Institut Curie’s key progress for the future of oncology

Researchers and physicians from Institut Curie are once again distinguishing themselves for the 2022 edition of the meeting of the American Association for Cancer Research (AACR), from April 8 to 13 in New Orleans, USA. They are presenting very encouraging and ground-breaking work and results in the fight against cancer, including changes of practice in the treatment of lung cancer, new therapeutic options in triple negative breast cancer, new hormone therapy in breast cancer, discoveries and applications in immuno-oncology, bio-informatic analyses and the study of the effect of comedications in breast cancer...

- **Lung cancer**: a new treatment combining immunotherapy and chemotherapy, already approved in the USA
- **Hormone-dependent breast cancer**: working towards a new hormone therapy targeting the progesterone receptors
- **Triple-negative breast cancer**: a new drug candidate molecule and the search for molecular signatures predictive of the effectiveness of chemotherapy
- **Immu-no-oncology**: a new bio-medication to deflect the anti-viral response against tumors, work to understand the role of dendritic cells and of the tumor micro-environment in responses to immunotherapy, and the analysis of biomarkers in primary tumors and metastases
- **Targeted therapies**: promising progress in ENT cancers and Ewing sarcoma, precision medicine in pediatric cancers
- **Big data and bioinformatics**: real-world oncology data and effect of comedications in breast cancer

“For this new AACR meeting, the quality of the work presented by Institut Curie is testament to the excellence of the research conducted by the research teams. This key meeting of the international scientific community creates emulation which will, without a doubt, boost or expand productive collaborations with our teams, to further worldwide research in oncology”, enthuses Prof. Alain Puisieux, Director of the Institut Curie Research Center.

Prof. Steven Le Gouill, Director of the Institut Curie Hospital Group, adds: “New drug candidates, treatment combinations, unique therapeutic strategies... the results presented by Institut Curie’s physicians and researchers are extremely promising. They are proof of the incredible acceleration of oncological research and the development of innovations that I am convinced will benefit patients”.
**Lung cancer: a new treatment combining immunotherapies and chemotherapy**

The leading cause of cancer death worldwide, lung cancer is responsible for around 1.8 million deaths a year. Among the two main types of lung cancer, non-small cell lung cancer (NSCLC) accounts for up to 84% of diagnoses, the majority of which (around 60%) are non-metastatic. The search for therapeutic options with neoadjuvant or adjuvant treatments is thus vital for improving the long-term treatment of these patients.

Coordinated since 2017 by teams from the Curie-Montsouris Chest Center, the results of the international phase-3 study CheckMate-816 reveal the effectiveness of administering a neoadjuvant treatment combining immunotherapies with chemotherapy in patients suffering from non-metastatic NSCLC. This treatment has just been approved by the FDA in the USA. **Prof. Nicolas Girard, oncologist and pulmonologist at the head of the Curie-Montsouris Chest Center, will present the results of this study at a plenary session of the AACR meeting.**

**Towards a new hormone therapy in breast cancer?**

Around 80% of all breast cancers are hormone-dependent (or hormone-sensitive) and are characterized by the presence or absence of estrogen and/or progesterone receptors on the surface of the cancer cells. Although hormone therapy treatments target the estrogen receptors, there is currently no approved medication that targets the progesterone receptors. **Elisabetta Marangoni, researcher in the translational research department at Institut Curie**, will give an oral presentation on the results of a study to test the effectiveness of an antagonist of the progesterone receptor, on preclinical models, administered alone or in combination with treatments (an antagonist of the estrogen receptor, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor or phosphoinositide 3-kinase (pi3k) inhibitor) on bone metastasis of breast cancer. **“We show that alone, our molecule targeting progesterone is not effective, but that when used in combination with the estrogen receptor antagonist and the CDK4/6 inhibitor, we find significant anti-tumor activity. These encouraging results offer us hope of a new therapeutic option for women with metastatic breast cancer with positive estrogen and progesterone receptors”, said Elisabetta Marangoni.**

**In the spotlight!** In 2020, work conducted by Fatima Mechta-Grigoriou, Assistant Director of the Cancer, Heterogeneity, Instability and Plasticity unit (Institut Curie, Inserm) was published in Cancer Discovery. This article is now among the most-cited articles in the 2022 Best of the AACR Journals collection, and will be presented to the AACR at a reception on April 9, 2022.

