joint application with SIRIC CURAMUS under the aegis of Canceropôle Ile-de-France to acquire Geo Nanostring as a complement of our Nanostring platform. We want to test rapidly the 10 Spatial Profiling systems and plan a budget of 80 000 € to acquire experience in this domain. First results are expected in the second semester of 2020. The second development concerning the IRP2 is about microfluidics capabilities for organoids cultures (3D cultures). We need, as recommended by SAB, to prioritize efforts, and more importantly to separate the research development functions from the Core functions of this program by participating with the University of Paris to the creation of Microfluidics platforms dedicated to cancer studies. The third development concerns the use of non-invasive technologies to identify new circulating markers to predict response to immunotherapy and targeted therapies as well as longer patient survival. Complementary to ctDNA characterization, we are developing multiplex immunofluorescence based software EXCYTE (Exhaustive eXploration of CYtometry data) to this purpose. Preliminary results being validated by Cytob suggest that we can identify lymphocyte populations in the blood which predict response to immunotherapy and longer DFS in clear cell renal carcinoma (Melan et al. in preparation)

These three developments should enable us to deepen the link between tumour cell phenotypes and immune cells of the microenvironment, which we consider to be a fundamental issue in understanding the mechanisms of resistance to treatment in cancer patients. We will encourage interaction between the teams in this field through targeted calls for tenders in order to put in place the innovative tools necessary for these approaches.

C. INTEGRATED RESEARCH PROGRAM 3: DYNAMIC CONSENT AND HEALTH DEMOCRACY

3.1 Initial action plan

Workpackages Tasks and Deliverables of Integrated Research program IRP3	Expected year of rendering
Workpackage 6: Establishment of guidelines for the CARPEM dynamic consent (DC) platform's specifications from patients and professional's expectations	
<i>Task 6: Identification of patients, physicians and researchers expectations on dynamic consent</i>	
D6.1 Patients' qualitative study: Identification of patients' perception and preferences toward data and sample sharing	1
D6.2 Professionals' qualitative study: Identification of professionals' needs and expectations toward DC	1
D6.3 Establishment of a first version of guidelines for the CARPEM DC platform	1
Workpackage 7: Specification of the CARPEM DC platform and integration into the translational research platform	
<i>Task 7: Specification of the CARPEM DC platform and integration into the translational research platform</i>	
<i>Task 7.1: Functionalities</i>	
D7.1 List of functionalities (including security, privacy) to be used to design the prototype	2
<i>Task 7.2: Information Technology (IT) aspects of data security and privacy</i>	
D7.2 Prototype to be presented to the users and to the ATEB for validation before implementing the functionalities	2
Workpackage 8: Implementation of the DC consent	
<i>Task 8.1: Modelling</i>	
D8.1 CARPEM platform implementing the DC functionalities first version	2
<i>Task 8.2: Implementation following the modeling phase</i>	
D8.2 Regulatory formalities (Authorization of the CNIL)	2
D8.3 CARPEM platform implementing the DC functionalities second release (final, validated)	3
Workpackage 9: Real-life test of acceptability of data linkage by CARPEM patients: the use case of data linkage with the NutriNet-Santé data-base	
<i>Task 9.1: CARPEM patient's participation to the NutriNet program</i>	
D9.1 Production of dedicated flyers	2
D9.2 Establishment of the 2 CARPEM patients' specific questionnaires	2
D9.3 Dietary intake data of the subjects from the two cohorts and statistical analyses of these questionnaires	4
<i>Task 9.2: Real-life test of acceptability of data linkage by CARPEM patients</i>	
D9.4 Identification of fears and reluctances of patients to individual personal data linkage	2
Workpackage 10: Identification of legal, ethical and human barriers encountered and ethical vigilance	
<i>Task 10.1: Ethical vigilance process</i>	
D10.1 Re-composition of the ATEB and elaboration of the meetings' schedule	1
<i>Task 10.2: Identification of barriers encountered</i>	
D10.2 Elaboration of the specific report form for encountered barriers and global report of the difficulties declared and their analysis	1
<i>Task 10.3: Organization of public meetings and debate surrounding legal and ethical issues linked to DC implementation and translational practices</i>	
D10.3 Proposal of a revised users' chart for the CARPEM DC platform CARPEM platform implementing the DC functionalities first version	3

The IRP3 addresses the legal, ethical, and human barriers encountered in modern translational research, which they term 'ethical vigilance'. Patients' opinions are extremely important, and researchers need to uphold their responsibility and accountability. Program 3 recognizes that current legal and regulatory texts are changing to adapt to precision medicine and new translational practices. In this program we aimed to build an "ethics by design" e-dynamic consent platform and test both the feasibility and the acceptance of such a platform in real life. These objectives were built at the end and in continuation of the first CARPEM period, considering the major results of our first integrated research program.

Its main objective was to explore the acceptance and the feasibility of the implementation of the concept of dynamic consent (DC) for the purpose of translational research in the "real life" context of CARPEM. Almost all the teams have been or will be implicated in this integrated program.

WP 6 relies on qualitative methodologies (to explore the

interest of CARPEM patients in actively participating to translational research cohorts, their perception of the dynamic consent concept, the conditions of their acceptance of translational research practices such as sample and data sharing or data linkage, and their expectation for the communication of global data, personal data, secondary findings, etc...). It will also investigate the professionals' fears and expectations for such an innovative concept (oncologists, geneticists, researchers, general practitioners).

The WP 7 and 8 constitute the second phase of this integrated research program with an interventional research action devoted to the building of a DC platform linked with the translational platform and to test its operability, and its acceptance by patients and professionals.

WP 9 is devoted to test the acceptance of data linkage in real-life conditions exemplified by the link of the NutriNet database to medical health records of CARPEM patients for research purposes. **The main purpose was to set up two cohorts of CARPEM patients followed via the NutriNet-Santé study platform** in order to test first in real conditions the acceptance by patients and the regulatory feasibility of the linkage of their

data collected through NutriNet-Santé platform with their CARPEM clinical data provided by HEGP. To this end, the initial plan was to recruit two cohorts of CARPEM cancer patients: patients with Lynch syndrome, genetically predisposed to cancer and patients diagnosed for a solid tumor and treated at HEGP and to propose them to integrate NutriNet-Santé program, testing the acceptability by patients of coupling, for research purposes, their hospital follow-up medical data from HEGP with the data they will provide as part of the NutriNet-Santé study. In addition, nutrition-related behaviors of both groups of CARPEM patients who will integrate the NutriNet-Santé platform will be analyzed from two angles: 1) descriptive, to better understand dietary practices, opinions and knowledge of cancer patients, 2) etiological, to provide insights into the understanding of nutrition role in quality of life, prognosis and risk of second event in cancer patients.

WP10 which is devoted to different actions of coordination and support is in process. It will rely on ethics and strongly implicate the Advisory Translational Ethics Board (ATEB), created during the first CARPEM period. This WP will coordinate and organize communication and debates with the public.

3.2 Achievements

From the start of this second period we were faced with **several unforeseen difficulties** that have interfered with our plan. **First, we had to renew the ATEB** as (1) a great number of its previous members left (retirement, job transfer, or overloaded agendas) and (2) we wanted to recruit locally treated patients, or at least patients included in the 2 studied cohorts. To do that, we had first to wait for the recruitment of the cohorts and thereafter we have been hindered by different social and sanitary obstacles to organize meetings. We have planned to consolidate the composition of the ATEB and to start its work during the last trimester of 2020. **The second difficulty encountered was that both the legal and the regulatory framework** for research practices are under revision in France since 2016. Thus, the establishment of the guidelines for the CARPEM DC platform has been held up.

Despite these difficulties several achievements were reached in establishing in the 2 carpem cohorts (CARPEM-LYNCH and CARPEM-cancer) on the Nutrinet-Santé platform

For the CARPEM Lynch Syndrom cohort (CARPEM-LYNCH):

- **Design and validation with physicians and nurses** of: Lynch Syndrome specific questionnaires, patients follow-up planning, design, validation and edition of communication tools, flyers (including the address of the study website and guidelines), posters (posted in the waiting room of the colorectal center at hospital and in the doctors' office), Lynch Syndrome questionnaires computerization
- **Development, operationalization and functional testing** of the CARPEM-LYNCH study online patient recruitment platform on NutriNet-Santé Website
- **Launch of CARPEM-LYNCH cohort:** Lynch Syndrome patients' enrolment: they are invited by oncologists and/or nurses to register on the NutriNet-Santé platform. They must tick a box in their online registration questionnaire in order to be identified as "participating in the CARPEM-LYNCH study" on NutriNet-Santé website and finally they fill in questionnaires available in their member's space. Weekly meetings are organized with patients after their medical consultation to answer any question they may have about the study and show them the registration procedure on the NutriNet-Santé website.
- To date **35 patients have joined the cohort**

For the CARPEM Solid Tumors Cohort (CARPEM-CANCER):

- **Design and validation of the cancer specific questionnaires**, patient's follow-up planning
- **Design, validation and edition of communication tools:** flyers and posters (including the address of the study website and guidelines), cancer related questionnaires computerization
- **Implementation, operationalization and functional testing** of the CARPEM-CANCER study online platform on NutriNet-Santé Website

3.3 Amendments to the original work plan

On one side, **the team ETRs took advantage of the difficulties described above to inventory new significant medical and research practices in order to understand them and identify new ethical or legal challenges** that would interfere with the DC platform project and that they will have to present and offer to the discussion of the ATEB. **A “new practices inventory” has been thus first realized** by the anthropologist that we have recruited (Caroline Despres), two PhD students of the team ETRs (Marie-Caroline Lai et Elise Jacquier) and a master student (Mar Valles Poch). Along with this inventory, Marie-France Mamzer, Manon de Fallois (lawyer and PhD student) and Julie Nevant (lawyer and master student) monitored the legal and regulatory situation related to these new practices, to identify and anticipate changes in legislation and regulation. We are still awaiting for the dispositions of the bioethics law that will probably impact the regulatory framework for biological samples storage and secondary uses as well as genetic research.

On the other side, the original work plan for the implementation of the Lynch Syndrome and solid tumors cohorts has not been substantially modified. **Following the successful pilot study conducted in 2019 on patients with Lynch Syndrome, the CARPEM-LYNCH cohort was launched in early 2020.** Unfortunately, recruitment has been slowed down due to the COVID-19 epidemic. From March to May 2020, medical visits for Lynch Syndrome patients at the colorectal center were suspended and medical staff mobilized to face the health emergency related to the epidemic. Communication actions towards patients will be reinforced to boost their participation in the CARPEM-LYNCH study. **With the agreement of the project medical partner team (CCR-HEGP physicians and nurses), we have planned to send letter to all Lynch Syndrome patients (N≈350 patients).** This action aims to encourage those who have not yet enrolled to participate in the study. The letter will contain an invitation to participate in the study as well as a flyer explaining how to proceed. The first descriptive analyses are planned to be carried out by the end of 2020. In the meantime, **we have submitted to the 16th World Congress of Public Health (WCPH), for a poster presentation, a methodological abstract** entitled: “CARPEM-LYNCH: a program linking hospital and NutriNet-Santé e-cohort data to test dynamic consent”. The abstract has been accepted and will be present at the WCPH that will be held from October 12th to October 16th, 2020.

3.4 Outstanding performances and successful developments

IRP3 has enabled implementing within the NutriNet-Santé study platform a specific interface for each of the CARPEM-LYNCH and CARPEM-CANCER cohorts by taking advantage from the simplicity and flexibility of the NutriNet-Santé platform in adding new protocols and questionnaires. It represents a unique platform for multidisciplinary collaborations. The following screenshots show some of the original tools of the platform.

Start of inclusion

Enrolment into the CARPEM-LYNCH cohort

Participant's personal space : Questionnaires section

Nom	Statut	Disponibilité
Questionnaire Alimentaire (Inscription)	Effectuer le tirage au sort	2 mois restants
Anthropométrique	Nouveau	3 mois restants
Socio-démographique et mode de vie	Nouveau	3 mois restants
Santé	Nouveau	3 mois restants
Activité physique	Nouveau	3 mois restants
Syndrome de Lynch	En cours	6 mois restants
Cuisine et repas	Nouveau	6 mois restants
Sources d'informations nutritionnelles	Nouveau	6 mois restants

Lynch Syndrome questionnaire layout

24HDR-questionnaire layout : food portions selection

Participant's personal space : consent forms

3.5 Quality of the collaboration

3.5.1 IntraSIRIC collaboration

An efficient collaboration has been set up within the SIRIC CARPEM around IRP3. **A two fields survey studying biological samples and data process from the collection to the use in research have been performed** between multidisciplinary teams and lead to a publication co-authored by Elise Jacquier, Pierre Laurent-Puig, Cécile Badoual, Anita Burgun and Marie-France Mamzer. This article is currently under review for publication in Journal of BMC Medical Ethics (METH-D-19-00218 entitled « New challenges of the informed consent process in the context of translational research: the case of the CARPEM consortium »).

Moreover, this collaboration is also very active on CARPEM-LYNCH & CARPEM-CANCER cohorts. Indeed, **the actions carried out at each stage of the implementation of these cohorts are systematically discussed between the different teams involved in this collaborative project through regular meetings** including the active participation of HEGP medical team. This operation method favours inter-teams communication, enriches the reflections thanks to the multidisciplinary of the actors and generates innovative ideas for the progress and success of the project. **Patients are also actively involved.** Almost all of those we met feel concerned by research on Lynch syndrome and showed a real interest in contributing, through their participation in the study, to the improvement of scientific knowledge on Lynch syndrome and the prevention of related cancers. Patients are particularly interested in the holistic dimension of the study which takes into account their health status as well as their dietary practices, lifestyle, quality of life, opinions and beliefs

regarding nutrition and diseases (cancer in particular), sources of information, perception of the impact of the disease on the household's diet.

3.5.2 ExtraSIRIC collaboration

Inclusions within the **CARPEM-LYNCH cohort will be extended to other medical follow-up centers for Lynch Syndrome patients**. These centers are members of the PRED-IdF network, a regional network dedicated to patients with hereditary predisposition to digestive cancers. The Ile-de-France PRED-IdF network brings together, in seven centers, specialists in the management of colorectal cancer risk and hereditary predisposition related cancers. **This extraSIRIC collaboration will begin with the medical team of the gastroenterology department of Avicenne hospital located at Bobigny and coordinated by Professor R. BENAMOZIG**. This collaboration will promote the rapid recruitment of a large number of patients, a better representativeness of the study population and will therefore give the possibility to generalize the results of analyses.

3.6 Programmes for the dissemination of knowledge and good practices

In accordance with the initial action plan, our research findings will be disseminated to the public, patients and their representatives/advocates, clinicians in the framework of public conferences, meetings or workshops. In addition, short summaries of our results will be posted on NutriNet-Santé as well as CARPEM websites to keep patients informed about the studies progress as we go along.

In this purpose, in 2019, Marie-France Mamzer chaired a colloquium co-organized by SIRIC and Cancéropôle francilien entitled "Health democracy in research" in June 2019.

Anita Burgun and B. Rance coorganize the 15th Annual Colloquium of the cancéropôle Ile-de-France, dedicated to the subject of health data in cancerology and their mapping, by evoking the technical and methodological aspects related to large health databases and open data. <https://www.canceropole-idf.fr/manifestation/15e-colloque-annuel-geocancer/>

Due to the viral pandemic, the communication and dissemination of our projects has been slowed down in 2020 (cancellation of congresses, priorities for information on COVID-19). However, we submitted for publication this article, currently under revision, in Journal of BMC Medical Ethics (METH-D-19-00218 entitled « New challenges of the informed consent process in the context of translational research: the case of the CARPEM consortium »). We also submitted an abstract entitled *"CARPEM-LYNCH : a program linking hospital and NutriNet-Santé e-cohort data to test dynamic consent"* to the <https://wcph2020.com/> and our work will be presented during the congress next October.

3.7 Impact of the SIRIC designation on the integrated research programme

The SIRIC designation, by promoting the synergy of multidisciplinary teams, has facilitated networking and collaboration between the EREN team and medical teams for the implementation of the CARPEM-LYNCH and CARPEM-CANCER cohorts.

3.8 Action plan for the 2nd period of the designation

The CARPEM program offers a unique opportunity to test in "real-life" the acceptance, and the feasibility of the implementation of this concept of DC (dynamic consent) in the context of translational research devoted to the cancer in France. The integrated program of research 3 will contribute to the production of **new knowledge concerning patients' expectations and fears towards their participation to specific research cohort**, but also concerning the sharing and the linkage of their data. It will also contribute to the production of a DC platform connected to the translational platform, thus offering the opportunity to patients to gather all their data at the same place. DC constitutes a major **opportunity to contribute to the shaping of renewed ethical principles and procedures** that will be **compatible with modern genomic translational research** and the advent of artificial intelligence. Extending the engagement of CARPEM in health democracy and

translational ethics, this integrated program 3 is coordinated by team 15 (ETRE Laboratory) and integrates an ethical expertise in CARPEM governance. Patients and patients' representatives must have a major role in the entire process. We assume that **this integrated research program will reinforce the integration of patients in CARPEM governance** and fuel the debate about ethical issues encountered in real-life practice and hence highlight the need for a pragmatic conception of translational ethics.

A first specific meeting will be organized gathering the ATEB and members of the different involved teams to expose the outline of the project, open the debate, and gather suggestions and advices on **October 2020**. Each ATEB meeting will be the occasion to make a progress report on the ongoing program and to share the main difficulties encountered. Videos and all information will be presented and discussed. Moreover, all potential ethical issues that might be identified all along CARPEM program will be discussed and analyzed by the ATEB (see below Task 5.2). The ATEB will also contribute to the establishment of the users' chart of the DC Platform. Additionally, **the partners of the CARPEM Dynamic Consent implementation program (see WP 1 above) will be invited to participate at a one-day meeting** with the ATEB to debate the DC program.

