Press release

January 24, 2024

World Cancer Day

Rare cancers: Institut Curie expertise leads to major breakthroughs in research and care

Sarcomas, uveal melanoma, rare hematological cancers: Institut Curie is one of the expert centers recognized at national, European and international level for the treatment of rare cancers. These specific tumors, with their variable prognosis, affect adults and children alike, and pose problems in terms of diagnosis and treatment. Highly specific treatments, tailored care pathways, innovative therapeutic strategies... Institut Curie teams are involved in promising research projects to improve patient survival and quality of life.

"*Rare cancers are cancers with an incidence of less than 6 per 100,000. They are also pathologies that require highly specialized care - because of their particular location, their complexity or their occurrence in a specific context. Today, too many patients suffering from these rare cancers suffer from misdiagnosis, inappropriate or even harmful treatments, and are left to fend for themselves,*" explains **Prof. Thierry Philip, Chairman of Institut Curie's Executive board.**

These rare cancers are complex and can occur anywhere in the body. They encompass many different types of cancer. The list of rare cancers is long, and ultimately concerns a significant proportion of cases. Dealing with the problem of rare cancers is a major challenge for oncology, which explains why special attention is paid to finding solutions and providing the best possible support for patients and their families. "*A better understanding of how these rare pathologies arise, from a genetic, molecular and biological point of view, enables Institut Curie researchers to grasp the phenomena involved and, above all, to develop new diagnostic and therapeutic approaches, thanks to cutting-edge technologies and, above all, to the work carried out jointly with medical teams. We need to invest, because academic and public research is even more important in the field of rare diseases,*" asserts **Prof. Alain Puisieux, director of Institut Curie' Research Center**.

"Rare cancer" networks and structured care paths

In France, national reference networks (structured around reference centers) and expert centers have been set up to optimize care for patients with rare cancers. **Réseau Mélachonat for uveal melanoma, LOC for oculocerebral lymphoma, NetSarc+ for sarcoma...**Institut Curie leads and actively participates in a number of these networks.

Thanks to this organization, every patient has access to medical expertise by joining integrated, specialized care pathways from the outset of their care (verified diagnosis with re-reading of tumor samples, collegial discussions of each medical file). At Institut Curie, for example, **CUSTOM (CUrie *Sarcomes et Tumeurs complexes des Os et tissus Mous*) provides a personalized diagnostic pathway that has been in place for over 5 years for patients presenting with a suspected sarcoma lesion** (from imaging to anatomopathological and molecular biology analyses, right through to the therapeutic decision at the "sarcoma" multidisciplinary consultation meeting).

Other key elements of these networks include training for healthcare professionals, relations with national patient associations and communication with the general public.

"*Several Institut Curie teams are involved in the national and European coordination of these rare cancer expertise networks. This ensures that patients have access to the latest therapeutic innovations. What's more, these networks offer shared access to patient databases, which is essential when you consider that one of the major challenges we face is conducting clinical trials, which is complicated by data scarcity*", says **Prof. Steven le Gouill, Director of Institut Curie Hospital Group.**

Highly specialized care and clinical research

"*The added value of expert centers such as Institut Curie is considerable. Studies have shown that, in sarcomas for example, when surgery is carried out in an expert center, patients have a better prognosis. On a day-to-day basis, we follow patients with very rare cancers. And we do our utmost to find therapeutic solutions,*" says **Dr. Sarah Watson, oncologist and researcher at Institut Curie.**

Interventional radiology, molecular characterization, anatomopathology, complex surgery, radiotherapy, clinical trials: Institut Curie teams are constantly exploring and perfecting every facet of the management of rare cancers. For example, concerning sarcomas, complex and heterogeneous tumors that can affect numerous tissues, a recent study showed that a **simple percutaneous biopsy[1] of retroperitoneal sarcomas** (in the abdomen) **carried out prior to any treatment enabled the diagnosis to be clarified in 98% of cases, enabling the therapeutic strategy to be adapted**.

Another example in pediatrics: strategies have progressed considerably in recent years, notably with the development of new targeted therapies. Larotrectinib (a TRK (Tropomyosin kinase) receptor inhibitor) is proving extremely effective in a very specific type of childhood sarcoma (linked to a TRK fusion protein anomaly), considerably changing the prognosis of young patients.