For more information: Resistance to immunotherapy: a brand new cellular type involved in the tumor microenvironment
**Triple negative breast cancer: a drug candidate and new molecular signatures**

Identifying new therapeutic strategies in patients with triple-negative breast cancer is a priority in oncology. Triple-negative breast cancer affects between 10 and 15% of breast cancer patients, and is more aggressive with higher risk of metastasis. At Institut Curie, many teams are focusing on research and customized medicine in this field.

**A new candidate molecule identified**

The team led by Thierry Dubois, head of the “Biology of Breast Cancer” group in Institut Curie’s (Translational Research department and Cell Biology and Cancer unit (Institut Curie, CNRS)), has just shown that a protein: PRMT1 (for Protein Arginine Methyltransferase 1) is highly expressed in breast cancers, including in triple negative breast cancer tumors. The researchers show that this PRMT1 protein stimulates oncogenic signaling pathways in triple negative breast cancers. Currently being evaluated in a phase-1 clinical trial, an anti-PRMT1 inhibitor prevents the cancerous cells from spreading *in vitro* and delays tumor growth. "We have also shown that the combination of this anti-PRMT1 inhibitor with certain chemotherapies used in a clinical setting to treat triple negative breast cancer patients has a beneficial proliferation effect on triple negative breast cancer cells. These results therefore provide us with promising insights for a new therapeutic strategy combining an anti-PRMT1 inhibitor with chemotherapy," announces Thierry Dubois.

**Signatures predictive of the effectiveness of chemotherapy: understanding the role of long non-coding RNA**

In hormone dependent breast cancers, “molecular signatures” (characteristic of RNA molecules of a given tumor), help us identify patients requiring chemotherapy in addition to surgery to prevent metastasis from occurring. In triple negative breast cancer, these molecular signatures do not work and almost all patients receive the same chemotherapy to reduce the tumor volume before surgical removal. Although this first chemotherapy increases the chances of recovery when it is effective, it reduces these chances when it is ineffective. The failure of these “classic” prediction signatures in triple negative breast cancer may be attributed to their incomplete nature, not taking into account the “long non-coding” RNAs (IncRNAs) which represent over 90% of the different RNA varieties of a cell and may play major roles in the functioning of the cell, and in the development or aggressiveness of cancers. “Using new analysis methods we succeeded in identifying over a hundred non-referenced IncRNAs deregulated in triple negative breast cancer patients resistant to chemotherapy, detectable even before administration of chemotherapy. These potential predictors of resistance to treatment could help us improve the customization of treatments from the very beginning of the course of care. We are now seeking to understand how they work, by ourselves disrupting the rates of triple negative breast cancer IncRNAs treated by chemotherapy in vitro and studying the results,” declares Nouritza Torossian, physician and PhD student in Antonin Morillon’s team, in the Dynamics of Genetic Information: fundamental bases and cancer unit (Institut Curie, CNRS).
**Immuno-oncology: adopting new strategies, discovering new medications and predicting the effectiveness of treatments**

Immunotherapy has revolutionized the way cancer patients are treated, but it is not yet effective in the majority of cases: responses remain very variable according to locations and types of tumor. It is thus vital to identify new biomarkers, new targets, and to understand how immune responses work.

**A new bio-medication to deflect the anti-viral response against tumors**

In collaboration with the biotech Stimunity, Bakhos Jneid, a researcher from Nicolas Manel’s team in the Immunity and Cancer unit (Institut Curie, Inserm) has just shown that subcutaneous administration of a non-infectious (inoffensive) virus-like particle - cGAMP-VLP - can be used, according to a preclinical study, to target the STING pathway (an innate immune system activation pathway). Bakhos Jneid describes the results achieved: “we managed to understand the events leading in our study to the complete and durable eradication of tumors. These results show that targeting the STING pathway improves the anti-tumor response of T-cells and reveals a therapeutic strategy with modulators of these immune cells, which may address the current limits of STING-based approaches in patients.”