The implementation and the development of the health democracy has been and remains one of the major objectives of the CARPEM project. **Given the new and great opportunity offered by the creation of the Paris Cancer Institute CARPEM, we have decided to increase the scale of this dimension by reinforcing the place of patients and their representatives through the development of the "patient experience" approach into both clinical and medical practices.**

Concerning our cohorts, the action plan for the next phase of the project will consist in:

- **Boosting inclusions** in the CARPEM-LYNCH cohort (sending letters to patients, extending inclusions to Lynch Syndrome patients followed at Avicennes Hospital)
- **Finalizing the implementation** of the solid tumor patient cohort and proceed with its launch
- **Invitation for each patient** participating in the cohorts to join the CARPEM dynamic consent Platform to express her/his consent to link her/his NutriNet-Santé study data to the CARPEM translational platform, with the aim of unifying all their individual data on the same informatics server (CARPEM translational research platform) and enabling CARPEM consortium to re-use them for further research
- **Performing statistical analyses** (descriptive and etiological)
- **Disseminating results**

4 GENERAL CONCLUSION OF THE MID-TERM REPORT

4.1 Added-value of the SIRIC designation

As we have already mentioned, SIRIC CARPEM is one of the only SIRICs that is not supported by a cancer centre. Obtaining the SIRIC label enabled us to build an integrated project involving 11 clinical and 23 research teams in the fields of epidemiology, genetics and immunology. This integration has enabled us to propose to our stakeholders the creation of a comprehensive cancer center at the level of three hospitals belonging to the Université de Paris. **This Paris Cancer Institute Carpem** has been set up in 2020 with the objective of an accreditation by the OECI. It is a direct consequence of the 2018 SIRIC designation. This creation fosters the **integration of physicians** into SIRIC CARPEM. Concerning the different research programs the designation of the new SIRIC programs enabled us to integrate **the metabolism dimension** to the previous research programs that enriches genetics and immunology. It appears to us it allows a holistic approach of the cancer patients. The different aspects of whole-body metabolism as well as the cellular metabolism reinforce the understanding of the interactions between tumor and immune cells. The designation of SIRIC CARPEM also allowed us to develop **shared tools** between the different teams to study the intratumor heterogeneity which is the new frontier for developing composite prognostic biomarkers. From this present designation we are able to construct **new large projects beyond the integrated research programs**. Furthermore, several CARPEM members coordinates large national translational studies in the framework of national or international therapeutic trials (PEATCC08, IDEA) as well as within the French cooperative groups in hematology (GRAALL, GFM). The results of CARPEM second period research form the basis of biomarkers guided large clinical trial (CIRCULATE, amended PEMBROSARC, BIONIKK). Finally, the SIRIC CARPEM has a strong leverage effect, the different CARPEM teams have been able to raise up to 12 M€ during the last 2 years.

4.2 General conclusion and action plan for the 2nd period of the SIRIC designation

The SIRIC CARPEM (Cancer Research for Personalized Medicine) is dedicated to integrate for the day to day care management of the patients, the new acquired knowledge in genomics and immunology of tumor cells and immune cells participating to the microenvironment. We have already succeeded to build a comprehensive analysis of tumor associated and microenvironment associated parameters and their links both at transcriptomic and cellular levels. It has been achieved in several cancers such as colon, renal, hepatocellular, lung cancers, soft tissues sarcoma and preleukemic syndromes and leukemias. Our next step will be to validate these previously defined transcriptomic composite markers to measure their clinical utility and their place in the medical care of cancer patients. We aim in next two years to design at least one clinical trial based on these approaches. One of the challenges is to be able to characterize the intra-tumoral heterogeneity which is major player in resistance to anticancer treatments. We obtained results showing that the heterogeneity participates to the definition of the prognostication of the disease. We will go deeper in the characterization of intratumor heterogeneity by the acquisition of spatial transcriptomic technologies such as Nanostring and the 10X systems. The study of the heterogeneity at tissue level may be difficult and the characterisation of circulating surrogate markers may help to apprehend it. In addition, these surrogate markers may allow to develop non invasive tools to predict patients response, survival and to follow the modifications induced by therapy. Using CtDNA determination, multiplex cellular analysis of plasma factors such as cytokine and metabolome, we aim at developing circulating novel composite biomarkers to guide and follow cancer therapies. To reach these objectives we will use the translational research platform, a tool created in the first period CARPEM and enriched during the second period, which fosters the integration of the data. Furthermore, we will set-up a dedicated bioinformatics platform which will be dedicated to the comprehensive analysis of these new data generated. Finally, the acceptance of the use of these composite biomarkers by the patients will be facilitated by the setting-up of the dynamic informed consent developed in the framework of the integrated research program 3.

5 ANNEXES

1. Publications

1.1 List of scientific publications (original articles only) resulting directly from work carried out within the framework of the integrated research programmes, published from 2018. The first and/or last author(s) of the listed publications must work within the SIRIC.

Do not include reviews, letters to the editor, editorial articles, author's views, etc.

*IRP = Integrated research programme

IRP* number	Publication title	Authors	Journal	Year of publication
1	Diet-Related Metabolomic Signature of Long-Term Breast Cancer Risk Using Penalized Regression: An Exploratory Study in the SU.VI.MAX Cohort	Lécuyer L, Dalle C, Lefevre-Arbogast S, Micheau P, Lyan B, Rossary A, Demidem A, Petera M, Lagree M, Centeno D, Galan P, Herberg S, Samieri C, Assi N, Ferrari P, Viallon V, Deschasaux M, Partula V, Srouf B, Latino-Martel P, Kesse-Guyot E, Druesne-Pecollo N, Vasson MP, Durand S, Pujos-Guillot E, Manach C, Touvier M.	Cancer Epidemiol Biomarkers Prev.	2020
1	Chemical activation of SAT1 corrects diet-induced metabolic syndrome	Castoldi F, Hyvönen MT, Durand S, Aprahamian F, Sauvat A, Malik SA, Baracco EE, Vacchelli E, Opolon P, Signolle N, Lefevre D, Bossut N, Eisenberg T, Dammbroeck C, Pendl T, Kremer M, Lachkar S, Einer C, Michalke B, Zischka H, Madeo F, Keinänen TA, Maiuri MC, Pietrocola F, Kroemer G.	Cell Death Differ	2020
1	Acyl-CoA-binding protein (ACBP): a phylogenetically conserved appetite stimulator	Champilas N, Ruckstuhl C, Sica V, Büttner S, Habernig L, Dichtinger S, Madeo F, Tavernarakis N, Bravo-San Pedro JM, Kroemer G.	Cell Death Dis	2020
1	Inhibition of transcription by dactinomycin reveals a new characteristic of immunogenic cell stress	Humeau J, Sauvat A, Cerrato G, Xie W, Loos F, Iannantuoni F, Bezu L, Lévesque S, Paillet J, Pol J, Leduc M, Zitvogel L, de Thé H, Kepp O, Kroemer G.	EMBO Mol Med	2020
1	Polyploidy spectrum: a new marker in HCC classification	Bou-Nader M, Caruso S, Donne R, Celton-Morizur S, Calderaro J, Gentric G, Cadoux M, L'Hermitte A, Klein C, Guilbert T, Albuquerque M, Couchy G, Paradis V, Couty JP, Zucman-Rossi J, C. Desdouets.	Gut	2020
1	Recurrent chromosomal rearrangements of ROS1, FRK and IL6 activating JAK/STAT pathway in inflammatory hepatocellular adenomas	Bayard Q, Caruso S, Couchy G, Rebouissou S, Bioulac Sage P, Balabaud C, Paradis V, Sturm N, de Muret A, Guettier C, Bonsang B, Copie C, Letouzé E, Calderaro J, Imbeaud S, Nault JC, Zucman-Rossi J.	Gut	2020
1	Clinical Impact of Genomic Diversity From Early to Advanced Hepatocellular Carcinoma	Nault, JC; Martin, Y; Caruso, S; Hirsch, TZ; Bayard, Q; Calderaro, J; Charpy, C; Copie-Bergman, C; Zioli, M; Bioulac-Sage, P; Couchy, G; Blanc, JF; Nahon, P; Amaddeo, G; Ganne-Carrie, N; Morcrette, G; Chiche, L; Duvoux, C; Faivre, S; Laurent, A; Imbeaud, S; Rebouissou, S; Llovet, JM; Seror, O; Letouze, E; Zucman-Rossi, J	Hepatology	2020
1	Autophagy induction by thiostrepton improves the efficacy of immunogenic chemotherapy	Wang Y, Xie W, Humeau J, Chen G, Liu P, Pol J, Zhang Z, Kepp O, Kroemer G.	J Immunother Cancer	2020
1	BAP1 mutations define a homogeneous subgroup of hepatocellular carcinoma with fibrolamellar-like features and activated PKA	Hirsch, TZ; Negulescu, A; Gupta, B; Caruso, S; Noblet, B; Couchy, G; Bayard, Q; Meunier, L; Morcrette, G; Scoazec, JY; Blanc, JF; Amaddeo, G; Nault, JC; Bioulac-Sage, P; Zioli, M; Beaufrere, A; Paradis, V; Calderaro, J; Imbeaud, S; Zucman-Rossi, J	Journal Of Hepatology	2020
1	Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort.	Chazelas E, Srouf B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, Druesne-Pecollo N, Galan P, Herberg S, Latino-Martel P, Deschasaux M, Touvier M.	BMJ	2019

1	Associations between consumption of dietary fibers and the risk of cardiovascular diseases, cancers, type 2 diabetes, and mortality in the prospective NutriNet-Santé cohort	Partula V, Deschasaux M, Druésne-Pecollo N, Latino-Martel P, Desmetz E, Chazelas E, Kesse-Guyot E, Julia C, Fezeu LK, Galan P, Hercberg S, Mondot S, Lantz O, Quintana-Murci L, Albert ML, Duffy D; Milieu Intérieur Consortium, Srour B, Touvier M.	Am J Clin Nutr.	2019
1	Plasma Metabolomic Signatures Associated with Long-term Breast Cancer Risk in the SU.VI.MAX Prospective Cohort. Cancer	Lécuyer L, Dalle C, Lyan B, Demidem A, Rossary A, Vasson MP, Petera M, Lagree M, Ferreira T, Centeno D, Galan P, Hercberg S, Deschasaux M, Partula V, Srour B, Latino-Martel P, Kesse-Guyot E, Druésne-Pecollo N, Durand S, Pujos-Guillot E, Touvier M.	Cancer Epidemiol Biomarkers Prev.	2019
1	Acyl-CoA-Binding Protein Is a Lipogenic Factor that Triggers Food Intake and Obesity	Bravo-San Pedro JM, Sica V, Martins I, Pol J, Loos F, Maiuri MC, Durand S, Bossut N, Arahamian F, Anagnostopoulos G, Niso-Santano M, Aranda F, Ramírez-Pardo I, Lallement J, Denom J, Boedec E, Gorwood P, Ramoz N, Clément K, Pelloux V, Rohia A, Pattou F, Raverdy V, Caiazzo R, Denis RGP, Boya P, Galluzzi L, Madeo F, Migrenne-Li S, Cruciani-Guglielmacci C, Tavernarakis N, López-Otín C, Magnan C, Kroemer G.	Cell Metab	2019
1	Poisoning of Cancer Cells by Respiratory Chain Inhibition plus Dimethyl α -Ketoglutarate.	Sica V, Bravo-San Pedro JM, Izzo V, Pol J, Pierredon S, Enot D, Durand S, Bossut N, Chery A, Souquere S, Pierron G, Vartholomaiou E, Zamzami N, Soussi T, Sauvat A, Mondragón L, Kepp O, Galluzzi L, Martinou JC, Hess-Stumpp H, Ziegelbauer K, Kroemer G, Maiuri MC	Cell Report	2019
1	Hypermetabolism is an independent prognostic factor of survival in metastatic non-small cell lung cancer patients.	Jouinot A, Ulmann G, Vazeille C, Durand JP, Boudou-Rouquette P, Arrondeau J, Tlemsani C, Fournel L, Alifano M, Wislez M, Chapron J, Le Bris C, Mansuet-Lupo A, Damotte D, Neveux N, De Bandt JP, Alexandre J, Cynober L, Goldwasser F.	Clin Nutr	2019
1	The cellular prion protein controls the mesenchymal-like molecular subtype and predicts disease outcome in colorectal cancer.	Le Corre D, Ghazi A, Balogoun R, Pilati C, Aparicio T, Martin-Lannerée S, Marisa L, Djouadi F, Poindessous V, Crozet C, Emile JF, Mulot C, Le Malicot K, Boige V, Blons H, de Reynies A, Taieb J, Ghiringhelli F, Bennouna J, Launay JM, Laurent-Puig P, Mouillet-Richard S.	EBioMedicine	2019
1	3,4-Dimethoxychalcone induces autophagy through activation of the transcription factors TFE3 and TFEB	Chen G, Xie W, Nah J, Sauvat A, Liu P, Pietrocola F, Sica V, Carmona-Gutierrez D, Zimmermann A, Pendl T, Tadic J, Bergmann M, Hofer SJ, Domuz L, Lachkar S, Markaki M, Tavernarakis N, Sadoshima J, Madeo F, Kepp O, Kroemer G.	EMBO Mol Med	2019
1	Analysis of Liver Cancer Cell Lines Identifies Agents With Likely Efficacy Against Hepatocellular Carcinoma and Markers of Response	Caruso, S; Calatayud, AL; Pilet, J; La Bella, T; Reikik, S; Imbeaud, S; Letouze, E; Meunier, L; Bayard, Q; Rohr-Udilova, N; Peneau, C; Grasl-Kraupp, B; de Koning, L; Ouine, B; Bioulac-Sage, P; Couchy, G; Calderaro, J; Nault, JC; Zucman-Rossi, J; Rebouissou, S	Gastroenterology	2019
1	Hepatocellular Carcinomas With Mutational Activation of Beta-Catenin Require Choline and Can Be Detected by Positron Emission Tomography.	Gougelet, A., Sartor, C., Senni, N., Calderaro, J., Fartoux, L., Lequoy, M., Wendum, D., Talbot, J.N., Prignon, A., Chalaye, J., Imbeaud, S., Zucman-Rossi, J., Tordjmann, T., Godard, C., Bossard, P., Rosmorduc, O., Amaddeo, G., and Colnot, S.	Gastroenterology	2019
1	beta-catenin-activated hepatocellular carcinomas are addicted to fatty acids.	Senni, N., Savall, M., Cabrerizo Granados, D., Alves-Guerra, M.C., Sartor, C., Lagoutte, I., Gougelet, A., Terris, B., Gilgenkrantz, H., Perret, C., Colnot, S., and Bossard, P.	Gut	2019
1	17-Beta-Hydroxysteroid Dehydrogenase 13 Variant Protects From Hepatocellular Carcinoma Development in Alcoholic Liver Disease	Yang J, Trépo E, Nahon P, Cao Q, Moreno C, Letouzé E, Imbeaud S, Bayard Q, Gustot T, Deviere J, Bioulac-Sage P, Calderaro J, Ganne-Carrié N, Laurent A, Blanc JF, Guyot E, Sutton A, Ziol M, Zucman-Rossi J, Nault JC.	Hepatology	2019

1	PNPLA3 and TM6SF2 variants as risk factors of hepatocellular carcinoma across various etiologies and severity of underlying liver diseases	Yang J, Trépo E, Nahon P, Cao Q, Moreno C, Letouzé E, Imbeaud S, Gustot T, Deviere J, Debette S, Amouyel P, Bioulac-Sage P, Calderaro J, Ganne-Carrié N, Laurent A, Blanc JF, Guyot E, Sutton A, Ziol M, Zucman-Rossi J, Nault JC.	Int J cancer	2019
1	The concomitant loss of APC and HNF4alpha in adult hepatocytes does not contribute to hepatocarcinogenesis driven by beta-catenin activation.	Sartor, C., Bachelot, L., Godard, C., Lager, F., Renault, G., Gonzalez, F.J., Perret, C., Gougelet, A., and Colnot, S.	Liver International	2019
1	Crizotinib-induced immunogenic cell death in non-small cell lung cancer.	Liu P, Zhao L, Pol J, Levesque S, Petrazzuolo A, Pfirschke C, Engblom C, Rickelt S, Yamazaki T, Iribarren K, Senovilla L, Bezu L, Vacchelli E, Sica V, Melis A, Martin T, Xia L, Yang H, Li Q, Chen J, Durand S, Aprahamian F, Lefevre D, Broutin S, Paci A, Bongers A, Minard-Colin V, Tartour E, Zitvogel L, Apetoh L, Ma Y, Pittet MJ, Kepp O, Kroemer G.	Nat Commun	2019
1	Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications	Blum, Y; Meiller, C; Quétel, L; Elarouci, N; Ayadi, M; Tashtanbaeva, D; Armenoult, L; Montagne, F; Tranchant, R; Renier, A; de Koning, L; Copin, MC; Hofman, P; Hofman, V; Porte, H; Le Pimpec-Barthes, F; Zucman-Rossi, J; Jaurand, MC; de Reynies, A; Jean, D	Nature Communications	2019
1	A synergistic triad of chemotherapy, immune checkpoint inhibitors, and caloric restriction mimetics eradicates tumors in mice	Levesque, S; Le Naour, J; Pietrocola, F; Paillet, J; Kremer, M; Castoldi, F; Baracco, EE; Wang, Y; Vacchelli, E; Stoll, G; Jolly, A; De La Grange, P; Zitvogel, L; Kroemer, G; Pol, JG	Oncoimmunology	2019
1	APC germline hepatoblastomas demonstrate cisplatin-induced intratumor tertiary lymphoid structures	Morcrette, G; Hirsch, TZ; Badour, E; Pilet, J; Caruso, S; Calderaro, J; Martin, Y; Imbeaud, S; Letouze, E; Rebouissou, S; Branchereau, S; Taque, S; Chardot, C; Guettier, C; Scoazec, JY; Fabre, M; Brugieres, L; Zucman-Rossi, J	Oncoimmunology	2019
1	Metabolic enzymes expressed by cancer cells impact the immune infiltrate	Stoll G, Kremer M, Bloy N, Joseph A, Castedo M, Meurice G, Klein C, Galluzzi L, Michels J, Kroemer G.	Oncoimmunology	2019
1	Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort	Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, Deschasaux M, Fassier P, Latino-Martel P, Beslay M, Hercberg S, Lavalette C, Monteiro CA, Julia C, Touvier M	BMJ	2018
1	Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Santé Cohort	Lavalette C, Adjibade M, Srour B, Sellem L, Fiolet T, Hercberg S, Latino-Martel P, Fassier P, Deschasaux M, Kesse-Guyot E, Touvier M.	Cancer Res	2018
1	eIF2α phosphorylation is pathognomonic for immunogenic cell death	Bezu L, Sauvat A, Humeau J, Gomes-da-Silva LC, Iribarren K, Forveille S, Garcia P, Zhao L, Liu P, Zitvogel L, Senovilla L, Kepp O, Kroemer G.	Cell Death Differ	2018
1	Resting energy expenditure in the risk assessment of anticancer treatments.	Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, Chapron J, Neveux N, De Bandt JP, Alexandre J, Cynober L, Goldwasser F.	Clin Nutr.	2018
1	Photodynamic therapy with redaporfin targets the endoplasmic reticulum and Golgi apparatus	Gomes-da-Silva LC, Zhao L, Bezu L, Zhou H, Sauvat A, Liu P, Durand S, Leduc M, Souquere S, Loos F, Mondragón L, Sveinbjørnsson B, Rekdal Ø, Boncompain G, Perez F, Arnaut LG, Kepp O, Kroemer G.	EMBO J	2018
1	Metabolic vulnerability of cisplatin-resistant cancers	Obrist F, Michels J, Durand S, Chery A, Pol J, Levesque S, Joseph A, Astesana V, Pietrocola F, Wu GS, Castedo M, Kroemer G	EMBO J	2018
1	Lect2 Controls Inflammatory Monocytes to Constrain the Growth and Progression of Hepatocellular Carcinoma.	L'Hermitte A, Pham S, Cadoux M, Couchy G, Caruso S, Anson M, Crain-Denoyelle AM, Celton-Morizur S, Yamagoe S, Zucman-Rossi J, Desdouets C, Couty JP.	Hepatology	2018