As for Institut Curie hematologists, their expertise has led to major developments, particularly in the treatment of lymphomas (cancers of the lymphatic system). Our work on oculocerebral lymphomas (lymphomas of the brain and/or primary intraocular lymphomas) has enabled us to standardize treatments and test new targeted therapies. In **mantle cell lymphoma**, results have just been published. "*Six years ago, we proved the value of adding immunotherapy to these very rare lymphomas, and changed the standard of treatment. Now, we have shown that the benefits of this treatment persist in three quarters of patients, without relapse, even after the treatment has been stopped*", says **Prof. Steven Le Gouill**, who led the study[2].

Key figures for rare cancers (source InCA)

- **Less than 6 people in 100,000 affected by a rare cancer**
- **17** "national reference networks for rare adult cancers" accredited by INCa
- **4 European reference networks for rare cancers:** *European reference network on rare adult cancers (EURACAN); European reference network on rare hematologic diseases (benign or malignant) (EuroBloodNet); European reference network for paediatric cancer (haemato-oncology) (PaedCan-ERN); European reference network on genetic tumour risk syndromes (ERN GENTURIS)*.
- **4,000 to 5,000 people diagnosed with sarcoma each year in France, around 500** with uveal melanoma.

[1] Percutaneous biopsy: removal of tissue fragments using a needle, through the skin
[2] Long-Term Follow-Up of Rituximab Maintenance in Young Patients With Mantle-Cell Lymphoma Included in the LYMA Trial: Une étude LYSA

Uveal melanoma, the most common malignant tumor of the eye, is another case in point. While this rare cancer can generally be successfully treated when diagnosed at an early stage, more than a third of patients develop metastases, mainly in the liver, which considerably limits therapeutic options and prognosis. However, **research coordinated by Institut Curie, a national expert center, has shown that a new immunotherapy molecule (a bispecific antibody), tebentafusp, considerably improves survival in a specific patient population.**

Excellent research and a state-of-the-art environment

By the end of 2023, Institut Curie researchers and physicians will have embarked on an **ambitious uveal melanoma project. It involves discovering new genetic risk factors to better understand the disease and develop a blood test; identifying new antigens specific to uveal melanoma to develop immunotherapies and therapeutic vaccines; and studying the mechanisms by which healthy melanocytes transform into melanomas.**

"In uveal melanoma, we are working to identify biomarkers in order to assess the efficacy of immunotherapies, find new radiological criteria for treatment efficacy, and explore the treatment process in terms of supportive care (in particular through our Early Together study). Institut Curie's medical-scientific environment is highly conducive to the emergence of new ideas and strategies. Every year, these innovations are presented to patients during an annual day of exchange, which will take place this year on February 2, 2024, just before International Cancer Day," enthuses **Dr. Manuel Rodrigues, oncologist and researcher at Institut Curie**.

Another example of research in progress: researchers and doctors are studying the **role of iron in the proliferation of sarcoma tumour cells.** Indeed, certain molecules developed by the "Chemical Biology" team at Institut Curie appear to be particularly effective in destroying tumor cells of certain sarcoma subtypes. In this context, a multi-disciplinary project involving radiologists at Institut Curie is currently being set up to quantify iron from MRI images and predict disease progression - before launching a clinical trial.

Numerous research projects also rely on **artificial intelligence analyses**. For example, **a current project on follicular lymphoma aims to establish specific disease profiles with response markers to treatment**, thanks to the integration of large clinical, imaging and sequencing datasets collected over the last 20 years (in compliance with current regulations).

Another study supported by Institut Curie focuses on leukemias, other blood cancers linked to the uncontrolled multiplication of immature blood cells in the bone marrow. More specifically, **the teams are working to understand and explain the appearance of a particular type of leukemia (secondary acute myeloid leukemia) that occurs years after another cancer has been treated with chemotherapy.** To achieve this, researchers are using single cell analysis and machine learning algorithms to decipher aspects of cell biology, aiming to develop ways of preventing leukemia.