**Cellular selectivity of STING stimulation determines priming of anti-tumor T cell Responses > Poster, April 13, 2022 (9:00 am - 12:30 pm US Central time)**

**Acting on the dendritic cells to gain a better understanding of immunotherapy**

Dendritic cells are key cells of our immune system. Often described as the sentinels of the body, they patrol the body to track down potential dangers then alert the other cells of the immune system and push them to action. They will thus “mature” and activate the T-cells capable of destroying tumors. The team of Dr. Caroline Hoffmann, physician in the ENT department at Institut Curie and researcher in the Immunity and Cancer unit (Institut Curie, Inserm) used a large in vitro database to study the types of maturation of dendritic cells. Researchers identified two archetypes of dendritic cells: one of them “Secretory” and the other “Assisting”. Then, they analyzed the dendritic cells from different human cancers and discovered that the dendritic cells had only a “Secretory” maturation. “This helps us better understand the dendritic cells of tumors, and learn how to use them to increase the response to immunotherapy, in particular by choosing the right treatment combinations,” explains Dr. Caroline Hoffmann.

**PD-L1 high ICOSL low Secretory dendritic cells infiltrate human solid tumors > Poster, April 11, 2022 (1:30 pm - 5:00 pm US Central time)**

**Examining the expression of PD-L1 and TILs (Tumor infiltrating lymphocytes)**

Today, the expression of PDL-1 - the most frequently used immunotherapy target - is a validated biomarker in some cancers, such as metastatic breast cancer or ENT cancer, but it remains imperfect. Another parameter, the presence of tumor infiltrating lymphocytes (TILs), is a prognostic biomarker for triple negative breast cancers, which may one day help offer de-escalation treatment in certain forms of breast cancer. To date, although expression of PD-L1 is evaluated on available samples, whether the primary tumor or the recurrence, it is still difficult to say which is the most relevant sample to use. The scientific coordination unit of Institut Curie’s Clinical trials department (D3i), in collaboration with Dr. Anne Vincent-Salomon, head of the Diagnostic and Theranostic Medicine division at Institut Curie, shows that “using the analysis of samples from patients included in the SHIVA01 clinical trial, we have shown that there was no difference in PD-L1 expression between the primary tumor and the metastasis, which is reassuring. However, the density of TILs is lower in metastases than in primary tumors, which certainly partly explains the lesser effectiveness of treatments in a situation of recurrence rather than at initial presentation.”

**Pancancer evaluation of Tumor Infiltrating Lymphocytes (TILs) and PD-L1 in SHIVA-01 trial patients with different biopsy sites and histological types > Poster, April 11, 2022 (1:30 pm - 5:00 pm US Central time)**
Uveal melanoma: understanding the role of the tumor micro-environment

With 500 to 600 new cases each year in France, uveal melanoma is the most common eye cancer in adults. A leading national and European center for treatment of this disease, Institut Curie is recognized at the worldwide level for its expertise in this cancer. In this field, Dr Sophie Piperno-Neumann, medical oncologist at Institut Curie, participated in a large international phase-3 study that demonstrated the effectiveness of a brand new immunotherapy molecule (tebentafusp) on the overall survival of patients with metastatic uveal melanoma. New results were obtained from the study of the tumor micro-environment in the biopsies of the patients in the study. The aim of this study was to understand how patients respond (or not) to tebentafusp.

“The results of our work in immuno-histochemistry reveal the important of the tumor micro-environment in the response to the medication. The ratio between two immune cell types, CD163/CD3, namely immune response inhibiting M2 macrophages and tumor cell killing T cells, correlated significantly with survival in patients treated with tebentafusp; this was not the case for patients in the group receiving another treatment, including a checkpoint inhibitor,” explains Dr. Sophie Piperno-Neumann. “These results are important for understanding the mechanisms of action of this new type of immunotherapy called bispecific; and beyond that, they help us to plan for new treatment combinations for metastatic uveal melanoma.”