1	Fasting and weight-loss restrictive diet practices among 2,700 cancer survivors: results from the NutriNet-Santé cohort	Fassier P, Srouf B, Raynard B, Zelek L, Cohen P, Bachmann P, Touillaud M, Druesne-Pecollo N, Belenchembre L, Cousson-Gélie F, Cottet V, Féliu F, Mas S, Deschasaux M, Galan P, Hercberg S, Latino-Martel P, Touvier M	Int J Cancer	2018
1	Association between a pro plant-based dietary score and cancer risk in the prospective NutriNet-santé cohort	Kane-Diallo A, Srouf B, Sellem L, Deschasaux M, Latino-Martel P, Hercberg S, Galan P, Fassier P, Guéraud F, Pierre FH, Kesse-Guyot E, Allès B, Touvier M.	Int J Cancer	2018
1	Assessment of signaling pathway inhibitors and identification of predictive biomarkers in malignant pleural mesothelioma	Tranchant R, Quétel L, Montagne F, De Wolf J, Meiller C, De Koning L, Le Pimpec-Barthes F, Zucman-Rossi J, Jaurand MC, Jean D.	Lung cancer	2018
1	Systemic AA Amyloidosis Caused by Inflammatory Hepatocellular Adenoma	Calderaro J, Letouzé E, Bayard Q, Boulai A, Renault V, Deleuze JF, Bestard O, Franco D, Zafrani ES, Nault JC, Moutschen M, Zucman-Rossi J.	N Engl J Med	2018
1	Cyclin A2/E1 activation defines a hepatocellular carcinoma subclass with a rearrangement signature of replication stress	Bayard Q, Meunier L, Peneau C, Renault V, Shinde J, Nault JC, Mami I, Couchy G, Amaddeo G, Tubacher E, Bacq D, Meyer V, La Bella T, Debailon-Vesque A, Bioulac-Sage P, Seror O, Blanc JF, Calderaro J, Deleuze JF, Imbeaud S, Zucman-Rossi J, Letouzé E.	Nature Communications	2018
1	Immune effectors responsible for the elimination of hyperploid cancer cells	Aranda F, Chaba K, Bloy N, Garcia P, Bordenave C, Martins I, Stoll G, Tesniere A, Kroemer G, Senovilla L.	Oncol Immunology	2018
1	Impact of chemotactic factors and receptors on the cancer immune infiltrate: a bioinformatics study revealing homogeneity and heterogeneity among patient cohorts.	Stoll G, Pol J, Soumelis V, Zitvogel L, Kroemer G	Oncoimmunology	2018
1	Nutritional quality of food as represented by the FSAM-NPS nutrient profiling system underlying the Nutri-Score label and cancer risk in Europe: Results from the EPIC prospective cohort study.	Deschasaux M, Huybrechts I, Murphy N, Julia C, Hercberg S, Srouf B, Kesse-Guyot E, Latino-Martel P, Biessy C, Casagrande C, Jenab M, Ward H, Weiderpass E, Dahm CC, Overvad K, Kyrgø C, Olsen A, Affret A, Boutron-Ruault MC, Mahamat-Saleh Y, Kaaks R, Kühn T, Boeing H, Schwingshackl L, Bamia C, Peppas E, Trichopoulos A, Masala G, Krogh V, Panico S, Tumino R, Sacerdote C, Bueno-de-Mesquita B, Peeters PH, Hjartåker A, Rylander C, Skeie G, Ramón Quirós J, Jakszyn P, Salamanca-Fernández E, Huerta JM, Ardanaz E, Amiano P, Ericson U, Sonestedt E, Huseinovic E, Johansson I, Khaw KT, Wareham N, Bradbury KE, Perez-Cornago A, Tsilidis KK, Ferrari P, Riboli E, Gunter MJ, Touvier M.	PLoS Med	2018
1	Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors	Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquélot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L.	Science	2018
1	The cellular prion protein is a stress protein secreted by renal tubular cells and a urinary marker of kidney injury	Bignon Y, Poindessous V, Lazareth H, Passet B, Vilotte JL, Djouadi F, Mouillet-Richard S, Pallet N.	Cell Death Dis	
2	Intratumor heterogeneity of prognostic DNA-based molecular markers in adrenocortical carcinoma.	Jouinot A, Lippert J, Fassnacht M, De la villeon B, Septier A, Neou M, Perlemoine K, Sibony M, Gaujoux S, Dousset B, Libe R, Groussin L, Ronchi C, Assie G, Bertherat J.	Endocrine Connections	2020
2	Circulating tumor DNA is prognostic and potentially predictive of erasapase efficacy in second-line in patients with advanced pancreatic adenocarcinoma	Bachet JB, Blons HF, Hammel P, El Hariry I, Portales F, Mineur L, Metges JP, Mulot C, Bourreau C, Cain J, Cros J, Laurent-Puig P.	Clin Cancer Res	2020

2	Chemoradiotherapy efficacy is predicted by intra-tumour CD8+/FoxP3+ double positive T cell density in locally advanced N2 non-small-cell lung carcinoma	Boulle G, Velut Y, Mansuet-Lupo A, Gibault L, Blons H, Fournel L, Boni A, Cremer I, Wislez M, Duchatelle V, Trédaniel J, Hammond SA, Herbst R, Alifano M, Giraud P, Damotte D.	Eur J Cancer	2020
2	Droplet Digital PCR Quantification of Mantle Cell Lymphoma Follow-up Samples From Four Prospective Trials of the European MCL Network	Drandi, D., Alcantara, M., Benmaad, I., Söhlbrandt, A., Lhermitte, L., Zaccaria, G., Ferrante, M., Genuardi, E., Mantoan, B., Villarese, P., Cheminant, M., Starza, I. D., Ciabatti, E., Bomben, R., Jimenez, C., Callanan, M., Abdo, C., Eckert, C., Ribrag, V., Cortelazzo, S., ... Macintyre, E	Hemasphere	2020
2	Concurrent imaging of vascularization and metabolism in a mouse model of paraganglioma under anti-angiogenic treatment	Facchin, C; Perez-Liva, M; Garofalakis, A; Viel, T; Certain, A; Balvay, D; Yoganathan, T; Woszczyk, J; De Sousa, K; Sourdon, J; Provost, J; Tanter, M; Lussey-Lepoutre, C; Favier, J; Tavitian, B	Theranostics	2020
2	Identification of a long non-coding RNA signature predictive of metastasis in SDH-mutated paraganglioma	Job S, Georges A, Burnichon B, Buffet A, Amar L, Bertherat J, Bouatia-Naji N, de Reyniès A, Favier J, Gimenez-Roqueplo AP, Castro-Vega LJ	J Clin Endocrinol Metab.	2020
2	CAR T cell entry into tumor islets is a two-step process dependent on IFN γ and ICAM-1.	Kantari-Mimoun C, Barrin S, Haghiri S, Gervais C, Mittelstat J, Mockel-Tenbrinck N, Kinkhabwala A, Damotte D, Lupo A, Sibony M, Alifano M, Vimeux L, Dondi E, Bercovici N, Trautmann A, Kaiser A and E Donnadieu	BioRxiv	2020
2	Chromatin immunoprecipitation followed by next-generation sequencing (ChIP-seq) in Ewing sarcoma	Kerdivel G & Boeva V	Methods in Molecular Biology	2020
2	Succinate detection by in vivo 1H-MR spectroscopy identifies germline and somatic SDHx mutations in paragangliomas.	Lussey-Lepoutre C, Bellucci A, Burnichon N, Amar L, Buffet A, Drossart T, Fontaine S, Clément O, Benit P, Rustin P, Groussin L, Meatchi T, Gimenez-Roqueplo AP, Tavitian B and Favier J.	Eur J Nucl Med Mol Imaging	2020
2	Analytical Validation of the Immunoscore and Its Associated Prognostic Value in Patients With Colon Cancer	Marliot F, Chen X, Kirilovsky A, Sbrarato T, El Sissy C, Batista L, Van den Eynde M, Haicheur-Adjouri N, Anitei MG, Musina AM, Scripcariu V, Lagorce-Pagès C, Hermitte F, Galon J, Fieschi J, Pagès F	J Immunother Cancer.	2020
2	Paraneoplastic Hyperleukocytosis Mimicking Hematologic Malignancy Revealing a Localized Lung Cancer.	Marouf A, Chapuis N, Alary AS, Burrioni B, Kosmider O, Alifano M, Bouscary D.	Ann Thorac Surg	2020
2	Plasma clearance of RAS mutation under therapeutic pressure is a rare event in metastatic colorectal cancer	Moati E, Blons H, Taly V, Garlan F, Wang-Renault SF, Pietrasz D, Didelot A, Garrigou S, Saint A, Pernot S, Taieb J, Laurent-Puig P, Zaanan A.	Int J Cancer	2020
2	TET-Mediated Hypermethylation Primes SDH-Deficient Cells for HIF2 α -Driven Mesenchymal Transition	Morin, A; Goncalves, J; Moog, S; Castro-Vega, LJ; Job, S; Buffet, A; Fontenille, MJ; Woszczyk, J; Gimenez-Roqueplo, AP; Letouze, E; Favier, J	Cell Reports	2020
2	The Microenvironment of Head and Neck Cancers: Papillomavirus Involvement and Potential Impact of Immunomodulatory Treatments.	Outh-Gauer S, Morini A, Tartour E, Lépine C, Jung AC, Badoual C.	Head Neck Pathol.	2020
2	Prognostic and Predictive Value of the Immunoscore in Stage III Colon Cancer Patients Treated With Oxaliplatin in the Prospective IDEA France PRODIGE-GERCOR Cohort Study	Pagès F, André T, Taieb J, Vernerey D, Henriques J, Borg C, Marliot F, Ben Jannet R, Louvet C, Mineur L, Bennouna J, Desrame J, Faroux R, Kirilovsky A, Duval A, Laurent-Puig P, Svrcek M, Hermitte F, Catteau A, Galon J, Emile J-F	Annals of Oncology	2020
2	B cells are associated with survival and immunotherapy response in sarcoma	Petitprez, F; de Reynies, A; Keung, EZ; Chen, TWW; Sun, CM; Calderaro, J; Jeng, YM; Hsiao, LP; Lacroix, L; Bougouin, A; Moreira, M; Lacroix, G; Natario, I; Adam, J; Lucchesi, C; Laizet, Y; Toulmonde, M; Burgess, MA; Bolejack, V; Reinke, D; Wani, KM; Wang, WL; Lazar, AJ; Roland, CL; Wargo, JA; Italiano, A; Sautes-Fridman, C; Tawbi, HA; Fridman, WH	Nature	2020
2	Low level CpG island promoter methylation predicts a poor outcome in adult T-cell acute lymphoblastic leukemia.	Touzar, A., Boissel, N., Belhocine, M., Smith, C., Graux, C., Latiri, M., Lhermitte, L., Mathieu, E. L., Huguet, F., Lamant, L., Ferrier, P., Ifrah, N.,	Haematologica	2020

		Macintyre, E., Dombret, H., Asnafi, V., & Spicuglia, S.		
2	Essential role for autophagy protein ATG7 in the maintenance of intestinal stem cell integrity.	Trentesaux C, Fraudeau M, Luana Pitasi C, Lemarchand J, Jacques S, Duche A, Letourneur F, Naser E, Bailly K, Schmitt A, Perret C, Romagnolo B.	Proc Natl Acad Sci U S A	2020
2	Value of Molecular Classification for Prognostic Assessment of Adrenocortical Carcinoma	Assié G, Jouinot A, Fassnacht M, Libé R, Garinet S, Jacob L, Hamzaoui N, NeouM, Sakat J, de La Villéon B, Perlemoine K, Ragazzon B, Sibony M, Tissier F, Gaujoux S, Dousset B, Sbiera S, Ronchi CL, Kroiss M, Korpershoek E, De KrijgerR, Waldmann J, Quinkler M, Haissaguerre M, Tabarin A, Chabre O, Luconi M, Mannelli M, Groussin L, Bertagna X, Baudin E, Amar L, Coste J, Beuschlein F, Bertherat J	JAMA Oncol	2019
2	Targeted next-generation sequencing detects rare genetic events in pheochromocytoma and paraganglioma	Ben Aim, L; Pigny, P; Castro-Vega, LJ; Buffet, A; Amar, L; Bertherat, J; Druil, D; Guilhem, I; Baudin, E; Lussey-Lepoutre, C; Corsini, C; Chabrier, G; Briet, C; Faivre, L; Cardot-Bauters, C; Favier, J; Gimenez-Roqueplo, AP; Burnichon, N	Journal Of Medical Genetics	2019
2	A variant erythroferrone disrupts iron homeostasis in SF3B1-mutated myelodysplastic syndrome	Bondu S, Alary AS, Lefèvre C, Houy A, Jung G, Lefebvre T, Rombaut D, Boussaid I, Bousta A, Guillonneau F, Perrier P, Alsafadi S, Wassef M, Margueron R, Rousseau A, Droin N, Cagnard N, Kaltenbach S, Winter S, Kubasch AS, Bouscary D, Santini V, Toma A, Hunault M, Stamatoullas A, Gyan E, Cluzeau T, Platzbecker U, Adès L, Puy H, Stern MH, Karim Z, Mayeux P, Nemeth E, Park S, Ganz T, Kautz L, Kosmider O, Fontenay M.	Sci Transl Med	2019
2	Influence of Molecular Status on Recurrence Site in Patients Treated for a Stage III Colon Cancer: a Post Hoc Analysis of the PETACC-8 Trial.	Bruzzi M, Auclin E, Lo Dico R, Voron T, Karoui M, Espin E, Cianchi F, Weitz J, Buggenhout A, Malafosse R, Denimal F, Le Malicot K, Vernerey D, Douard R, Emile JF, Lepage C, Laurent-Puig P, Taieb J.	Ann Surg Oncol	2019
2	Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma	Calderaro, J; Petitprez, F; Becht, E; Laurent, A; Hirsch, TZ; Rousseau, B; Luciani, A; Amaddeo, G; Derman, J; Charpy, C; Zucman-Rossi, J; Fridman, WH; Sautes-Fridman, C	Journal Of Hepatology	2019
2	Integrative multi-omics analysis identifies a prognostic miRNA signature and a targetable miR-21-3p/TSC2/mTOR axis in metastatic pheochromocytoma/paraganglioma.	Calsina B, Castro-Vega LJ, Torres-Pérez R, Inglada-Pérez L, Currás-Freixes M, Roldán-Romero JM, Mancikova V, Letón R, Remacha L, Santos M, Burnichon N, Lussey-Lepoutre C, Rapizzi E, Graña O, Álvarez-Escolá C, de Cubas AA, Lanillos J, Cordero-Barreal A, Martínez-Montes AM, Bellucci A, Amar L, Fernandes-Rosa FL, Calatayud M, Aller J, Lamas C, Sastre-Marcos J, Canu L, Korpershoek E, Timmers HJ, Lenders JW, Beuschlein F, Fassnacht-Capeller M, Eisenhofer G, Mannelli M, Al-Shahrour F, Favier J, Rodríguez-Antona C, Cascón A, Montero-Conde C, Gimenez-Roqueplo AP, Robledo M.	Theranostics	2019
2	RCD-II Study Group Investigators. Safety and efficacy of AMG 714 in patients with type 2 refractory coeliac disease: a phase 2a, randomised, double-blind, placebo-controlled, parallel-group study	Cellier C, Bouma G, van Gils T, Khater S, Malamut G, Crespo L, Collin P, Green PHR, Crowe SE, Tsuji W, Butz E, Cerf-Bensussan N, Macintyre E, Parnes JR, Leon F, Hermine O, Mulder CJ	Lancet Gastroenterol Hepatol	2019
2	The tumor inflammation signature (TIS) is associated with anti-PD-1 treatment benefit in the CERTIM pan-cancer cohort	Damotte, D; Warren, S; Arrondeau, J; Boudou-Rouquette, P; Mansuet-Lupo, A; Biton, J; Ouakrim, H; Alifano, M; Gervais, C; Bellesoeur, A; Kramkimel, N; Tlemsani, C; Burroni, B; Duche, A; Letourneur, F; Si, H; Halpin, R; Creasy, T; Herbst, R; Ren, X; Morel, P; Cesano, A; Goldwasser, F; Leroy, K	Journal Of Translational Medicine	2019
2	A Single-Tube, EuroClonality-Inspired, TRG Clonality Multiplex PCR Aids Management of Patients with	Derriex C, Trinquand A, Bruneau J, Verkarre V, Lhermitte L, Alcantara M, Villaresse P, Meresse B,	J Mol Diagn	2019