ZOOM on... cancers of unknown origin. These rare cancers are detected by the presence of metastases, without identifying the first organ affected. This type of cancer accounts for 2 to 3% of all cancer cases (approximately 7,000 patients per year in France) and is particularly challenging to treat. In 2019, Dr. Sarah Watson's team developed **the first effective, reproducible and clinically routine method to help identify the origin of these cancers**. Using next-generation RNAseq sequencing (to sequence all the genes expressed in a tumor), the researchers established a "diagnostic classifier" (TransCUPtomics) based on the expression profiles of over 20,000 tumors and normal tissues. They then succeeded in developing a deep-learning algorithm that learnt to successfully match a given RNA profile to a specific organ or tissue, whether cancerous or not.

Find out more: 3 appendices:

Sarcomas in adults and children: Institut Curie, a national expert center for multidisciplinary care. Sarcomas affect between 4,000 and 5,000 people every year in France. They are rare, extremely complex, heterogeneous tumors that can occur anywhere in the body, in bone tissue (osteosarcoma) or soft tissue (liposarcoma, fibrosarcoma, rhabdomyosarcoma...). Institut Curie is an expert center for the treatment of adult and pediatric sarcomas.

Uveal melanoma: treatment and research to improve patients' quality of life. With 500 new cases every year in France[3], uveal melanoma is the most common malignant tumor of the eye, particularly in people in their sixties with fair skin and eyes. Institut Curie welcomes the majority of French patients, as the national referral center for this still poorly understood cancer

Expertise and promising research in rare hematological cancers. Hematological cancers are numerous, and their great diversity is one of the reasons behind the complexity of therapeutic strategies for these blood disorders. With 16,000 new cases every year, lymphomas, cancers of the lymphatic system, account for almost half of all hematological cancers, with around sixty sub-types. Institut Curie is an expert in these pathologies, recognized for its clinical, translational and more fundamental research.

Press contacts:

Elsa Champion – elsa.champion@curie.fr / 07 64 43 09 28
Juliette Mamelonet - juliette.mamelonet@havas.com / 01 58 47 90 12

About Institut Curie

Institut Curie, France's leading cancer center, combines an internationally-renowned research center with a cutting-edge Hospital Group, treating 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 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, Twitter, Facebook, LinkedIn, Instagram

[3] https://www.medecinesciences.org/en/articles/medsci/full_html/2018/02/medsci20183402p155/medsci20183402p155.html

Sarcomas: collaborative expertise drives major advances in research and care

Sarcomas are rare, complex and heterogeneous mesenchymal cancers. They account for 1% of cancers in adults and less than 10% in children. Overall, there are 4,000 to 5,000 new cases every year in France. Institut Curie is a national center of expertise in sarcoma research and management, and has been a driving force in improving patient survival.

A sarcoma is a rare cancerous tumor that forms at the expense of bone and soft tissue (connective, adipose, muscular, vascular, fibrous...). They can occur anywhere in the body (55% in the limbs, 45% in the central regions of the trunk and abdomen, and 5% in the head and neck), in both children and adults. *"Not only are sarcomas uncommon, but they also include more than a hundred different cancers in adult patients,"* notes **Dr. Sarah Watson, medical oncologist and researcher at Institut Curie.** *"Under these conditions, a non-specialist doctor will find it extremely difficult to make the right diagnosis of such a rare and poorly understood pathology. This is why, as soon as there is a suspicion of sarcoma and before any therapeutic procedure, it is essential to refer patients to a dedicated expert center in theNETSARC+ network, of which Institut Curie is a member, for diagnostic workup and therapeutic management."* **Analysis[4] of NETSARC+ results after 10 years of existence demonstrates the relevance of this recommendation, with an increase in patient survival[5],** as presented at the European Society for Medical Oncology (ESMO) congress in 2022.

The benefits of an expert center such as Institut Curie for multidisciplinary management of sarcoma patients

As one of France's leading sarcoma expert centers, Institut Curie boasts a comprehensive technical platform and offers a dedicated diagnostic pathway (CUSTOM) to support patients presenting with a soft tissue mass of undetermined etiology. This pathway is based on a medical imaging consultation combining clinical examination, analysis of radiological examinations, and biopsy if necessary, leading to anatomopathological and molecular biological analysis. **A recent study[6] by Institut Curie showed that a simple percutaneous biopsy of retroperitoneal tumors prior to any treatment enabled the diagnosis to be clarified in 98% of cases, so that the therapeutic strategy could be adapted** (possible preoperative treatment and surgical modalities). All this information is discussed at the "Sarcoma" multidisciplinary consultation meeting at Institut Curie. **This ensures that the patient receives the right diagnosis, and is already in the right circuit to benefit from an appropriate therapeutic strategy.** When sarcomas require surgery, it is performed by experienced surgeons, bearing in mind that these tumors can measure 30 centimetres and weigh several kilograms. If surgery is poorly performed, the chances of survival without recurrence are reduced. **Institut Curie teams have also shown that surgery in an expert center improves patients' prognosis. Another strength of Institut Curie is that it enables patients to take part in clinical trials, giving them access to the latest therapeutic innovations. What's more, a support team dedicated to the care of patients with advanced sarcomas collaborates with the whole team.**