LB510: Low baseline macrophage to T cell ratio is predictive of overall survival with tebentafusp in a Phase 3 trial in metastatic uveal melanoma > Poster on April 8, 2022 (12:00pm - 1:00 pm US Central time)

► Promising progress in targeted therapies:

Results of the PREDICTOR trial in ENT cancer

The PREDICTOR trial is a pre-operative randomized trial conducted by Prof. Christophe Le Tourneau, head of the Early Clinical Trials department (D3i) and sponsored by UNICANCER. This study compared the biological effectiveness of afatinib, a pan-HER inhibitor (inhibiting both EGFR and HER2 tyrosine kinase) in patients with operable ENT cancer. The aim was to identify predictive biomarkers of the response to afatinib, which was possible due to the randomization. Prof. Christophe Le Tourneau, Prof. Ivan Bièche (PMDT), Maud Kamal and Grégoire Marret, oncologist in the D3i, explain: “the results in terms of tumor efficiency of PREDICTOR were presented at the ASCO meeting a few years ago. Today we are showing extensive DNA and RNA sequencing analyses conducted at Institut Curie, suggesting that modifications of B lymphocyte populations are identified as new predictive markers of the response to afatinib.”

Randomized phase II trial of pre-operative afatinib in non-metastatic head and neck squamous cell carcinoma patients: identification of predictive biomarkers of response> April 11, 2022, 9:00 am - 12:30 pm US Central time

New therapeutic strategy in Ewing sarcoma

It is estimated that 50% of cancers are related to deregulation of the signaling pathway known as “PI3K/PDK-1/Akt” in which PDK-1 plays a role in cell survival and oncogenesis. Furthermore, overexpression and activation of the protein known as “Aurora-A kinase” (Aur-A) are linked to oncogenic transformation (mainly by the developed amplification of centrosomes and chromosome instability). The team headed by Dr. Keyvan Rezai, assistant head of the Radio-pharmacology department at Institut Curie, explored the molecular mechanisms, in vitro, of dual inhibition of PDK-1/Aur-A by pyridine-N oxides. Dr. Keyvan Rezai states: “Our results suggest that the pyridine-N oxides are an attractive basis for the design and synthesis of dual target PDK-1/Aur-A molecules, representing a potential new therapeutic strategy, for Ewing sarcoma in particular.”

Development of potent dual PDK1/AurA kinase inhibitors for Ewing sarcoma therapy – April 12, 2022 > 9:00 am - 12:30 pm US Central time
Precision medicine in pediatric cancer

Analyzing all the coding genes for a tumor to find one or more anomalies in tumor genes lets us not only better understand the disease in order to better treat it, but also guide children and adolescents towards new treatment options when they relapse. This has been shown by the MAPPYACTS study, a large European trial conducted in 4 countries, sponsored by Gustave Roussy and coordinated by Dr. Birgit Georg, pediatric oncologist at Gustave Roussy, and Dr. Gudrun Schleiermacher, pediatric oncologist at Institut Curie. The final results of MAPPYACTS provide the basis for access to customized precision medicine for the youngest cancer patients when traditional treatment has failed. Following these highly encouraging results, it will now be possible for pediatric oncologists from SFCE (French Childhood Cancer and Leukemia Society) centers, to prescribe a detailed molecular profile for patients with pediatric cancers for whom treatment has failed, or in certain situations from the time of diagnosis, through the Médecine France Génomique 2025 plan, as part of their care. Note that the MICCHADO study sponsored by Institut Curie and involving Gustave Roussy and the Léon Bérard center allows us to conduct further molecular biology analyses during the treatment and follow-up of young patients, through sequential analyses performed in liquid biopsies, from simple blood samples.