	Enteropathic Diseases, including from Formaldehyde-Fixed, Paraffin-Embedded Tissues.	Sibon D, Hermine O, Brousse N, Molina T, Cellier C, Cerf-Bensussan N, Malamut G, Macintyre E.		
2	Gray-level discretization impacts reproducible MRI radiomics texture features.	Duron L, Balvay D, Vande Perre S, et al.	PLoS One	2019
2	TGF beta blocks IFN alpha/beta release and tumor rejection in spontaneous mammary tumors	Guerin, MV; Regnier, F; Feuillet, V; Vimeux, L; Weiss, JM; Bismuth, G; Altan-Bonnet, G; Guilbert, T; Thoreau, M; Finisguerra, V; Donnadiou, E; Trautmann, A; Bercovici, N	Nature Communications	2019
2	Multiplexed Immunohistochemistry for Molecular and Immune Profiling in Lung Cancer-Just About Ready for Prime-Time?	Hofman P, Badoual C, Henderson F, Berland L, Hamila M, Long-Mira E, Lassalle S, Roussel H, Hofman V, Tartour E, Ilié M. M	Cancers (Basel)	2019
2	Telomerase Activation and ATRX Mutations Are Independent Risk Factors for Metastatic Pheochromocytoma and Paraganglioma	Job, S; Draskovic, I; Burnichon, N; Buffet, A; Cros, J; Lepine, C; Venisse, A; Robidel, E; Verkarre, V; Meatchi, T; Sibony, M; Amar, L; Bertherat, J; de Reynies, A; Londono-Vallejo, A; Favier, J; Castro-Vega, LJ; Gimenez-Roqueplo, AP	Clinical Cancer Research	2019
2	Combining Multiple Magnetic Resonance Imaging Sequences Provides Independent Reproducible Radiomics Features	Lecler A, Duron L, Balvay D, Savatovsky J, Bergès O, Zmuda M, Farah E, Galatoire O, Bouchouicha A, Fournier LS.	Sci Rep	2019
2	Proposal for a Combined Histomolecular Algorithm to Distinguish Multiple Primary Adenocarcinomas from Intrapulmonary Metastasis in Patients with Multiple Lung Tumors	Mansuet-Lupo, A; Barritault, M; Alifano, M; Janet-Vendroux, A; Zarmaev, M; Biton, J; Velut, Y; Le Hay, C; Cremer, I; Regnard, JF; Fournel, L; Rance, B; Wislez, M; Laurent-Puig, P; Herbst, R; Damotte, D; Blons, H	Journal Of Thoracic Oncology	2019
2	Immune evasion before tumour invasion in early lung squamous carcinogenesis	Mascaux C, Angelova M, Vasaturo A, Beane J, Hijazi K, Anthoine G, Buttard B, Rothe F, Willard-Gallo K, Haller A, Ninane V, Burny A, Sculier JP, Spira A, Galon J	Nature	2019
2	Chromogenic In Situ Hybridization as a Tool for HPV-Related Head and Neck Cancer Diagnosis	Outh-Gauer S, Augustin J, Mandavit M, Grard O, Denize T, Nervo M, Lépine C, Rassy M, Tartour E, Badoual C	J Vis Exp	2019
2	PD-L1 Expression and CD8(+) T-cell Infiltrate are Associated with Clinical Progression in Patients with Node-positive Prostate Cancer	Petitprez, F; Fossati, N; Vano, Y; Freschi, M; Becht, E; Luciano, R; Calderaro, J; Guedet, T; Lacroix, L; Rancoita, PMV; Montorsi, F; Fridman, WH; Sautes-Fridman, C; Briganti, A; Doglioni, C; Bellone, M	European Urology Focus	2019
2	Tumor Cells Hijack Macrophage-Produced Complement C1q to Promote Tumor Growth	Roumenina LT, Daugan MV, Noé R, Petitprez F, Vano YA, Sanchez-Salas R, Becht E, Meilleroux J, Clec'h BL, Giraldo NA, Merle NS, Sun CM, Verkarre V, Validire P, Selves J, Lacroix L, Delfour O, Vandenberghe I, Thuilliez C, Keddani S, Sakhi IB, Barret E, Ferré P, Corvaia N, Passioukov A, Chetaille E, Botto M, de Reynies A, Oudard SM, Mejean A, Cathelineau X, Sautès-Fridman C, Fridman WH.	Cancer Immunol Res	2019
2	Tumor Cells Hijack Macrophage-Produced Complement C1q to Promote Tumor Growth	Roumenina, LT; Daugan, MV; Noe, R; Petitprez, F; Vano, YA; Sanchez-Salas, R; Becht, E; Meilleroux, J; Le Clec'h, B; Giraldo, NA; Merle, NS; Sun, CM; Verkarre, V; Validire, P; Selves, J; Lacroix, L; Delfour, O; Vandenberghe, I; Thuilliez, C; Keddani, S; Sakhi, IB; Barret, E; Ferre, P; Corvaia, N; Passioukov, A; Chetaille, E; Botto, M; de Reynies, A; Oudard, SM; Mejean, A; Cathelineau, X; Sautes-Fridman, C; Fridman, WH	Cancer Immunology Research	2019
2	NF1 mutations identify molecular and clinical subtypes of lung adenocarcinomas	Tlemsani, C; Pecuchet, N; Gruber, A; Laurendeau, I; Danel, C; Riquet, M; Le Pimpec-Barthes, F; Fabre, E; Mansuet-Lupo, A; Damotte, D; Alifano, M; Luscan, A; Rousseau, B; Vidaud, D; Varin, J; Parfait, B; Bieche, I; Leroy, K; Laurent-Puig, P; Terris, B; Blons, H; Vidaud, M; Pasmant, E	Cancer Medicine	2019
2	Epigenetic Silencing Affects L-Asparaginase Sensitivity and Predicts Outcome in T-ALL	Touzaert, A; Lengline, E; Latiri, M; Belhocine, M; Smith, C; Thomas, X; Spicuglia, S; Puthier, D; Pflumio, F; Leguay, T; Graux, C; Chalandon, Y;	Clinical Cancer Research	2019

		Huguet, F; Lepretre, S; Ifrah, N; Dombret, H; Macintyre, E; Hunault, M; Boissel, N; Asnafi, V		
2	HPV circulating tumoral DNA quantification by droplet-based digital PCR: A promising predictive and prognostic biomarker for HPV-associated oropharyngeal cancers	Veyer, D; Wack, M; Mandavit, M; Garrigou, S; Hans, S; Bonfils, P; Tartour, E; Bélec, L; Wang-Renault, SF; Laurent-Puig, P; Mirghani, H; Rance, B; Taly, V; Badoual, C; Péré, H	Int J Cancer	2019
2	Evolution of Metastases in Space and Time under Immune Selection.	Angelova M, Mlecnik B, Vasaturo A, Bindea G, Fredriksen T, Lafontaine L, Buttard B, Morgand E, Bruni D, Jouret-Mourin A, Hubert C, Kartheuser A, Humblet Y, Ceccarelli M, Syed N, Marincola FM, Bedognetti D, Van den Eynde M, Galon J.	Cell	2018
2	HPV RNA CISH score identifies two prognostic groups in a p16 positive oropharyngeal squamous cell carcinoma population	Augustin J, Mandavit M, Outh-Gauer S, et al.	Mod Pathol.	2018
2	RAS mutation analysis in circulating tumor DNA from patients with metastatic colorectal cancer: the AGEO RASANC prospective multicenter study.	Bachet JB, Bouché O, Taieb J, Dubreuil O, Garcia ML, Meurisse A, Normand C, Gornet JM, Artru P, Louafi S, Bonnetain F, Thiriot-Bidault A, Baumgaertner I, Coriat R, Tougeron D, Lecomte T, Mary F, Aparicio T, Marthey L, Taly V, Blons H, Vernerey D, Laurent-Puig P.	Annals of Oncology	2018
2	Rapalog combined with CCR4 antagonist improves anticancer vaccines efficacy.	Beziaud L, Boullerot L, Tran T, Mansi L, Marie-Joseph EL, Ravel P, Johannes L, Bayry J, Tartour E, Adotévi O.	Int J Cancer	2018
2	TP53, STK11 and EGFR Mutations Predict Tumor Immune Profile and the Response to anti-PD-1 in Lung Adenocarcinoma	Biton J, Mansuet-Lupo A, Pécuchet N, Alifano M, Ouakrim H, Arrondeau J, Boudou-Rouquette P, Goldwasser F, Leroy K, Goc J, Wislez M, Germain C, Laurent-Puig P, Dieu-Nosjean MC, Cremer I, Herbst R, Blons HF, Damotte D	Clin Cancer Res	2018
2	Impaired Tumor-Infiltrating T Cells in Patients with Chronic Obstructive Pulmonary Disease Impact Lung Cancer Response to PD-1 Blockade.	Biton J, Ouakrim H, Dechartres A, Alifano M, Mansuet-Lupo A, Si H, Halpin R, Creasy T, Bantsimba-Malanda C, Arrondeau J, Goldwasser F, Boudou-Rouquette P, Fournel L, Roche N, Burgel PR, Goc J, Devi-Marulkar P, Germain C, Dieu-Nosjean MC, Cremer I, Herbst R, Damotte D.	Am J Respir Crit Care Med	2018
2	Germline Mutations in the Mitochondrial 2-Oxoglutarate/Malate Carrier SLC25A11 Gene Confer a Predisposition to Metastatic Paragangliomas.	Buffet A, Morin A, Castro-Vega LJ, Habarou F, Lussey-Lepoutre C, Letouzé E, Lefebvre H, Guilhem I, Haissaguerre M, Raingeard I, Padilla-Girola M, Tran T, Tchara L, Bertherat J, Amar L, Ottolenghi C, Burnichon N, Gimenez-Roqueplo AP, Favier J.	Cancer Res	2018
2	Improving PET Quantification of Small Animal [68Ga]DOTA-Labeled PET/CT Studies by Using a CT-Based Positron Range Correction	Cal-Gonzalez J, Vaquero JJ, Herraiz JL, Pérez-Liva M, Soto-Montenegro ML, Peña-Zalbidea S, Desco M, Udías JM.	Mol Imaging Biol	2018
2	NKp46 is a diagnostic biomarker and may be a therapeutic target in gastrointestinal T-cell lymphoproliferative diseases: a CELAC study.	Cheminant M, Bruneau J, Malamut G, Sibon D, Guegan N, van Gils T, Cording S, Trinquand A, Verkarre V, Lhermitte L, Brousse N, Jannot AS, Khater S, Frenzel L, Delarue R, Suarez F, Marçais A, Mulder CJ, Macintyre E, Asnafi V, Pouyet L, Bonnafous C, Lhospice F, Molina TJ, Meresse B, Cellier C, Cerf-Bensussan N, Hermine O; CELAC network°.	Gut	2018
2	Toll like receptor 7 expressed by malignant cells promotes tumor progression and metastasis through the recruitment of myeloid derived suppressor cells.	Dajon M, Iribarren K, Petitprez F, Marmier S, Lupo A, Gillard M, Ouakrim H, Victor N, Vincenzo DB, Joubert PE, Kepp O, Kroemer G, Alifano M, Damotte D, Cremer I.	Oncoimmunology	2018
2	Prognostic Value of Methylator Phenotype in Stage III Colon Cancer Treated with Oxaliplatin-based Adjuvant Chemotherapy	Gallois C, Taieb J, Le Corre D, Le Malicot K, Tabernero J, Mulot C, Seitz JF, Aparicio T, Folprecht G, Lepage C, Mini E, Van Laethem JL, Emile JF, Laurent-Puig P; PETACC8 investigators.	Clin Cancer Res	2018
2	Detection and monitoring of circulating tumor DNA in adrenocortical carcinoma.	Garinet S, Nectoux J, Neou M, Pasmant E, Jouinot A, Sibony M, Orhant L, Pipoli da Fonseca J, Perlemoine K, Bricaire L, Groussin L, Soubrane	Endocr Relat Cancer.	2018

		O, Dousset B, Libe R, Letourneur F, Bertherat J, Assié G.		
2	Multiplexed Immunofluorescence Analysis and Quantification of Intratumoral PD-1+ Tim-3+ CD8+ T Cells.	Granier C, Vinatier E, Colin E, Mandavit M, Dariane C, Verkarre V, Biard L, El Zein R, Lesaffre C, Galy-Fauroux I, Roussel H, De Guillebon E, Blanc C, Saldmann A, Badoual C, Gey A, Tartour É.	Journal Of Visualized Experiments	2018
2	Lenalidomide-mediated erythroid improvement in non-del(5q) myelodysplastic syndromes is associated with bone marrow immuno-remodeling.	Kerdivel G, Chesnais V, Becht E, Toma A, Cagnard N, Dumont F, Rousseau A, Fenaux P, Chevret S, Chapuis N, Boeva V, Fridman WH, Fontenay M, Kosmider O.	Leukemia	2018
2	Rodent models of pheochromocytoma, parallels in rodent and human tumorigenesis	Lussey-Lepoutre C, Buffet A, Morin A, Goncalves J, Favier J.	Cell Tissue Res	2018
2	Sunitinib Prior to Planned Nephrectomy in Metastatic Renal Cell Carcinoma: Angiogenesis Biomarkers Predict Clinical Outcome in the Prospective Phase II PREINSUT Trial	Mauge L, Mejean A, Fournier L, Pereira H, Etienne-Grimaldi MC, Levionnois E, Caty A, Abadie-Lacourtoisie S, Culine S, Le Moulec S, Linassier C, Théodore C, Ravaud A, Albiges L, Grine A, Tartour E, Milano G, Gille AS, Verkarre V, Helley D, Oudard S	Clin Cancer Res	2018
2	Comprehensive Intrametastatic Immune Quantification and Major Impact of Immunoscore on Survival.	Mlecnik B, Van den Eynde M, Bindea G, Church SE, Vasaturo A, Fredriksen T, Lafontaine L, Haicheur N, Marliot F, Debetancourt D, Pairet G, Jouret-Mourin A, Gigot JF, Hubert C, Danse E, Dragean C, Carrasco J, Humblet Y, Valge-Archer V, Berger A, Pagès F, Machiels JP, Galon J.	J Natl Cancer Inst.	2018
2	High Therapeutic Efficacy of a New Survivin LSP-Cancer Vaccine Containing CD4+ and CD8+ T-Cell Epitopes	Onodi F, Maherzi-Mechalikh C, Mougel A, Ben Hamouda N, Taboas C, Gueugnon F, Tran T, Nozach H, Marcon E, Gey A, Terme M, Bouzidi A, Maillere B, Kerzerho J, Tartour E, Tanchot C	Front Oncol	2018
2	International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study.	Pagès F, Mlecnik B, Marliot F, Bindea G, Ou FS, Bifulco C, Lugli A, Zlobec I, Rau TT, Berger MD, Nagtegaal ID, Vink-Börger E, Hartmann A, Geppert C, Kolwelter J, Merkel S, Grützmann R, Van den Eynde M, Jouret-Mourin A, Kartheuser A, Léonard D, Remue C, Wang JY, Bavi P, Roehrl MHA, Ohashi PS, Nguyen LT, Han S, MacGregor HL, Hafezi-Bakhtiari S, Wouters BG, Masucci GV, Andersson EK, Zavadova E, Vocka M, Spacek J, Petruzelka L, Konopasek B, Dundr P, Skalova H, Nemejcova K, Botti G, Tatangelo F, Delrio P, Ciliberto G, Maio M, Laghi L, Grizzi F, Fredriksen T, Buttard B, Angelova M, Vasaturo A, Maby P, Church SE, Angell HK, Lafontaine L, Bruni D, El Sissy C, Haicheur N, Kirilovsky A, Berger A, Lagorce C, Meyers JP, Paustian C, Feng Z, Ballesteros-Merino C, Dijkstra J, van de Water C, van Lent-van Vliet S, Knijn N, Muşinǎ AM, Scripcariu DV, Popivanova B, Xu M, Fujita T, Hazama S, Suzuki N, Nagano H, Okuno K, Torigoe T, Sato N, Furuhashi T, Takemasa I, Itoh K, Patel PS, Vora HH, Shah B, Patel JB, Rajvik KN, Pandya SJ, Shukla SN, Wang Y, Zhang G, Kawakami Y, Marincola FM, Ascierto PA, Sargent DJ, Fox BA, Galon J.	Lancet	2018
2	Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment.	Peranzoni E, Lemoine J, Vimeux L, Feuillet V, Barrin S, Kantari-Mimoun C, Bercovici N, Guérin M, Biton J, Ouakrim H, Régnier F, Lupo A, Alifano M, Damotte D, Donnadiou E	Proc Natl Acad Sci U S A.	2018
2	Performance evaluation of the PET component of a hybrid PET/CT-ultrafast ultrasound imaging instrument	Perez-Liva M, Viel T, Yoganathan T, Garofalakis A, Sourdon J, Facchin C, Tanter M, Provost J, Tavitian B.	Phys Med Biol	2018
2	Simultaneous positron emission tomography and ultrafast ultrasound for hybrid molecular, anatomical and functional imaging	Provost J, Garofalakis A, Sourdon J, Bouda D, Berthon B, Viel T, Perez-Liva M, Lussey-Lepoutre C, Favier J, Correia M, Pernot M, Chiche J, Pouysségur J, Tanter M, Tavitian B.	Nat Biomed Eng	2018
2	Pan-European Trials in Alimentary Tract Cancer (PETACC)-8 Investigators. Association of Prognostic Value of Primary	Taieb J, Kourie HR, Emile JF, Le Malicot K, Balogoun R, Tabernero J, Mini E, Folprecht G,	JAMA Oncol	2018

	Tumor Location in Stage III Colon Cancer With RAS and BRAF Mutational Status.	Van Laethem JL, Mulot C, Bouché O, Aparicio T, Michel P, Thaler J, Bridgewater J, Van Cutsem E, Perkins G, Lepage C, Salazar R, Laurent-Puig P;		
2	Association of IL-36γ with tertiary lymphoid structures and inflammatory immune infiltrates in human colorectal cancer	Weinstein AM, Giraldo NA, Petitprez F, Julie C, Lacroix L, Peschaud F, Emile JF, Marisa L, Fridman WH, Storkus WJ, Sautès-Fridman C.	Cancer Immunology Immunotherapy	2018
3	Perceptions of artificial intelligence in healthcare: findings from a qualitative survey study among actors in France	Lai, MC; Brian, M; Mamzer, MF	Journal Of Translational Medicine	2020
3	Deep Learning and Radiomics predict complete response after neo-adjuvant chemoradiation for locally advanced rectal cancer.	Bibault JE, Giraud P, Durdux C, Taïeb J, Berger A, Coriat R, Chaussade S, Dousset B, Nordlinger B, Burgun A.	Scientifics Reports	2018
3	Labeling for Big Data in radiation oncology: The Radiation Oncology Structures ontology	Bibault JE, Zapletal E, Rance B, Giraud P, Burgun A,.	Plos One	2018
3	Next generation phenotyping using narrative reports in a rare disease clinical data warehouse.	Garcelon N, Neuraz A, Salomon R, Bahi-Buisson N, Amiel J, Picard C, Mahlaoui N, Benoit V, Burgun A, Rance B	Orphanet J Rare Dis	2018
3	A clinician friendly data warehouse oriented toward narrative reports: Dr. Warehouse.	Garcelon N, Neuraz A, Salomon R, Faour H, Benoit V, Delapalme A, Munnich A, Burgun A, Rance B.	J Biomed Inform.	2018
3	Molecular Tumor Boards: Ethical Issues in the New Era of Data Medicine	Henri-Corto Stoeklé, Marie-France Mamzer-Bruneel, Charles-Henry Frouart, Christophe Le Tourneau, Pierre Laurent-Puig, Guillaume Vogt and Christian Hervé	Science And Engineering Ethics	2018
3	The Need of an Open Data Quality Policy: The Case of the "Transparency - Health" Database in the Prevention of Conflict of Interest.	Jantzen R, Rance B, Katsahian S, Burgun A, Looten V.	Stud Health Technol Inform.	2018
1&3	Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Santé Cohort	Lavalette C, Adjibade M, Srour B, Sellem L, Fiolet T, Hercberg S, Latino-Martel P, Fassier P, Deschasaux M, Kesse-Guyot E, Touvier M.	Cancer Res	2018

1.2 List of publications having benefited from the structuring actions of the SIRIC (use of a platform supported by the SIRIC, collaboration initiated thanks to the SIRIC, projects outside the integrated research programmes, ...)