Pooling Institut Curie expertise to reduce treatment costs

[4] Sylvie Bonvalot et al. *Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study of the French sarcoma group from the NetSarc database*. Ann Surg Oncol 2019 Jul;26(7):2286e93.

[5] *Jean-Yves Blay et al., Improved nationwide survival of sarcoma patients 10 years after establishment of the NETSARC+ reference center network,* Annals of Oncology 33, S1145-S1146, en cours.

[6] Walter Nardi et al., Diagnostic accuracy and safety of percutaneous core needle biopsy of retroperitoneal tumours., Eur J Surg Oncol. 2023 Nov 30;50(1):107298.

As an expert center for sarcoma patients, Institut Curie has coordinated "*a French national clinical and radiological follow-up study of desmoid tumors, which are soft tissue tumors characterized by a proliferation of fibroblastic cells associated with collagen production. These tumors are locally aggressive and invasive*", explains **Prof. Sylvie Bonvalot, a surgical oncologist specializing in soft tissue sarcomas at Institut Curie.** *"In the study, patients underwent MRI scans at 1, 3, 6, 9 and 12 months, then every 6 months for 3 years*[7]*. Only tumors shown to be progressive were treated."* **The study showed that half the tumours stabilized over the months, or even regressed spontaneously. This is beneficial for patients, as it shows that heavy treatment need not be systematic for this condition.**

A collaborative organization conducive to the discovery of new treatments

The expert center's resources also enable us to make available study aids for research: X-rays, biopsies, samples... Highly applied research, with patient consent of course, to track down the origin of sarcomas, better adapt therapeutic strategies and find new treatments. In addition, I**nstitut Curie collaborations are prolific, benefiting research advances.** *"Institut Curie's "Chemical Biology" team led by Dr. Raphaël Rodriguez studies the metabolism of metals and in particular iron in cancer cells,"* emphasizes Dr. Sarah Watson. *"Knowing about his research led me to believe that this pathway could be of potential interest in certain mesenchymal tumors."* A collaboration therefore arose between the two teams **to study iron metabolism in these tumors, demonstrating that iron plays a crucial role in their proliferation. What's more, the molecules developed by the Chemical Biology team appear to be particularly effective in destroying diseased cells.** *"To go even further, a multi-disciplinary project is currently being set up, involving radiologists from Institut Curie as well, to quantify iron from MRI images and predict the evolution of the disease. The idea is then to launch a national clinical trial within the Groupe Sarcome Français ."*

[7] Sylvie Bonvalot et al., *Initial Active Surveillance Strategy for Patients with Peripheral Sporadic Primary Desmoid-Type Fibromatosis: A Multicentric Phase II Observational Trial*, Annals of Surgical Oncology (2023).

Children's sarcomas: impressive recent progress

In addition to adult sarcomas, Institut Curie is also interested in children's sarcomas. *"Whether in terms of research or clinical management, situations vary according to age,"* admits **Dr. Olivier Delattre, pediatrician, Inserm research director and director of Institut Curie's SIREDO oncology center**[8]."*Bone tissue sarcomas appear in adolescence, whereas soft tissue sarcomas are seen in very young children, sometimes infants.* Children are referred to specialized pediatric facilities, such as Necker or Robert Debré hospitals. If sarcoma is suspected, they enter the CUSTOM program at Institut Curie to undergo the necessary tests as quickly as possible. ***"We are fortunate to have a dedicated unit for the molecular analysis of sarcomas, enabling us to make a precise diagnosis,"* enthuses Dr. Olivier Delattre.** *Surgery is not immediate afterwards, unlike in adults. Children undergo chemotherapy first, to reduce the tumor mass as much as possible and thus facilitate the surgical procedure in pediatric hospitals."*