MAPPYACTS: European prospective trial for patients with recurrent malignancies – Main results and next steps – Forum, April 12, 2022, 12:15 am - 12:35 am
+ Press release Gustave Roussy – Institut Curie (March 17 2022): Children and adolescents in cancer relapse: the promise of new therapies through tumor genome sequencing

► Real-life oncology data: a paradigm shift for clinical research

Improved knowledge of the biology of cancers has led cancer types to be divided into smaller groups based on specific molecular alterations, with certain groups so small that they can be said to represent orphan diseases. The development of these medications for these small patient populations cannot be based on the traditional development structure with large randomized trials. One of the ways to move forward is to use real-world clinical and biological databases that give patients’ clinical data as well as biological data. Prof. Christophe Le Tourneau, head of the Early Clinical Trials department (D3i) at Institut Curie and Maud Kamal, scientific manager in the D3i, explain: “these databases include many patients and help us retrace the natural history of small-population cancers and answer some major scientific questions, which will potentially accelerate market approval for new treatments. This is exactly the goal of WAYFIND-R, a global registry whose purpose is to propose ever-more customized therapies.”

WAYFIND-R: Delivering a high-quality real-world data (RWD) global registry of patients diagnosed with a solid tumor and profiled with next generation sequencing (NGS) April 13, 2022, 9:00 am - 12:30 pm
+ poster on April 8 from 12:00 pm to 1:00 pm, online session (clinical research excluding Trials): Conceptualization of core clinic-molecular variables for registries enrolling patients diagnosed with a solid tumor and profiled with next generation sequencing (NGS)
Bioinformatics analyses:

Studying the effect of comedications in breast cancer

Comedications, i.e. medications that are not anti-cancer but taken for co-existing diseases, may influence the effectiveness of treatments and the growth of breast cancer. A retrospective bioinformatics analysis led by Béatriz Grandal-Rejo, a physician and researcher in the Immunity and Cancer unit (Institut Curie, Inserm), helped analyze the effect of comedications on neoadjuvant therapy and relapse in breast cancer, based on data from a cohort of 664 patients from Saint-Louis hospital in Paris. “In this observational analysis, the use of chronic cardiovascular diuretics during neoadjuvant chemotherapy was associated with an improved response rate, unlike with psychoanaleptics (which stimulate mental activity in mental disorders) which are associated with lower response rates and a higher likelihood of relapse. This result prompts us to continue to research the interactions between chemotherapy and nervous system medications” concludes Béatriz Grandal-Rejo.

Impact of comedications on pCR rates and relapse in breast cancer. Analysis of the Saint-Louis observational cohort >
April 12, 2022 (1:30 pm - 5:00 pm US Central time)

Easy access to data from single-cell sequencing

Single-cell sequencing data are very valuable and costly and are systematically made public. However, their analysis is complex and it is difficult to find relevant oncology data sets in all of the literature. Thanks to the European consortium Immucan, involving Institut Curie and a number of academic and industrial players, an atlas of single-cell sequencing data sets for all types of cancers was created and made available to the medical and scientific community. Dr. Caroline Hoffmann, ENT department at Institut Curie and researcher in the Immunity and Cancer unit (Institut Curie, Inserm) explains: “The atlas is uniform, integrated and annotated with the most up-to-date knowledge. Without any knowledge in bioinformatics, anyone can access these complex data and easily observe gene expression in all tumor infiltrating cell types and states. This work will be presented by Jordi Camps (Bayer, Germany).

Meta-analysis of human cancer single cell RNAseq datasets using the fully integrated IMMUCan database >
April 8, 2022, 12:00 pm - 1:00 pm US Central time

About Institut Curie

Institut Curie, France’s leading cancer center, combines an internationally-renowned research center with a cutting-edge hospital group, which treats all types of cancer, including the rarest. Founded in 1909 by Marie Curie, Institut Curie employs 3,700 researchers, physicians, and health professionals across three sites (Paris, Saint-Cloud, and Orsay), all of whom contribute to its three missions of treatment, teaching, and research. A private foundation with public utility status, Institut Curie is authorized to accept donations and bequests, and thanks to the support of its donors, is able to accelerate discoveries and improve patient treatment and quality of life. Find out more at curie.fr

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