IRP* number	Publication title	Authors	Journal	Year of publication
1	Inhibition of receptor-interacting protein kinase 1 improves experimental non-alcoholic fatty liver disease	Majdi A, Aoudjehane L, Ratziu V, Islam T, Afonso MB, Conti F, Mestiri T, Lagouge M, Fougelle F, Ballenghien F, Ledent T, Moldes M, Cadoret A, Fouassier L, Delaunay JL, Ait-Slimane T, Courtois G, Fève B, Scatton O, Prip-Buus C, Rodrigues CMP, Housset C, Gautheron J.	J Hepatol	2020
1	Gut Bacteria Composition Drives Primary Resistance to Cancer Immunotherapy in Renal Cell Carcinoma Patients	Derosa L, Routy B, Fidelle M, Iebba V, Alla L, Pasolli E, Segata N, Desnoyer A, Pietrantonio F, Ferrere G, Fahrner JE, Le Chatellier E, Pons N, Galleron N, Roume H, Duong CPM, Mondragón L, Iribarren K, Bonvalet M, Terrisse S, Rauber C, Goubet AG, Daillère R, Lemaitre F, Reni A, Casu B, Alou MT, Alves Costa Silva C, Raoult D, Fizazi K, Escudier B, Kroemer G, Albiges L, Zitvogel L.	Eur Urol	2020
1	Compensation between Wnt-driven tumorigenesis and cellular responses to ribosome biogenesis inhibition in the murine intestinal epithelium	Raveau A, Stedman A, Coqueran S, Vandormael-Pournin S, Owens N, Romagnolo B, Cohen-Tannoudji M	Cell Death Dis	2020
1	Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice	Bárcena C, Valdés-Mas R, Mayoral P, Garabaya C, Durand S, Rodríguez F, Fernández-García MT, Salazar N, Nogacka AM, Garatachea N, Bossut N, Aprahamian F, Lucia A, Kroemer G, Freije JMP, Quirós PM, López-Otín C.	Nature Med	2019
1	Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity	Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, Lin S, Chen J, Calmette J, Lu M, Fu L, Yang J, Pan Z, Yu K, He J, Morand E, Schlecht-Louf G, Krzysiek R, Zitvogel L, Kang B, Zhang Z, Leader A, Zhou P, Lanfumey L, Shi M, Kroemer G, Ma Y.	Nature Med	2019
1	Reactive cholangiocytes differentiate into proliferative hepatocytes with efficient DNA repair in mice with chronic liver injury	Manco R, Clerbaux LA, Verhulst S, Bou Nader M, Sempoux C, Ambroise J, Bearzatto B, Gala JL, Horsmans Y, van Grunsven L, Desdouets C, Leclercq I	J Hepatol	2019
1	AIF-regulated oxidative phosphorylation supports lung cancer development	Rao S, Mondragón L, Pranjić B, Hanada T, Stoll G, Köcher T, Zhang P, Jais A, Lercher A, Bergthaler A, Schramek D, Haigh K, Sica V, Leduc M, Modjtahedi N, Pai TP, Onji M, Uribealago I, Hanada R, Kozieradzki I, Kogelgruber R, Cronin SJ, She Z, Quehenberger F, Popper H, Kenner L, Haigh JJ, Kepp O, Rak M, Cai K, Kroemer G, Penninger JM.	Cell Res	2019
1	β -catenin-activated hepatocellular carcinomas are addicted to fatty acids	Senni N, Savall M, Cabrerizo Granados D, Alves-Guerra MC, Sartor C, Lagoutte I, Gougelet A, Terris B, Gilgenkrantz H, Perret C, Colnot S, Bossard P	Gut	2019
1	SM1 as a Marker of Macrotrabecular-Massive Hepatocellular Carcinoma	Calderaro J, Meunier L, Nguyen CT, Boubaya M, Caruso S, Luciani A, Amaddeo G, Regnault H, Nault JC, Cohen J, Oberti F, Michalak S, Bouattour M, Vilgrain V, Pageaux GP, Ramos J, Barget N, Guiu B, Paradis V, Aubé C, Laurent A, Pawlotsky JM, Ganne-Carrié N, Zucman-Rossi J, Seror O, Ziol M	Clin Cancer Res	2019
1	Akt-mediated phosphorylation of MICU1 regulates mitochondrial Ca(2+) levels and tumor growth	Marchi S, Corricelli M, Branchini A, Vitto VAM, Missiroli S, Morciano G, Perrone M, Ferrarese M, Giorgi C, Pinotti M, Galluzzi L, Kroemer G, Pinton P	EMBO J	2019
1	Impact of Oral Immunonutrition on Postoperative Morbidity in Digestive Oncologic Surgery: A Nation-Wide Cohort Study	Challine A, Rives-Langes C, Danoussou D, Katsahian S, Ait Boudaoud A, Gaujoux S, Dousset B, Carette C, Lazzati A, Czernichow S.	Ann Surg	2019

1	Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer	Fournel L, Wu Z, Stadler N, Damotte D, Lococo F, Bouille G, Ségal-Bendirdjian E, Bobbio A, Icard P, Trédaniel J, Alifano M, Forgez P.	Cancer Lett	2019
1	Comedications influence immune infiltration and pathological response to neoadjuvant chemotherapy in breast cancer	Hamy AS, Derosa L, Valdelièvre C, Yonekura S, Opolon P, Priour M, Guerin J, Pierga JY, Asselain B, De Croze D, Pinheiro A, Lae M, Talagrand LS, Laas E, Darrigues L, Grandal B, Marangoni E, Montaudon E, Kroemer G, Zitvogel L, Reyat F.	Oncoimmunology	2019
1	Suppression of tumor antigen presentation during aneuploid tumor evolution contributes to immune evasion	Tripathi R, Modur V, Senovilla L, Kroemer G, Komurov K.	Oncoimmunology	2019
1	Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women	Hoyles L, Fernández-Real JM, Federici M, Serino M, Abbott J, Charpentier J, Heymes C, Luque JL, Anthony E, Barton RH, Chilloux J, Myridakis A, Martinez-Gili L, Moreno-Navarrete JM, Benhamed F, Azalbert V, Blasco-Baque V, Puig J, Xifra G, Ricart W, Tomlinson C, Woodbridge M, Cardellini M, Davato F, Cardolini I, Porzio O, Gentileschi P, Lopez F, Fougelle F, Butcher SA, Holmes E, Nicholson JK, Postic C, Burcelin R, Dumas ME.	Nature Med	2018
1	Dietary exacerbation of metabolic stress leads to accelerated hepatic carcinogenesis in glycogen storage disease type Ia	Gjorgjieva M, Calderaro J, Monteillet L, Silva M, Raffin M, Brevet M, Romestaing C, Rousset D, Zucman-Rossi J, Mithieux G, Rajas F	J Hepatol	2018
1	Stratification of Pancreatic Ductal Adenocarcinomas Based on Tumor and Microenvironment Features	Puleo F, Nicolle R, Blum Y, Cros J, Marisa L, Demetter P, Quertinmont E, Svrcek M, Elarouci N, Iovanna J, Franchimont D, Verset L, Galdon MG, Devière J, de Reyniès A, Laurent-Puig P, Van Laethem JL, Bachet JB, Maréchal R.	Gastroenterology	2018
1	microRNA 193a-5p Regulates Levels of Nucleolar- and Spindle-Associated Protein 1 to Suppress Hepatocarcinogenesis.	Roy S, Hooiveld GJ, Seehawer M, Caruso S, Heinzmann F, Schneider AT, Frank AK, Cardenas DV, Sonntag R, Luedde M, Trautwein C, Stein I, Pikarsky E, Loosen S, Tacke F, Ringelhan M, Avsaroglu SK, Goga A, Buendia MA, Vucur M, Heikenwalder M, Zucman-Rossi J, Zender L, Roderburg C, Luedde T.	Gastroenterology	2018
1	Argininosuccinate synthase 1 and periportal gene expression in sonic hedgehog hepatocellular adenomas.	Nault JC, Couchy G, Caruso S, Meunier L, Caruana L, Letouze E, Rebouissou S, Paradis V, Calderaro J, Zucman-Rossi J,.	Hepatology	2018
1	Lkb1 as a gatekeeper of hepatocyte proliferation and genomic integrity during liver regeneration	Maillet V, Boussetta N, Leclerc J, Fauveau V, Foretz M, Viollet B, Couty JP, Celton-Morizur S, Perret C, Desdouets C	Cell Report	2018
1	NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer	Lécuyer L, Victor Bala A, Deschasaux M, Bouchemal N, Nawfal Triba M, Vasson MP, Rossary A, Demidem A, Galan P, Hercberg S, Partula V, Le Moyec L, Srouf B, Fiolet T, Latino-Martel P, Kesse-Guyot E, Savarin P, Touvier M.	Int J Epidemiol	2018
1	Higher spermidine intake is linked to lower mortality: a prospective population-based study	Kiechl S, Pechlaner R, Willeit P, Notdurfter M, Paulweber B, Willeit K, Werner P, Ruckenstein C, Iglseder B, Weger S, Mairhofer B, Gartner M, Kedenko L, Chmelikova M, Stekovic S, Stuppner H, Oberhollenzer F, Kroemer G, Mayr M, Eisenberg T, Tilg H, Madeo F, Willeit J.	Am J Clin Nutr	2018
1	Liver Cancer Initiation Requires p53 Inhibition by CD44-Enhanced Growth Factor Signaling.	Dhar D, Antonucci L, Nakagawa H, Kim JY, Glitzner E, Caruso S, Shalapur S, Yang L, Valasek MA, Lee S, Minnich K, Seki E, Tuckermann J, Sibilia M, Zucman-Rossi J, Karin M	Cancer Cell	2018
2	Blueprint of human thymopoiesis reveals molecular mechanisms of stage-specific TCR enhancer activation.	Cieslak A, Charbonnier G, Tesio M, Mathieu EL, Belhocine M, Touzart A, Smith C, Hypolite G, Andrieu GP, Martens JHA, Janssen-Megens E, Gut M, Gut I, Boissel N, Petit A, Puthier D,	J Exp Med	2020

		Macintyre E, Stunnenberg HG, Spicuglia S, Asnafi V.		
2	A transcriptomic continuum of differentiation arrest identifies myeloid interface acute leukemias with poor prognosis.	Bond J, Krzywon A, Lhermitte L, Roumier C, Roggy A, Belhocine M, Kheirallah A, Villarese P, Hypolite G, Garnache-Ottou F, Castaigne S, Boissel B, Asnafi V, Preudhomme C, Dombret H, Laurenti E, Macintyre E	Leukemia	2020
2	CBFβ-SMMHC Affects Genome-wide Polycomb Repressive Complex 1 Activity in Acute Myeloid Leukemia.	Cordonnier G, Mandoli A, Cagnard N, Hypolite G, Lhermitte L, Verhoeyen E, Asnafi V, Dillon N, Macintyre E, Martens JHA, Bond J.	Cell Reports	2020
2	Antileukemic activity of the VPS34-IN1 inhibitor in acute myeloid leukemia	Meunier G, Birsén R, Czelles C, Belhadj M, Cantero-Aguilar L, Kosmider O, Fontenay M, Azar N, Mayeux P, Chapuis N, Tamburini J, Bouscary D.	Oncogenesis	2020
2	Isothermal digital detection of microRNAs using background-free molecular circuit	Gines, G; Menezes, R; Nara, K; Kirstetter, AS; Taly, V; Rondelez, Y	Science Advances	2020
2	Adult T-cell acute lymphoblastic leukemias with IL7R pathway mutations are slow-responders who do not benefit from allogeneic stem-cell transplantation.	Kim R, Boissel N, Touzart A, Leguay T, Thonier F, Thomas X, Raffoux E, Huguet F, Villarese P, Fourrage C, Passini L, Hunault M, Lepretre S, Chevallier P, Braun T, Lhéritier V, Chantepie S, Maury S, Escoffre M, Tavernier E, Chalandon Y, Graux C, Macintyre E, Ifrah N, Asnafi V, Dombret H, Lhermitte L	Leukemia	2020
2	Targeted deep sequencing reveals clonal and subclonal mutational signatures in Adult T-cell leukemia/lymphoma and defines an unfavorable indolent subtype.	Marçais, A., Lhermitte, L., Artesi, M., Laurent, C., Durkin, K., Hahaut, V., Rosewick, N., Suarez, F., Sibon, D., Cheminant, M., Avettand-Fenoel, V., Bruneau, J., Georges, M., Pique, C., Van den Broeke, A., Asnafi, V., & Hermine, O	Leukemia	2020
2	Mechanical Characterization of Cells and Microspheres Sorted by Acoustophoresis with In-Line Resistive Pulse Sensing	Riaud, A; Wang, W; Thai, ALP; Taly, V	Physical Review Applied	2020
2	High IGF1R protein expression correlates with disease-free survival of patients with stage III colon cancer	Zaanán A, Calmel C, Henriques J, Svrcek M, Blons H, Desbois-Mouthon C Merabtene F, Goumard C, Parc Y, Gayet B, Taieb J, Validire P, Louvet C, Fléjou JF, Le Bouc Y, Praz F.	Cell Oncol	2020
2	Phenotypic landscape of granulocytes and monocytes by multiparametric flow cytometry: A prospective study of a 1-tube panel strategy for diagnosis and prognosis of patients with MDS.	Barreau S, Green AS, Dussiau C, Alary AS, Raimbault A, Mathis S, Willems L, Bouscary D, Kosmider O, Bardet V, Fontenay M, Chapuis N.	Cytometry B Clin Cytom	2020
2	Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes.	Bernard E, Nannya Y, Hasserjian RP, Devlin SM, Tuechler H, Medina-Martinez JS, Yoshizato T, Shiozawa Y, Saiki R, Malcovati L, Levine MF, Arango JE, Zhou Y, Solé F, Cargo CA, Haase D, Creignou M, Germing U, Zhang Y, Gundem G, Sarian A, van de Loosdrecht AA, Jädersten M, Tobiasson M, Kosmider O, Follo MY, Thol F, Pinheiro RF, Santini V, Kotsianidis I, Boulwood J, Santos FPS, Schanz J, Kasahara S, Ishikawa T, Tsurumi H, Takaori-Kondo A, Kiguchi T, Polprasert C, Bennett JM, Klimek VM, Savona MR, Belickova M, Ganster C, Palomo L, Sanz G, Ades L, Della Porta MG, Smith AG, Werner Y, Patel M, Viale A, Vanness K, Neuberg DS, Stevenson KE, Menghrajani K, Bolton KL, Fenaux P, Pellagatti A, Platzbecker U, Heuser M, Valent P, Chiba S, Miyazaki Y, Finelli C, Voso MT, Shih LY, Fontenay M, Jansen JH, Cervera J, Atsuta Y, Gattermann N, Ebert BL, Bejar R, Greenberg PL, Cazzola M, Hellström-Lindberg E, Ogawa S, Papaemmanuil E.	Nature Medicine	2020

2	Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19.	Silvin A, Chapuis N, Dunsmore G, Goubet AG, Dubuisson A, Derosa L, Almiré C, Hénon C, Kosmider O, Droin N, Rameau P, Catelain C, Alfaro A, Dussiau C, Friedrich C, Sourdeau E, Marin N, Szwebel TA, Cantin D, Mouthon L, Borderie D, Deloger M, Bredel D, Mouraud S, Drubay D, Andrieu M, Lhonneur AS, Saada V, Stoclin A, Willekens C, Pommeret F, Griscelli F, Ng LG, Zhang Z, Bost P, Amit I, Barlesi F, Marabelle A, Pène F, Gachot B, André F, Zitvogel L, Ginhoux F, Fontenay M, Solary E.	Cell	2020
2	Pairing MCL-1 inhibition with venetoclax improves therapeutic efficiency of BH3-mimetics in AML.	Hormi M, Birsén R, Belhadj M, Huynh T, Cantero Aguilar L, Grignano E, Haddaoui L, Guillonéau F, Mayeux P, Hunault M, Tamburini J, Kosmider O, Fontenay M, Bouscary D, Chapuis N.	Eur J Haematol	2020
2	Vitamin D Receptor Controls Cell Stemness in Acute Myeloid Leukemia and in Normal Bone Marrow.	Paubelle E, Zylbersztejn F, Maciel TT, Carvalho C, Mupo A, Cheok M, Lieben L, Sujobert P, Decroocq J, Yokoyama A, Asnafi V, Macintyre E, Tamburini J, Bardet V, Castaigne S, Preudhomme C, Dombret H, Carmeliet G, Bouscary D, Ginzburg YZ, de Thé H, Benhamou M, Monteiro RC, Vassiliou GS, Hermine O, Moura IC.	Cell Reports	2020
2	Clinical and biological features of PTPN2-deleted adult and pediatric T-cell acute lymphoblastic leukemia.	Alcantara M, Simonin M, Lhermitte L, Touzart A, Dourthe ME, Latiri M, Gardel N, Cayuela JM, Chalandon Y, Graux C, Dombret H, Ifrah N, Petit A, Macintyre E, Baruchel A, Boissel N, Asnafi V.	Blood Advances	2019
2	The NRF2 transcriptional target NQO1 has low mRNA levels in TP53-mutated endometrial carcinomas	Beinse, G; Just, PA; Rance, B; Izac, B; Letourneur, F; Saidu, NEB; Chouzenoux, S; Nicco, C; Goldwasser, F; Pasmant, E; Batteux, F; Borghese, B; Alexandre, J; Leroy, K	Plos One	2019
2	DNMT3A mutation is associated with increased age and adverse outcome in adult T-cell acute lymphoblastic leukemia	Bond J, Touzart A, Leprêtre S, Graux C, Bargetzi M, Lhermitte L, Hypolite G, Leguay T, Hicheri Y, Guillem G, Bilger K, Lhéritier V, Hunault M, Huguet F, Chalandon Y, Ifrah N, Macintyre E, Dombret H, Asnafi V, Boissel N.	Haematologica	2019
2	Revisiting immune escape in colorectal cancer in the era of immunotherapy	Ijsselsteijn, ME; Petitprez, F; Lacroix, L; Ruano, D; van der Breggen, R; Julie, C; Morreau, H; Sautes-Fridman, C; Fridman, WH; de Miranda, NFDC	British Journal Of Cancer	2019
2	Microfluidic extraction and digital quantification of circulating cell-free DNA from serum	Perez-Toralla, K; Pereiro, I; Garrigou, S; Di Federico, F; Proudhon, C; Bidard, FC; Viovy, JL; Taly, V; Descroix, S	Sensors And Actuators B-Chemical	2019
2	Sustained Type I interferon signaling as a mechanism of resistance to PD-1 blockade	Jacquelot N, Yamazaki T, Roberti MP, Duong CPM, Andrews MC, Verlingue L, Ferrere G, Becharef S, Vétizou M, Daillère R, Messaoudene M, Enot DP, Stoll G, Ugel S, Marigo I, Foong Ngiew S, Marabelle A, Prevost-Blondel A, Gaudreau PO, Gopalakrishnan V, Eggermont AM, Opolon P, Klein C, Madonna G, Ascierto PA, Sucker A, Schadendorf D, Smyth MJ, Soria JC, Kroemer G, Bronte V, Wargo J, Zitvogel L.	Cell Res	2019
2	Distinct prognostic value of circulating anti-telomerase CD4(+) Th1 immunity and exhausted PD-1(+)/TIM-3(+) T cells in lung cancer	Laheurte C, Dosset M, Vernerey D, Boullerot L, Gaugler B, Gravelin E, Kaulek V, Jacquin M, Cuhe L, Eberst G, Jacquet P, Fabre E, Le Pimpec-Barthes F, Tartour E, De Carvalho Bittencourt M, Westeel V, Adotévi O	Br J Cancer	2019
2	Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer	Fournel L, Wu Z, Stadler N, Damotte D, Lococo F, Boule G, Ségal-Bendirdjian E, Bobbio A, Icard P, Trédaniel J, Alifano M, Forgez P	Cancer Lett	2019
2	Dyserythropoiesis evaluated by the RED score and hepcidin:ferritin ratio predicts response to erythropoietin in lower-risk myelodysplastic syndromes.	Park S, Kosmider O, Maloïsel F, Drenou B, Chapuis N, Lefebvre T, Karim Z, Puy H, Alary AS, Ducamp S, Verdier F, Bouilloux C, Rousseau A, Jacob MC, Debliquis A, Charpentier A, Gyan E, Anglaret B, Leyronnas C, Corm S, Slama B, Cheze S, Laribi K, Amé S, Rose C, Lachenal F, Toma A,	Haematologica	2019