For many years, therapeutic strategies for childhood sarcomas have evolved little. In recent years, however, they have progressed enormously, particularly in the field of targeted treatments. *Let's take the example of TRK-fused childhood sarcomas, which present a very specific molecular anomaly that activates the TRK receptor," explains Dr. Olivier Delattre. The development of a TRK receptor inhibitor (larotrectinib) has produced spectacular results in young patients."*[9] More recently, Dr. Olivier Delattre's team has highlighted the expression of highly specific genes in Ewing's sarcoma and certain other pediatric sarcomas[10]. *"The existence of these genetic mutations opens up the possibility of immunotherapies targeting tumor-specific proteins. We are collaborating with immunologists at the Institut to see whether these proteins represent relevant therapeutic targets for the development of immunotherapies. This breakthrough demonstrates once again the extent to which multidisciplinary collaboration at Institut Curie is a major asset for research", concludes Olivier Delattre.* This project is supported by Inca (*Institut National du Cancer*) and the European Fight Kids Cancer program.

References :

- Sylvie Bonvalot et al., *Initial Active Surveillance Strategy for Patients with Peripheral Sporadic Primary Desmoid-Type Fibromatosis: A Multicentric Phase II Observational Trial*, Annals of Surgical Oncology (2023).
- Walter Nardi et al., *Diagnostic accuracy and safety of percutaneous core needle biopsy of retroperitoneal tumours*, European Journal of Surgical Oncology (2023).
- Julien Vibert et al., ***Oncogenic chimeric transcription factors drive tumor-specific transcription, processing, and translation of silent genomic regions***, *Molecular Cell (2022)*.
- Sylvie Bonvalot et al. *Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study of the French sarcoma group from the NetSarc database*. Ann Surg Oncol, 2019 Jul;26(7):2286e93.

[8] SIREDO "Care, Innovation, Research in pediatric, adolescent and young adult oncology"

[9] Cancers pédiatriques : l'expertise de l'Institut Curie sur le devant de la scène internationale | Institut Curie

[10] Julien Vibert et al., ***Oncogenic chimeric transcription factors drive tumor-specific transcription, processing, and translation of silent genomic regions***, *Molecular Cell (2022).*

Uveal melanoma: treatment and research to improve patients' quality of life

Although rare, uveal melanoma is also the most common malignant tumor of the eye in adults, particularly people in their sixties with fair skin and eyes. With 500 new cases per year in France, it can cause severe visual impairment and sometimes metastasize to the liver. Institut Curie receives most of these patients, acting as a national referral center for this still poorly understood cancer.

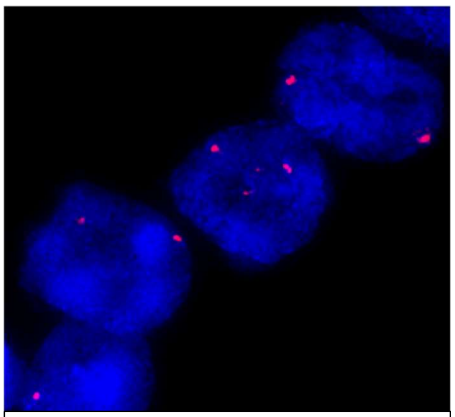
Ocular tumors are not harmless. If detected too late, they can become so large that they require removal of the eye. Institut Curie therefore advocates early diagnosis, to access treatments that preserve vision as far as possible and reduce the risk of relapse. *"To facilitate patient care for patients with uveal melanoma, we have set up the Mélachonat network,"* **explains Prof. Nathalie Cassoux, Deputy Director of the Paris site and Head of the Ocular Oncology Department at Institut Curie**, who coordinates the network. *Our goal is to standardize care across the country, with the support of seven regional centers in Bordeaux, Clermont-Ferrand, Lille, Lyon, Nice, Rennes and Strasbourg, for consultations and patient follow-up."*

A highly efficient organization dedicated to the fight against uveal melanoma

Proton therapy is performed exclusively at Institut Curie in Orsay (which also offers brachytherapy, depending on the position and size of the tumor) or at the Centre Antoine Lacassagne in Nice. The value of the Mélachonat network lies in collegial medical decision-making and the creation of the largest clinical database in Europe, comprising over 9,000 patients. A wealth of information for developing new strategies! The benefits brought to patients have enabled the Mélachonat network to be accredited by the French National Cancer Institute (INCA) in 2019. In addition, a group of doctors and researchers at Institut Curie, led by Dr. Sergio Roman-Roman, is dedicated to translational research into uveal melanoma.