		Pica GM, Carre M, Garban F, Mariette C, Cahn JY, Meunier M, Herault O, Fenaux P, Wagner-Ballon O, Bardet V, Dreyfus F, Fontenay M		
2	TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups.	Haase D, Stevenson KE, Neuberg D, Maciejewski JP, Nazha A, Sekeres MA, Ebert BL, Garcia-Manero G, Haferlach C, Haferlach T, Kern W, Ogawa S, Nagata Y, Yoshida K, Graubert TA, Walter MJ, List AF, Komrokji RS, Padron E, Sallman D, Papaemmanuil E, Campbell PJ, Savona MR, Seegmiller A, Adès L, Fenaux P, Shih LY, Bowen D, Groves MJ, Tauro S, Fontenay M, Kosmider O, Bar-Natan M, Steensma D, Stone R, Heuser M, Thol F, Cazzola M, Malcovati L, Karsan A, Ganster C, Hellström-Lindberg E, Boulwood J, Pellagatti A, Santini V, Quek L, Vyas P, Tüchler H, Greenberg PL, Bejar R; International Working Group for MDS Molecular Prognostic Committee.	Leukemia	2019
2	Vitamin K antagonism impairs the bone marrow microenvironment and hematopoiesis.	Verma D, Kumar R, Pereira RS, Karantanou C, Zanetti C, Minciacci VR, Fulzele K, Kunz K, Hoelper S, Zia-Chahabi S, Jabagi MJ, Emmerich J, Dray-Spira R, Kuhlee F, Hackmann K, Schroeck E, Wenzel P, Müller S, Filmann N, Fontenay M, Pajevic PD, Krause DS.	Blood	2019
2	Impact of genotype in relapsed and refractory acute myeloid leukaemia patients treated with clofarabine and cytarabine: a retrospective study.	Mondesir J, Alary AS, Sibon D, Willems L, Deau B, Suarez F, Hermine O, Fontenay M, Bouscary D, Kosmider O, Tamburini J.	Br J Haematol	2019
2	Bone marrow oxidative stress and specific antioxidant signatures in myelodysplastic syndromes.	Picou F, Vignon C, Debeissat C, Lachot S, Kosmider O, Gallay N, Foucault A, Estienne MH, Ravalet N, Bene MC, Domenech J, Gyan E, Fontenay M, Herault O.	Blood Advances	2019
2	The fraction of CD117/c-KIT-expressing erythroid precursors predicts ESA response in low-risk myelodysplastic syndromes.	Raimbault A, Itzykson R, Willems L, Rousseau A, Chapuis N, Mathis S, Clauser S, Radford-Weiss I, Bouscary D, Fontenay M, Kosmider O, Bardet V.	Cytometry B Clin Cytom	2019
2	Novel intergenically Spliced Chimera, NFATC3-PLA2G15, Is Associated with Aggressive T-ALL Biology and Outcome.	Bond, J., Tran Quang, C., Hypolite, G., Belhocine, M., Bergon, A., Cordonnier, G., Ghysdael, J., Macintyre, E., Boissel, N., Spicuglia, S., & Asnafi, V. (2018). Novel Intergenically Spliced Chimera, NFATC3-PLA2G15, Is Associated with Aggressive T-ALL Biology and Outcome.	Molecular cancer research	2018
2	Drug monitoring of sunitinib in patients with advanced solid tumors: a monocentric observational French study.	Cabel L, Blanchet B, Thomas-Schoemann A, Huillard O, Bellesoeur A, Cessot A, Giroux J, Boudou-Rouquette P, Coriat R, Vidal M, Saidu NEB, Golmard L, Alexandre J, Goldwasser F.	Fundam Clin Pharmacol.	2018
2	A Single-Tube, EuroClonality-Inspired, TRG Clonality Multiplex PCR Aids Management of Patients with Enteropathic Diseases, including from Formaldehyde-Fixed, Paraffin-Embedded Tissues.	Derriex C, Trinquand A, Bruneau J, Verkarre V, Lhermitte L, Alcantara M, Villarese P, Meresse B, Sibon D, Hermine O, Brousse N, Molina T, Cellier C, Cerf-Bensussan N, Malamut G, Macintyre E.	J Mol Diagn	2018
2	T-cell large granular lymphocyte leukemia transformation into aggressive T-cell lymphoma: a report of two cases with molecular characterization	Maya Belhadj, Dalila Mansour, Sophie Kaltenbach, Benedicte Deau-Fischer, Patricia Franchi, Jérôme Tamburini, Nicolas Chapuis, Diane Damotte, Olivier Kosmider, Barbara Burroni, Didier Bouscary	Haematologica	2018
2	Oncogenetic mutations combined with MRD improve outcome prediction in pediatric T-cell acute lymphoblastic leukemia.	Petit A, Trinquand A, Chevret S, Ballerini P, Cayuela JM, Grardel N, Touzart A, Brethon B, Lapillonne H, Schmitt C, Thouvenin S, Michel G, Preudhomme C, Soulier J, Landman-Parker J, Leverger G, Macintyre E, Baruchel A, Asnafi V; French Acute Lymphoblastic Leukemia Study Group (FRALLE).	Blood	2018
2	Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment	Peranzoni E, Lemoine J, Vimeux L, Feuillet V, Barrin S, Kantari-Mimoun C, Bercovici N, Guérin M, Biton J, Ouakrim H, Régnier F, Lupo A, Alifano M, Damotte D, Donnadieu E.	Proc Natl Acad Sci U S A	2018

2	RSK2 is a new Pim2 target with pro-survival functions in FLT3-ITD-positive acute myeloid leukemia.	Hospital MA, Jacquel A, Mazed F, Saland E, Larrue C, Mondesir J, Birsen R, Green AS, Lambert M, Sujobert P, Gautier EF, Salnot V, Le Gall M, Decroocq J, Poulain L, Jacque N, Fontenay M, Kosmider O, Récher C, Auberger P, Mayeux P, Bouscary D, Sarry JE, Tamburini J.	Leukemia	2018
2	Lenalidomide-mediated erythroid improvement in non-del(5q) myelodysplastic syndromes is associated with bone marrow immuno-remodeling.	Kerdivel G, Chesnais V, Becht E, Toma A, Cagnard N, Dumont F, Rousseau A, Fenaux P, Chevret S, Chapuis N, Boeva V, Fridman WH, Fontenay M, Kosmider O.	Leukemia	2018
2	Assessment of ASC specks as a putative biomarker of pyroptosis in myelodysplastic syndromes: an observational cohort study.	Basiorka AA, McGraw KL, Abbas-Aghababazadeh F, McLemore AF, Vincelette ND, Ward GA, Eksioglu EA, Sallman DA, Ali NA, Padron E, Pinilla-Ibarz J, Komrokji R, Masala E, Santini V, Kosmider O, Fontenay M, Fenaux P, Sokol L, Wei S, Fridley B, List AF.	Lancet Hematol	2018

2. List of deliverables

From the initial workplan described in Annex B3 of the application, report the deliverables list and indicate the state of progress: not started, in progress and on time, in progress but delayed, completed, postponed or canceled. Justify in the column “comments” the delays or cancellations.

IRP* number	Deliverable title	To be completed by year	State of progress	Comments
1	Clinical correlations between metabolic and immunological features of major cancers.	3	In progress and on time	
1	Mechanistic comprehension of the immunometabolic crosstalk in cancer	4	In progress and on time	
1	Impact of whole-body metabolism on anticancer immunosurveillance	3	In progress and on time	
1	Crosstalk between whole-body metabolism and tumor-intrinsic immunometabolism	3	In progress and on time	
1	Epidemiological associations between metabolism and cancer using “big data”	2	Completed	See publication from Touvier teams
1	Pilot trials to modulate metabolism in the context of cancer treatment.	5	In progress and on time	
1	Identification and validation of genetic markers predisposing to hepatocellular adenoma and carcinoma	2	Completed	See publication Zucman-Rossi teams
1	Identification of cooperative interactions between exposure, metabolic defect and genetic predisposition in liver tumor occurrence	5	In progress and on time	
1	Assessment of the role of the metabolic partners of the WNT/ β -catenin in murine liver carcinogenesis	4	In progress and on time	Several publications
1	Validation in Human HCC of the WNT/ β -catenin metabolic partners, cooperative effects and translation in biomarkers	5	In progress and on time	
1	Interaction of polyploidy and immune response in NASH and HCC development	3	In progress and on time	Manuscript in preparation
1	Role of sphingolipid metabolism and mineralocorticoid receptor inhibitor in NASH/HCC transition	5	In progress and on time	
1	Interaction between metabolic features and molecular subclasses of colon cancer in patients based on PETACC08	1	Completed	Analysis completed, publication in progress
1	Models of Immune response and molecular metabolic alteration in malignant colon cells and patients	5	In progress and on time	
1	Modeling microbiota and high fat diet interaction in murine intestine carcinogenesis	5	In progress and on time	
2	Development and validation of scRNA-seq and scATAC-seq (or scChIP-seq) on hematological and solid tumors	4	In progress and on times	
2	Validation of a multiplex immunofluorescence analysis on paraffin embedded tissue	3	Completed	See publication of § Task 3.2.1
2	Application of the microfluidic probe (MFP) technology to perform multiple testing of solid tumors (IHC) coupled with cell lysis and genetic or epigenetic analysis	4	In progress and on time	

2	Demonstration that the modulation of tumor microenvironment may improve CAR trafficking	5	In progress and on time	Kantari-Mimoun C, et al. CAR T cell entry into tumor islets is a two-step process dependent on IFN γ and ICAM-1. BioRxiv, 2020
2	Development of universal cancer methylation markers as form of signature (detected by a NGS panel) allowing to highlight presence of several cancer types (lung, digestive and gynecologic cancers)	3	Completed	Several patents and manuscript in preparations
2	Optimization of droplet digital PCR to characterize clonal architecture at single cell level and to detect minimal residual disease in myeloid and lymphoid malignancies.	2	Completed	Le Gouill S et al. Lancet Hematology accepted
2	Validation of newly discovered targets in the CRISPR screen and identification of efficient therapeutic tools by using a pharmacological screen	3	Completed	Manuscript in preparation
2	Set-up and analysis of heterogeneity of 3D multicellular tissues derived from cell lines and patient colon cancer samples	5	In progress and on time	Several technical publications
2	Use of humanized scaffolds to investigate the relationship between transplantation efficiency and genotype and for in vivo testing of genotype-targeted therapy.	4	In progress and on time	
2	Comprehensive analysis of the composition of tumor microenvironment (CD8+T cells) in the presence or absence of Math1	2	Delayed	
2	Identification of the immune cell population in contact of β -catenin activated hepatocytes and required for the transcriptomic control of the Dlk1/Dio3 locus involved in tumor formation	4	In progress and on time	
2	Identification of the consequence of the loss of ARID1A or ARID2 on the composition of immune cell in the tumor microenvironment as well as of the genetic or pharmacological inactivation of immune players on the oncogenic mutations (β catenin, ARID1A, ARID2) mediated tumor formation	3	In progress and on time	R Riou et al. ARID1A loss in adult hepatocytes activates β -catenin-mediated erythropoietin transcription. In revision in eLife
2	Comparative analysis of tumor microenvironment in wild type, transgenic or complement deficient mouse strains grafted with wild type tumor cell lines and deciphering of the complement proteins role in response and resistance to various therapeutic strategies (chemotherapy, antiangiogenic molecules, immunotherapies)	5	In progress and on time	
2	Comparative analysis of lung tumor microenvironment in tumor bearing mice (orthotopic and spontaneous models) infected or not with influenza virus and with RSV and consequences in resistance to therapy	1	In progress and on time	
2	Looking for the expression of human virus in the tumor microenvironment of human lung cancer.	5	In progress and on time	
2	Correlation of the sensitivity and resistance to cancer vaccine and the tumor heterogeneity of the various tumor microenvironment influenced by the site of priming and location of the tumor in mice	3	In progress and on time	
2	Characterization of circulating tumor DNA and Immunoscore™ in IDEA & PETAC-8	1	Completed	Publication IDEA: Pagès et al., Annals of Oncology 2020 Circulated tumor DNA in IDEA submitted
2	Molecular classification of the 1450 IDEA tumors and characterization of the main genetic and epigenetic	4	In progress and on time	Publication IDEA: Pagès et al., Annals of Oncology 2020

	alterations and establishment of the nomogram for predicting recurrence			
2	Predictive value of the PD-L1 expression, immune contexture and mutational load on immunotherapy clinical response on the COLCHECKPOINT collection and Ionesco trial	2	In progress but delayed	Obtention of support by ARC
2	Integration of the different biomarkers before and after therapy into a common database to produce a reliable composite biomarker to predict response to anti-PD-L1 in lung cancer	4	In progress and on time	The Immunoteam database is in the process of being set up and already contains some clinical, biological and radiological information.
2	Development of MDD measurement in FFPE samples and validation in a selected cohort of lymphoma samples	2	Completed for lymphoblastic lymphomas and being	Prepared for publication
2	Prognostic value of ctDNA detection in selected lymphoma (prospective cohorts)	4	In progress and on time	
2	Diagnostic performances of PPGL molecular signature	1	Completed	
2	Diagnostic performances of circulating PPGL biomarkers	5	In progress and on time	
2	Novel Immune classification in ccRCC which CD8+T cell exhibit a poor prognosis	3	In progress and on time	
2	Predictive value of this immune signature on the recurrence in ccRCC and on the response to immunotherapy	5	In progress and on time	
2	Validation of an immunoscore like from colon and rectal cancer biopsies	4	In progress and on time	Publication Marliot et al., J. Immunother Cancer 2020
2	Developing a routine panel for the molecular classification of ACC	1	Completed	
2	Validation of the use of the new panel for ACC patient stratification and set-up of a clinical trial for validating the use of panel stratification for comparing mitotane to mitotane + chemotherapy	4	In progress and on time	Start late 2020
2	Predictive value complete geriatric assessment and immunosenescence biomarkers on the clinical response toxicity following immunotherapy	5	In progress and on time	Support from canceropole obtained collection of samples on going
3	Patients' qualitative study: Identification of patients' perception and preferences toward data and sample sharing	1	In progress	
3	Professionals' qualitative study: Identification of professionals' needs and expectations toward DC	1	In progress	
3	Establishment of a first version of guidelines for the CARPEM DC platform	1	In progress and delayed	Legal and the regulatory framework for research practices are under revision in France since 2016
3	List of functionalities (including security, privacy) to be used to design the prototype	2	In progress	
3	Prototype to be presented to the users and to the ATEB for validation before implementing the functionalities	2	Delayed	
3	CARPEM platform implementing the DC functionalities first version	2	Delayed	
3	Regulatory formalities (Authorization of the CNIL)	2	Delayed	

3	CARPEM platform implementing the DC functionalities second release (final, validated)	3	not started	
3	Production of dedicated flyers	2	Completed for Lynch Syndrom patients cohort (CARPEM-LYNCH)	In progress for Solid tumors patients cohort (CARPEM-CANCER)
3	Establishment of the 2 CARPEM patients' specific questionnaires	2	Completed for Lynch Syndrom patients cohort (CARPEM-LYNCH)	In progress for Solid tumors patients cohort (CARPEM-CANCER)
3	Dietary intake data of the subjects from the two cohorts and statistical analyses of these questionnaires	4	In progress for Lynch Syndrom patients cohort (CARPEM-LYNCH)	In progress for Solid tumors patients cohort (CARPEM-CANCER)
3	Identification of fears and reluctances of patients to individual personal data linkage	2	In progress	
3	Re-composition of the ATEB and elaboration of the meetings' schedule	1	In progress	Due to Covid crisis
3	Elaboration of the specific report form for encountered barriers and global report of the difficulties declared and their analysis	1	In progress	Due to Covid crisis
3	Proposal of a revised users' chart for the CARPEM DC platform	3	In progress	

3. Clinical trials

IRP* number	Title of the clinical trial and NCT number	Phase	Start and end dates	Sponsor	Name of the PI and affiliation
2	<u>Circulating tumor dna based decision for adjuvant treatment in colon cancer stage ii (circulate)</u> NCT04120701	III	2019-2027	CHU Dijon	J Taieb CARPEM
1	<u>Pilot study of a diagnostic test for the presence of a succinate dehydrogenase (SDH) mutation in patients with pheochromocytoma paraganglioma by a method of metabolic flow of carbon-13 labelled glucose</u>	II	2020-2023	APHP	L. Amae CARPEM
2	<u>A BIOMarker Driven Trial With Nivolumab and Ipilimumab or VEGFR tKi in Naïve Metastatic Kidney Cancer (BIONIKK)</u> NCT02960906	II	2018-2020	Artic	Y. Vano
2	A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors NCT02715284	First in man	15/05/2018	TESARO, Inc.	J Medioni, CARPEM
2	A Phase 1 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET-Fusion Non-Small Cell Lung Cancer, Medullary Thyroid Cancer and Other Tumors with Increased RET Activity. NCT02715284	First in man	10/12/2018	Loxo	J Medioni, CARPEM
2	A Study of INCMGA00012 in Participants With Selected Solid Tumors (POD1UM-203) NCT03679767	II	04/08/2019	INCYTE	J Medioni, CARPEM
2	Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors NCT03170960	Ib/II	03/06/2020	EXELIXIS	Y Vano, CARPEM
2	A Study to Assess the Antitumor Activity, Safety, Pharmacokinetics and Biomarkers of Zolbetuximab (IMAB362) in Participants With Claudin (CLDN) 18.2 Positive, Metastatic or Advanced Unresectable Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma (ILUSTRO) NCT03505320	II	01/12/2019	Astellas	J Taieb, CARPEM
1	Anti-programmed Cell Death-1 Ligand 1 (aPDL-1) Antibody Atezolizumab, Bevacizumab and Acetylsalicylic Acid in Recurrent Platinum Resistant Ovarian Cancer NCT02659384	II	17/12/2018	EORTC	N Delanoy, HEGP
2	Study of Dose Escalation of Abiraterone Actetate in Prostate Cancer (OPTIMABI) NCT03458247	II	06/07/2018	APHP	S Oudard, CARPEM
2	A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in With Advanced Solid Cancers NCT03547037	Ib/II	11/12/2018	JANSSEN	Y Vano, CARPEM
2	A Phase 2, Single-Arm Study of Bempegaldesleukin (NKTR-214) in Combination With Nivolumab in Cisplatin Ineligible, Locally Advanced or Metastatic Urothelial Cancer Patients NCT03785925	II	23/08/2019	Nektar Therapeutics	S Oudard, CARPEM
2	NEoadjuvant Dose-dense MVAC In cOmbination With Durvalumab and Tremelimumab in Muscle-invasive Urothelial Carcinoma (NEMIO) NCT03549715	I	15/11/2018	ARTIC	C Thibault, HEGP
2	CANTATA: CB-839 With Cabozantinib vs. Cabozantinib With Placebo in Patients With Metastatic Renal Cell Carcinoma (CANTATA) NCT03428217	II	04/12/2018	Calithera	Y Vano, CARPEM
2	Study of Efficacy, Safety, and Quality of Life of Pazopanib in Patients With Advanced and/or Metastatic Renal Cell	II	20/06/2018	Novartis	S Oudard, CARPEM

	Carcinoma After Prior Checkpoint Inhibitor Treatment (IO-PAZ) NCT03200717				
2	A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination With Durvalumab Versus Nivolumab Monotherapy in Subjects With Select Advanced Malignancies NCT02118337	II	25/01/2018	MedImmune	S Oudard, CARPEM
2	The XENERA™ 1 Study Tests Xentuzumab in Combination With Everolimus and Exemestane in Women With Hormone Receptor Positive and HER2-negative Breast Cancer That Has Spread NCT03659136	II	14/12/2018	Boehringer Ingelheim	J Medioni, CARPEM
2	Chemotherapy-free Trastuzumab and Pertuzumab in HER2-positive Breast Cancer: FDG-PET Response-adapted Strategy. (PHERGain) NCT03161353	II	30/05/2018	MedImmune	J Medioni, CARPEM
2	PALbociclib and Circulating Tumor DNA for ESR1 Mutation Detection (PADA-1) NCT03079011	II	15/02/2018	Unicancer	J Medioni, CARPEM
2	PALbociclib Rechallenge in hormone Receptor-positive/HER2- Negative Advanced Breast Cancer (PALMIRA) NCT03809988	II	15/03/2019	Medsir	J Medioni, CARPEM
2	Nivolumab in Association With Radiotherapy and Cisplatin in Locally Advanced Cervical Cancers Followed by Adjuvant Nivolumab for up to 6 Months (NICOL) NCT03298893	I	08/10/2018	Institut Curie	C Durdux, CARPEM

4. Leverage effect

List of grants (call for proposals from national or regional institutions, charities, European calls, private companies, etc) which have been obtained thanks to the direct support of the 2018 SIRIC.

IRP* number	Title of the project	Funding organisation	Start and end dates	Name of the coordinator	Granted budget (€)
1	PGL.EXPO: impact des expositions environnementales sur le risque tumoral chez les sujets à risque de paragangliome SDH-déterminé	ANSES	2019-2023	Anne-Paule Gimenez-Roqueplo	340 830 €
1	Points de Contrôle des Dommages à l'ADN et de la Polyploidie : les Gardiens de la Cancérogenèse Hépatique associée aux Désordres Métaboliques.	INCa PLBIO	2018 - 2021	Chantal Desdouets	540 000 €
1	Oncoimmunologie des cancers du foie pédiatrique	BMS fondation	2019 - 2021	Jessica Zucman-Rossi	120 000 €
1	Génomique intégrée des Hépatoblastomes	SFCE	2018 - 2020	Jessica Zucman-Rossi	120 000 €
1	Labellisation Equipe ligue	Ligue	2019 - 2021	Jessica Zucman-Rossi	240 000 €
1	Modèle cellulaire préclinique de la reponse thérapeutique	ARC	2019 - 2021	Sandra Rebouissou	50 000 €
1	PREMALEP : Génomique des tumeurs préneoplasiques du foie	INCA	2019-2022	Jean-Charles Nault	240 000€
1	Etude ancillaire de l'essai IDEA France	ARC	2018 - 2021	Pierre Laurent-Puig	322 900 €
1	Nouvelles cibles thérapeutiques mésothéliomes	Ligue	2019-2020	Didier Jean	50 000 €
1	Téломérase dans la carcinogénèse hépatique : fonction et transfert vers la clinique	PRTK	2018 - 2021	Jessica Zucman-Rossi/ Pierre Laurent-Puig/ Chantal Dedouets	420 000 €
1	Antigen cross-presentation in anticancer immuno-surveillance	INCa	2018 -2021	Guido Kroemer	624 000 €
1	Interference to netrin-1 as a promoter of anti-tumor immunity	INCa	2018 -2021	Guido Kroemer	150 000€
1	Immunoadjuvant effects of autophagy in the context of anticancer chemotherapy	Ligue de lutte contre le cancer	2018 - 2020	Guido Kroemer	450 000 €
1	Nutrition and cancer: mechanistic links at the level of the microbiome	Seerave foundation	2018-2021	Guido Kroemer	250 000 €
1	Onco-Biome	EU Horizon 2020	2019-2025	Laurence Zitvogel (G. Kroemer Pariticipants)	825 000€
2	Identification de facteurs prédictifs de réponse aux thérapies ciblant le microenvironnement tumoral dans les sarcomes des tissus mous	Foncer contre le cancer	2018 - 2020	Catherine Sautès-Fridman	50 000€
2	Biomarqueurs sanguins prédictifs de l'efficacité des traitements par immunothérapies inhibiteurs de checkpoints ou par anti-angiogéniques dans le cancer du rein à cellules claires. Analyse ancillaire de l'étude prospective de phase II BIONIKK	Foncer contre le cancer	2019 - 2020	Cheng Ming Sun	50 000 €
2	Analyse de microenvironnement de soft-tissue sarcome et son impact sur immunothérapies	INCa	20182 - 2020	Cheng Ming Sun	332 612€

2	Evaluation of CTLA4 and PD1 in TLS	Medimmune	20/09/2019 ; 20/11/2020	Catherine Sautès-Fridman	18 600 €
2	PEMBROSARC	Institut Bergonié	14/09/2018 ; 31/12/2022	Catherine Sautès-Fridman	12 800 €
2	EX037503 : favoriser la formation des jeunes chercheurs en optoacoustique par le Professeur Vasilis Ntziachristos et développer un nouvel instrument d'imagerie multimodale non invasive du vivant.	Chaires Blaise Pascal	2019	Bertrand Tavitian	174 800 €
2	ITMO-Cancer « Physique pour la Médecine »	ITMO-Cancer	2018-200	Bertrand Tavitian	288 880 €
2	RADIOSUCCE Evaluation de la detection in vivo du succinate par imagerie de résonance magnétique spectroscopique (1H-SRM) comme biomarqueur de réponse au traitement chez des patients atteints de paragangliomes cervicaux avec mutations SDHx traités par radiothérapie externe	Société Française d'Endocrinologie	2018 - 2019	Charlotte Lussey-Lepoutre	30 000 €
2	Implementation of coMplex PeRi-OperatiVe intervEntion in olDer patients with cancer (IMPROVED) : a multicenter randomized controlled trial » - IMPROVED	Ministère des solidarités et de la santé	2019-2025	Elena Paillaud	540 000 €
2	Projet BIOELCAPA. Développer des bases de données biologiques multicentriques pour la recherche de spécificités tumorales et de facteurs biologiques prédictifs chez le sujet âgé.	INCa/Canvéropol e Ile de France	2018-2021	Elena Paillaud	105 000 €
2	Quantification de la maladie résiduelle des lymphomes du manteau du protocole MCLR2	Celgène via. LYSA	2019-2021	Elizabeth Macintyre	105 000 €
2	Accelerating Development and Improving Access to CAR and TCR-engineered T cell therapy	EU IMI (Innovative Medicines Initiative)	2019-2023	Emmanuel Donnadieu	180 000 €
2	Amélioration des lymphocytes CAR T et reprogrammation du microenvironnement tumoral dans le but d'éradiquer les tumeurs solides.	Ligue Contre le Cancer. Equipe Labellisée	2019-2022	Emmanuel Donnadieu	270 000 €
2	Tracking preexisting anti-tumor CD8+T cells to predict clinical response to the blocking of PD-1/PD-L1 axis (AAP Sign'it 2018)	Fondation ARC	2019 - 2021	Eric Tartour	568 000 €
2	Profil check point inhibiteur dans le microenvironnement des cancers	Servier	2019 - 2020	Eric Tartour	160 000 €
2	Prise en compte de la composante immunitaire in situ pour une nouvelle prise en charge des patients présentant un cancer du rectum localement avancé	ARC	2018-2021	Franck Pagès	395 000 €
2	Etude d'observationnelle de populations présentant un cancer colorectal afin de déterminer l'influence du statut immunitaire sur l'incidence, la gravité et la mortalité des pathologies hors-cancer	BMS	2018-2020	Franck Pagès	75 000 €
2	Projet ONCOSEN-IMM Patients de plus de 70 ans atteints de cancer traités par immunothérapie anti-PD-1/PD-L1 (cohorte ELCAPA) : biomarqueurs d'immunosénescence, facteurs de fragilité clinique et impact sur la réponse thérapeutique et la survie	Canceropôle IdF	2020	Granier Clemence	30 000 €
2	Développement de signatures moléculaires basées sur la méthylation de l'ADN pour améliorer la prise en charge du cancer de l'endomètre	MSD	2019 - 2021	Jérôme Alexandre	33 400 €
2	Development of prognostic and predictive biomarkers based on DNA methylation analysis in endometrial carcinoma	INCA	2019 - 2021	Jérôme Alexandre	150 000 €
2	Étude observationnelle de populations présentant un cancer colorectal afin de déterminer l'influence du statut immunitaire du patient sur l'incidence, la gravité et la mortalité des pathologies hors-cancer	Fondation BMS	2018 - 2019	Jérôme Galon	75 000 €

2	Analyse de l'expression de CD277, BTLA et HVEM dans les tumeurs colorectales et leurs métastases	Imcheck Therapeutics	2018 - 2021	Jérôme Galon	74 936 €
2	Identification de biomarqueurs prédictifs de la réponse thérapeutique des cancers du foie	Canceropole	2019-2019	Sandra Rebouissou	30 000 €
2	MIRENVI: impact des miRNAs sécrétés par les cellules SDHB-déficientes sur le microenvironnement tumoral et la réponse aux agents antiangiogéniques	INCA	2019 - 2023	Judith Favier	370 000 €
2	Radiomics applied to cancerology	ARC	2019-2021	Laure Fournier	375 000 €
2	Methodological developments on radiomics	FRM	2018	Laure Fournier	23 000 €
2	Etude pilote d'un test diagnostique de la présence d'une mutation de la succinate deshydrogénase (SDH) chez les patients ayant un paragangliome ou un phéochromocytome par une méthode de flux métabolique du glucose marqué au carbone 13	APHP	2019 - 2022	Laurence Amar	70 000 €
2	Role of complement C1s in tumor progression	Ligue régionale contre le cancer	2019 - 2019	Lubka Roumenina	22 500 €
2	ADN circulant dans le cancer du rein métastatique	Foncer contre le cancer	2018 - 2019	Nelly Burnichon	50 000 €
2	Humanized scaffolds to mimic bone marrow niches in mice	3R	2019 - 2023	Olivier Kosmider	127 440 €
2	Assessment of genetic and immunogenetic biomarkers in myeloid malignancies	Association Force Hemato/ Association Laurette Fugain	2019-2021	Olivier Kosmider	98 000 €
2	Classification moléculaire des cancers du côlon	Fondation ARCAD	2019 - 2021	Pierre Laurent-Puig	236 000 €
2	Etude ancillaire de l'essai NIVOREM (cancer du rein et immunothérapie)	PRTK	2019 2021	Catherine Sautes-Fridman Jessica-Zucman-Rossi	250 000 €
2	Colon Cancer Heterogeneity measured at Single Cell Level	ITMO Cancer	2018-2022	Pierre Laurent-Puig/ G Kroemer	450 000 €
2	ADIUVO-2 : Participation française à l'étude internationale prospective randomisée comparant le traitement adjuvant par mitotane vs mitotane associé à etoposide et cisplatine après chirurgie du primitif dans les corticosurrénales localisés avec risque élevé de rechute. PHRC-K19-042	INCA/DGOS	2019-2024	Rossella Libe	420 000 €
2	ActnDie : When the TCR acts as a tumor suppressor: therapeutic potential in T-Acute Lymphoblastic Leukemia	INCA PRTK	2019-2022	Vahid Asnafi	280 000 €
2	Mechanisms of resistance in T-ALL related to NOTCH1 and PTEN mutations	Fondation de France	2019-2020	Vahid Asnafi	165 000 €
2	Epigenetic evaluation of T-ALL as a basis for therapeutic intervention	INCA, soutien à la recherche translationnelle	2019-2020	Vahid Asnafi	190 000 €
2	L fvtabellisation equipe	ARC	2018-2020	Vahid Asnafi	245 000 €
2	Recherche de séquence rares par PCR digitale dans les cavernomes	Institut Necker	2018 - 2019	Valérie Taly	8 050 €
2	Labellisation Equipe ligue	Ligue régionale contre le cancer	2018 - 2020	Valérie Taly	264 000 €
2	CHIVA GINECO-OV119	ARCAGY-GINECO	2018 - 2020	Valérie Taly	116 844 €
2	Cancer evolution in droplet digital PCR	MSCA ITN H2020	2019 - 2022	Valérie Taly	243 000 €
2	Etude pilote visant à étudier l'ADN tumoral circulant dans le cancer de l'endomètre par l'utilisation d'un profil de méthylation	Canceropole Ile de France	2019- 2020	Valérie Taly	30 000 €

5. National and international synergistic collaborations and partnerships (public and private)

List of public or private national and international synergistic collaborations and partnerships that have been built thanks to the SIRIC designation (with universities, cancéropôles, technology transfer offices, regional authorities, private companies, biotechs, patients' organisations, etc)

IRP* number	Partners involved	Brief description of the joint action or collaboration	Results
1	F. Lecuru's team has set up new partnerships for the international development of the SENTICOL III trial, with: the European Network of Gynaecological Oncological Trial groups (ENGOT), the Gynecologic Cancer InterGroup (GCIg), the Cervical Cancer Research Network (CCRN)	Collaboration with F. Lecuru team	
1	Eric Deutsch, Inserm 1030, Gustave Roussy institute, France	Collaboration with Guido Kroemer	
1	Patrick Révy, Imagine Institute, Team Genome dynamics in the immune system, Paris.	Collaboration with C. Desdouets team	
1	Phillipe Gual, C3M, Inserm U1065, Team Hepatic Complications in obesity, Nice.	Collaboration with C. Desdouets team	
1	Mathias Heikenwalder, Division of Chronic Inflammation and Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany.	Collaboration with C. Desdouets team	
1	Nadia Guerra, Inflammation Cancer Immunity, Department of Life Sciences, Imperial College London, London, UK.	Collaboration with C. Desdouets team	
1	P. Sansonetti at the Pasteur Institute.	Collaboration with the team of C. Perret / B. Romagnolo	
2	INRA Gif sur Yvette - Docteur Evelyne Benoit	Collaboration with Romain Coriat	
2	Ecole normale supérieure de chimie ENS Ulm	Collaboration with Romain Coriat	
2	Mouhammed Amir Habra, Department of Endocrine Neoplasia and Hormonal Disorders, Unit 1461, The University of Texas MD Anderson Cancer Center, Houston, TX, USA	Collaboration with Jérôme Bertherat	
2	Institute for Biomedical Imaging, Technical university and Helmholtz Center of Munich, Germany	Collaboration with Bertrand Tavitian. The project considers 1) technological advancements in imaging technology and in data analysis techniques that accurately extract quantitative information from images (e.g. machine learning, clustering approaches etc) propagated into 2) a biomedical environment associated with advancing our ways of studying tissue metabolism in cancer, brown fat metabolism and baseline tissue energetics. The scientific project will have a study design and experimental and data-analysis nature, including theoretical aspects in particular in relation to the analysis of optoacoustic measurements and their correlation with PET and ultrasonic measurements. Experiments will be conducted at the laboratory of Prof. Tavitian and data compared with measurements from the laboratories of Prof. Ntziachristos. The activity will solidify interactions and collaboration not only during the tenure of the Chair but longer term.	Postdoc hired November 2019. First phase (physics, Cordeliers) submitted for publication. Second phase (Cochin) in progress.
2	H2020 EU network on CAR T cells : CARAT	Collaboration with Emmanuel Donnadieu	
2	EU IMI consortium : T2EVOLVE : on genetically engineered T cells	Collaboration with Emmanuel Donnadieu	
2	A. Gessaint, Institut Pasteur and J. Ghysdael, Institut Curie	Collaboration on therapeutic potential of inducing T lymphoid cancer cell death via TCR activation as a follow-up from the Thesis work of A. Touzart	Started in 2019

2	C. PLASS, DKZF, Heidelberg, DE	Collaboration on T-ALL epigenetic signatures as a follow-up from the Thesis work of A. Touzart (Post-Doc fellow DKZF 2018-20)	Manuscript under revision in Science Translational Medicine.
2	Prof. Kimberley Steigmeier (Dana Farber Cancer Institute, Boston, USA)	Collaboration with Jerome Tamburini (team Fontenay/Bouscary). Validation of MARCH5 as a therapeutic target in AML using multi-omics approaches including RNAseq, proteomics and massive pharmacological screens.	Manuscript in preparation
2	Elli Papaemmanuil (Memorial Sloan Kettering, New-York, USA)	International Working Group – Molecular prognosis of myelodysplastic syndromes	Publication in Nature Medicine, 2020
2	H2020 EU MDS-RIGHT consortium- J Janssen ; Nijmegen (The Netherlands), M Dugas, Muenster University (Germany)	Management guidelines of myelodysplastic syndromes Multi-omics approaches to assess disease heterogeneity and prognosis	https://mds-europe.eu/ Manuscript in preparation
2	Sharham Kordasti (Guy's Hospital, London, and Systems Cancer Immunology Laboratory, King's College London, United Kingdom)	ImmunoCluster: A computational tool to explore the immune profile and cellular heterogeneity of hematological diseases using liquid and imaging mass, and flow cytometry data	Manuscript submitted
2	Tomas Ganz, Ella Nemeth, UCLA, Leon Kautz, IRSD, Toulouse	Identification of a variant protein translated from a a variant transcript in SF3B1-mutated myelodysplastic syndromes	Publication in Science Translational Medicine, 2019
2	SIRIC CURAMUS, Dassault Systems, BioSerenity (a French startup that provides diagnostic and patient monitoring solutions, ranging from data capture via connected medical devices to data analysis via artificial intelligence tools for automatic identification of digital biomarkers and healthcare professionals) and Owkin (a French-American startup that uses AI and machine learning to augment medical and biology research) and 2 national collaborative groups in digestive cancer research FFCD and GERCOR	Collaboration of the SIRIC CARPEM: PreciCompanion. It will support personalized medical decisions during follow-up of resected colon cancer patients based on precise survival risk estimation over-time. Specifically, the companion will compute the risk of relapse for a specific patient based on multiple markers proven for their high prognostication value.	
1&2	Mayo Clinic	In November 2018, the 1st symposium was held in Paris . It consisted of one day of public scientific presentations and half a day of closed-door work. The alternation of the annual holding of the Paris vs USA symposium was agreed. The structuring of the partnership for the training of researchers is in progress.	A first version of the partnership was submitted in 2018 by the Paris Descartes Faculty of Medicine at the end of 2018.
1&2	Frank Sinicrope, Mayo Clinic, USA	Collaboration with Jérôme Galon. Validation of Immunoscore to predict survival in colon cancer	
1&2	Céline Mascaux, Hôpitaux Universitaires de Strasbourg (CHRU Strasbourg), France	Collaboration with Jérôme Galon. Giving access to 122 carefully annotated biopsies from 77 patients—of 9 morphological stages of the carcinogenesis of lung squamous cell carcinoma (stages 0–8)	
1&2	Marc Van den Eynde, Université catholique de Louvain, Belgium	Collaboration with Jérôme Galon. Inclusion of patients in Immunoscore validation studies.	
1&2	Davide Bedognetti: Sidra Medicine, Doha, Qatar	Collaboration with Jérôme Galon. Sequencing of a DNA library with 150bp paired-end reads.	
1&2	Francesco Marincola, Refuge Biotechnologies Inc., USA	Collaboration with Jérôme Galon and Refuge Biotechnologies, a company aiming to create cell therapies that sense their surroundings and conditionally activate or repress multiple genes simultaneously – resulting in more potent and targeted treatments beyond a single target and function.	

6. Technology transfer

List of technology transfer actions (patent, licensing, spin off, etc) which have been possible thanks to the direct support of the 2018 SIRIC designation.

IRP* number	Title of the action	Type of action (patent, licensing, spin off, etc)	Date	Inventor(s)
2	EP20305730?2 Methods for predicting the risk of recurrence and/or death of patients suffering from a solid cancer after preoperative adjuvant therapy and radical surgery (Numéro de dépôt : EP20305730.2)	Patent	2020	Pages
2	EP20305729.4 Methods for predicting the disease-free survival of patients suffering from a solid cancer after preoperative adjuvant therapies	Patent	2020	Pages
2	PCT/EP2020/065099 : Detection of hypermethylated genes for diagnosing pancreatic cancer	Patent	2020	Shufang Wang-Renault,, Aziz Zaanan , Pierre Laurent-Puig , Valérie Taly
2	PCT/EP2020/050946 : new variants of erythroferrone and their use	Patent	2020	Michaela Fontenay, Olivier Kosmider, François Guillonneau, Leon kautz, Marc-Henri Stern
2	EP19305811.2: Detection of hypermethylated genes for diagnosing gastric cancer	Patent	2019	Shufang Wang-Renault,, Aziz Zaanan , Pierre Laurent-Puig , Valérie Taly
2	EP19305669.4. : Digital biomolecules detection and/or quantification using isothermal amplification	Patent	2019	Guillaume Gines , Yannick Rondelez,, Roberta Lima de Castro , Valérie Taly
2	PCT/EP2019073357 : ZP3 fragments in immunotherapy of ovarian cancer	Patent	2019	Anson M, Duval C, Resche-Rigon M, Tartour E
2	In vitro method for the prognosis of progression of a cancer and of the outcome in a patient and means for performing said method	Patent	2019	J Galon, B Mlenick, G Bindea
2	WO2019/043138: method for the prognosis of survival time of a patient suffering from a solid cancer	Patent	2019	M-C Dieu-Nosjean, WH Fridman, R Remark, C Sautes-Fridman
2	Methods for predicting metastatic potential in patients suffering from SDHB-mutated paraganglioma	Patent	2018	Gimenez-Roqueplo AP; Castro-Vega LJ; Favier J; De Reynies A
2	EP3261673 A1 : Combined vaccination/radiotherapy for cancer treatment	Patent	2018	Johannes L, Deutsch E, Tartour E, Mondini M, Perfettini JL, Tran T
2	EP3400443 A1 : Methods and pharmaceutical compositions for predicting and treating a subject suffering from renal cell carcinoma	Patent	2018	Darlane C, Granier C, Gey A, Tartour E
2	TIM-3 FOR ASSESSING THE SEVERITY OF CANCER	Patent	2018	J Galon, B Mlenick, G Bindea

7. List of dissemination actions towards professionals

List of dissemination actions and communication events towards professionals which have been organised by the SIRIC since the beginning of the 2018 SIRIC designation.

IRP* number	Title of the action	Type of action (conference, training, workshop, video, etc)	Date	Partner(s) involved, if relevant
2	Oncomolpath 9ème édition	Conference	01/12/2019	AP-HP
1 & 2	7ème journée de pharmacologie des anti-tumoraux	Conference	01/11/2019	AP-HP
2	3 rd Gilles Thomas Symposium	Symposium	01/10/2019	CRCL, Centre Léon Bérard, SIRIC Lyrican
3	Ethique des pratiques en santé : quelles places pour les Sciences Humaines et Sociales dans l'enseignement, la recherche et les soins ?	Conference	01/10/2019	Université de Paris
1	15 th annual meeting Geocancer	Conference	01/10/2019	Cancéropole Ile-de-France
2	TLS in the Era of Cancer Therapies symposium	Symposium	01/09/2019	Bristol-Myers Squibb, Programme HTE
3	Démocratie sanitaire en recherche	Colloque	20/06/2019	Cancéropole Ile-de-France, SIRIC Curamus, SIRIC Curie, SIRIC Socrate 2.0
1	1 st Mayo-clinic symposium	Symposium	01/11/2018	Université de Paris
2	Institut 3IA PRAIRIE : Laure Fournier Chair in medical imaging	Training	2020	Université de Paris
1, 2 & 3	Plateforme de ressource biologique	Plaquette	2018	Ligue contre le cancer
2	13e COLLOQUE ANNUEL DU CANCEROPOLE : CANCERS RARES	Colloque	2018	Cancéropole Ile-de-France
3	GrOupe inter-SIRIC sur le paRtage et l'Intégration des données clinico-biologiques en cancérologie : OSIRIS	Network	2011	SIRICs: Marseille ; ONCO LILLE C2RC ; SOCRATE ; MONTPELLIER ; BRIO ; SIRIC-Curie ; Lyric
1	Romain Donne : Metabolism and cancer: signaling pathways in NASH and HCC	Young scientist seminary	11/01/2019	Centre de Recherche des Cordeliers
1	MAXIME WACK : A bioinformatics approach to determine HPV insertion loci in the human genome . E.Pramil : CD47 peptide targeting : a promising approach against refractory chronic lymphocytic leukemia	Young scientist seminary	22/02/2019	Centre de Recherche des Cordeliers
1	ABHISHEK D. GARG : Necroptosis in immunology and cancer	EATI seminary	19/04/2019	EATI
1	Marie Daugan : Tumor cells hijack macrophage produced complement C1q to promote tumor growth	Young scientist seminary	03/05/2019	Centre de Recherche des Cordeliers
1	CEDRIC COULOUARN : Characterization of TFOX, a novel effector of TGFβ-associated EMT in hepatocellular carcinoma	Invited Scientist	24/05/2019	Centre de Recherche des Cordeliers
1	LYDIA LYNCH : Interdependence of Systemic and Cellular Immunometabolism	Invited Scientist	06/06/2019	Centre de Recherche des Cordeliers

1	DROR MEVORACH : Clearance and Therapeutic Applications of Apoptotic Cells	Invited Scientist	07/06/2019	Centre de Recherche des Cordeliers
1	PHILIPPE GUAL : New players of the NAFLD progression	Invited Scientist	28/06/2019	Centre de Recherche des Cordeliers
1	ROBIN LOESCH : CRISPR for in vivo gene editing of the WNT/ β -catenin activation in mouse	Technical seminary	06/09/2019	Centre de Recherche des Cordeliers
1	Luca Valenti : From genetic studies to personalised medicine in the management of fatty liver disease	Invited Scientist	06/09/2019	Centre de Recherche des Cordeliers
1	MATHIAS HEIKENWALDER : On the role of immune cells in metabolic reprogramming in fatty liver disease – provoking NASH and liver cancer	Invited Scientist	13/09/2019	Centre de Recherche des Cordeliers
1	Claire MAGNON : How the central and peripheral nervous systems regulate cancer development?	Invited Scientist	27/09/2019	Centre de Recherche des Cordeliers
1	José Manuel Bravo San pedro : Acyl CoA-binding protein, a lipogenic factor that triggers food intake and obesity	Young scientist seminary	04/10/2019	Centre de Recherche des Cordeliers
1	Ronald P. Taylor : The mechanism of antibody-induced complement-mediated killing of tumor cell	Invited Scientist	07/10/2019	Centre de Recherche des Cordeliers
1	MATIAS AVILA : Novel epigenetic strategies for experimental liver cancer treatment	Invited Scientist	25/10/2019	Centre de Recherche des Cordeliers
1	Alain Fischer : "When inherited mutations of immune genes predispose to cancer"	EATI seminary	15/11/2019	EATI
1	Thomas Gajewski : "Mechanisms of cancer immunotherapy response versus resistance"	EATI seminary	15/11/2019	EATI
1	Sandrine PHAM : Lect2, a new hepatokine regulating cholesterol metabolism and inflammatory response during NAFLD	Young scientist seminary	29/11/2019	Centre de Recherche des Cordeliers
1	Camille Peneau : Oncogenic consequences of Hepatitis B Virus integration in liver tissues	Young scientist seminary	14/02/2020	Centre de Recherche des Cordeliers
1	Naresh Rambabu : Regulation of immune cell metabolism by therapeutic normal IgG intravenous immunoglobulin (IVIG)	Young scientist seminary	28/02/2020	Centre de Recherche des Cordeliers
1 & 2	Journée scientifique du CRC	Symposium	14/06/2019	Centre de Recherche des Cordeliers
2	ERIC TARTOUR : Microenvironnement heterogeneity in cancer	EATI seminary	18/01/2019	EATI
2	NICOLAS GIRALDO : Tumor immunoprofiling : Novel tissue-based biomarkers in precision oncology	Invited Scientist	08/02/2019	Centre de Recherche des Cordeliers
2	SALEM CHOUAIB : Hypoxia as another check point during the anti-tumor response	EATI seminary	15/02/2019	EATI
2	ANGELA VASATURO : High Performance Tissue Multiplexing	Young scientist seminary	08/03/2019	Centre de Recherche des Cordeliers
2	IntegraGen : Development of new tools for sequencing analysis of heterogeneity in tumors	Technical seminary	12/04/2019	Centre de Recherche des Cordeliers
2	ELIANE PIAGGIO : Unraveling human tumor-Treg heterogeneity by single-cell coupled TCR/transcriptome RNAseq analysis	EATI seminary	17/05/2019	EATI

2	MAHA AYYOUB : Exhausted tumor-specific tissue-resident memory like CD8 T cells and clinical response to immune checkpoint blockade in epithelial malignancies	EATI seminary	21/06/2019	EATI
2	Jordan Dimitrov : Generation of human monoclonal antibodies by cloning immunoglobulin genes from single B cells	Technical seminary	08/11/2019	Centre de Recherche des Cordeliers
2	Christophe Klein : Intelligence artificielle en histologie et histopathologie	Technical seminary	22/11/2019	Centre de Recherche des Cordeliers
2	Ruben Pio : The role of the complement system in cancer progression	Invited Scientist	25/11/2019	Centre de Recherche des Cordeliers
2	Sarah Levesque : "Open access FlowSOM-based toolbox for efficient, exhaustive and semi-supervised phenotyping of immune cell populations »	Technical seminary	13/12/2019	Centre de Recherche des Cordeliers
2	Alison Hargreaves : cell classification, biomarker discovery, combining multi-omics data	Technical seminary	07/02/2020	Centre de Recherche des Cordeliers
2	Vassili Soumelis : Immune intercellular communication : tumor microenvironment and beyond	EATI seminary	21/02/2020	EATI

8. List of dissemination actions towards public

List of dissemination actions and communication events towards patients and general public which have been organised by the SIRIC since the beginning of the 2018 SIRIC designation.

IRP* number	Title of the action	Type of action (conference, workshop, video, etc)	Date	Partner(s) involved, if relevant
1, 2 et 3	IA et médecine personnalisée	Vidéo	2020	
1, 2 et 3	IA et éthique	Vidéo	2020	
3	Consentement dynamique	Vidéo	2020	
3	Projet de recherche NutriNet-Santé CARPEM Lynch	Affiche	2019	
3	Projet de recherche NutriNet-Santé CARPEM Lynch	Dépliant	2019	
1, 2 et 3	Nous sommes tous acteurs de la recherche contre le cancer	Vidéo	2018	
1, 2 et 3	Nous sommes tous acteurs de la recherche contre le cancer	Affiche	2018	
1, 2 et 3	Nous sommes tous acteurs de la recherche contre le cancer	Plaquette	2018	
1	Immunosurveillance of breast cancer http://carpem.fr/immunosurveillance-du-cancer-du-sein/	Vidéo	2019	Association Ruban Rose
1	Avancées dans les traitements anticancéreux in Le Journal de la Santé on french TV http://carpem.fr/avancees-dans-les-traitements-anticancereux/	Vidéo	2018	Journal de la santé

9. Budget

Fill in the Excel sheet template (annexes 9.1, 9.2 and 9.3)

ANNEXE 9-3

DETAILED GLOBAL SIRIC BUDGET

Expenses details	EXPENSES (€)				Allocation details
	2018	2019	june 2020	Total	
MANAGEMENT AND GOVERNANCE	94 211 €	131 528 €	101 564 €	327 303 €	Management staff, management fees, meetings organisation, trip funding, ...
Staff	85 717 €	127 749 €	79 620 €	293 086 €	
Operating costs	8 494 €	3 779 €	21 944 €	34 216 €	
Equipment				0 €	
DISSEMINATION OF KNOWLEDGE AND GOOD PRACTICES	27 477 €	42 072 €	4 752 €	74 301 €	Dissemination programs towards professionals (training, dissemination of information on new knowledge), and interactions with patients and general public (meetings, workshops,...)
Staff				0 €	
Operating costs	11 793 €	16 473 €		28 266 €	
Equipment	15 684 €	25 599 €	4 752 €	46 035 €	
INFRASTRUCTURES AND PLATFORMS	139 174 €	198 912 €	176 384 €	514 470 €	Organisation and layout of biological and technological resources in terms of operating costs, equipment and staff
Staff	137 685 €	196 309 €	107 654 €	441 648 €	
Operating costs		2 603 €	23 313 €	25 916 €	
Equipment	1 489 €		45 417 €	46 906 €	
INTEGRATED RESEARCH PROGRAM 1 <i>specify title</i>	0 €	57 207 €	77 872 €	135 080 €	
Staff		18 067 €	76 892 €	94 959 €	
Operating costs	0 €	39 140 €	980 €	40 120 €	Necessary expenses for the organisation and animation of the program
<i>Implementation of the projects</i>				0 €	Emergence of new projects and new teams
<i>Actions supporting emergence and training</i>		39 140 €	980 €	40 120 €	National and international academic or industrial partnerships (collaborations, exchanges, mobility, company-researcher meetings, ...)
<i>Partnerships and collaborations</i>				0 €	Others if relevant
Equipment				0 €	
...					
INTEGRATED RESEARCH PROGRAM 2 <i>specify title</i>	122 716 €	326 879 €	177 200 €	626 795 €	
Staff	116 275 €	249 446 €	159 932 €	525 653 €	
Operating costs	6 441 €	77 433 €	17 268 €	101 142 €	
<i>Implementation of the projects</i>				0 €	
<i>Actions supporting emergence and training</i>	6 441 €	77 433 €	17 268 €	101 142 €	
<i>Partnerships and collaborations</i>				0 €	
Equipment				0 €	
...					
INTEGRATED RESEARCH PROGRAM 3 <i>specify title</i>	17 043 €	118 471 €	69 332 €	204 846 €	
Staff	16 292 €	117 070 €	66 897 €	200 259 €	
Operating costs	751 €	1 401 €	2 435 €	4 587 €	
<i>Implementation of the projects</i>	751 €	1 401 €	2 435 €	4 587 €	
<i>Actions supporting emergence and training</i>				0 €	
<i>Partnerships and collaborations</i>				0 €	
Equipment				0 €	
...				0 €	
OTHER WP OR TRANSVERSAL ACTION : <i>specify title</i>	0 €	0 €	0 €	0 €	
Staff					
Operating costs					
<i>Implementation of the projects</i>					
<i>Actions supporting emergence and training</i>					
<i>Partnerships and collaborations</i>					
Equipment					
...					
TOTAL	400 620 €	875 070 €	607 104 €	1 882 794 €	

EVALUATION CRITERIA

The SIRIC designation aims to offer new opportunities for conducting translational cancer research, thus helps optimising, accelerating and disseminating the production of new knowledge and its application to cancer care. The SIRIC programme should increase the link between the different dimensions of research (basic, clinical, public health, epidemiology, and human and social sciences), by concentrating a critical mass of experts (physicians, researchers, engineers, healthcare workers and patients).

The role of a SIRIC is to make big improvements in the quality of research organisation, knowledge production, transfer of innovation into practice and care organisation, and new outcomes dissemination to all potential beneficiaries.

The mid-term report will be evaluated by the scientific evaluation committee based on the following criteria:

1. SIRIC governance and management structure with executive and scientific committees
2. Establishment of shared resource facilities to support the SIRIC integrated research programmes: platforms, databases and teams with specific expertise (methodology, biostatistics, bioinformatics, regulatory and ethical procedures, etc). Establishment or development of high-quality biobanks with linkage to clinical and follow-up data
3. Commitment to support the emergence of research projects (e.g. pump-priming grants)
4. Commitment to a programme of training in translational and integrated research
5. Progress of the SIRIC multidisciplinary integrated programmes
6. Availability of a sufficient patient population or rate of patient recruitment to support bench to bedside studies in all the integrated research programmes
7. Effective integration between basic and applied scientists (e.g. clinicians, population scientists)
8. Commitment to develop and integrate human and social sciences, epidemiology and public health studies
9. Involvement of patient advocates
10. National and international synergistic collaborations as well as public-private partnerships
11. Dissemination of new knowledge and good practices resulting from the research toward professionals and patients, incitation in technology transfer for economic development
12. Ability to leverage funding and/or resources obtained as a result of an “excellent” designation
13. Global vision of the SIRIC, scientific directions, goals and perspectives for the 2nd designation period