Discovering the causes of uveal melanoma

To properly treat uveal melanoma, we need to know what triggers it. Institut Curie is working on the genetic causes of the disease. A few years ago, the **"DNA Repair and Uveal Melanoma" team led by Dr. Marc-Henri Stern identified the *BAP1* predisposition gene, then the[11] *MBD4* gene[12], by analyzing the genetic background of a thousand uveal melanoma patients.** *"Unlike cutaneous melanomas, uveal melanomas generally accumulate a low number of mutations,"* notes Dr. Manuel Rodrigues, medical oncologist and researcher at Institut Curie. *Yet we have shown that cases linked to the MBD4 gene are associated with high mutation rates, thus rendering the tumor more sensitive to immunotherapies."* This same team, in collaboration with immunologist Dr. Olivier Lantz, has shown that it is possible to **develop immune therapies in a sub-group of these "SF3B1-mutated" uveal melanomas[13].** This work has already led to clinical development of a therapeutic vaccine in collaboration with the French laboratory Transgene. *"All of this*



Eye melanoma cells (in pink: chromosome 3 labelling by in situ hybridization (FISH)). The cells in this image have two chromosomes 3, which is a good prognostic factor.

[11] Samar Alsafadi et al., *Uveal melanoma, a model disease for spicing alterations and oncogenesis*, Med Sci (Paris), 2018, 34 :255-160.

[13] Jérémy Bigot et al., *Splicing Patterns un SF3B1-Mutated Uvel Melanoma Generate Shared Immunogenic Tumor-Specific Neoepitopes*, Cancer Discov (2021).

research is currently being pursued as part of an ambitious project[14]*, in collaboration with the Melanoma Patients Network Europe association and supported by the US Department of Defense."* **The project involves discovering new genetic risk factors, to better understand the disease and develop a blood test; identifying new antigens specific to uveal melanoma, to develop immunotherapies and therapeutic vaccines; and studying the mechanisms by which healthy melanocytes transform into melanomas.**

Research to limit the risk of disease relapse

Indeed, one of the major problems with uveal melanoma after treatment is the **risk of the disease relapsing, with the appearance of metastases in the liver.** *"When there are few metastases, the idea is to remove them surgically or burn them off with radiofrequency,"* states Dr. Manuel Rodrigues. *"Otherwise, we opt for systemic treatment, often with immunotherapies, such as the one based on tebentafusp, a drug that has been routinely available to us for two years following a vast international clinical trial in which Institut Curie played a significant role.*[15]" For the first time, **tebentafusp has been shown to significantly improve the life expectancy of patients with metastatic disease.** However, only patients with the HLA*A02 marker may be sensitive to tebentafusp, and **work is currently underway at the Institute to use circulating tumor DNA in the blood**[16] **to monitor the drug's action** (and perhaps also in the aqueous humor of the eye to aid diagnosis). *"We're confident that we can develop other effective immunotherapies for other patients, and we're working on this SF3B1-mutated vaccinotherapy project,"* emphasizes **Prof. Nathalie Cassoux.** *"In addition, patients at high risk of relapse, with tumors larger than 15 mm or with genomic alterations on chromosomes 3 or 8, are being monitored as part of a major study, dubbed SALOME, to detect metastases as early as possible. This study is already recommending follow-up with MRI imaging every six months."*

Ethical care for patients

Supportive care is also important at Institut Curie, which is coordinating a trial to evaluate the patient care process: **Early together. The aim is to improve patients' experience and quality of life by including supportive care from the very start of any metastatic treatment, even if there are no specific symptoms.** Patients are asked to complete a questionnaire to measure their satisfaction with this joint care.
Institut Curie's expertise in uveal melanoma does not stop there. *"For example, we are researching biomarkers to assess the efficacy of immunotherapies, developing cell lines and preclinical models (PDX) to test new drugs, and developing new radiological criteria for treatment efficacy. More generally, the medical-scientific environment at Institut Curie is highly conducive to the emergence of new ideas and strategies.* ***We share these innovations with patients every year, at Institut Curie, during a one-day event which this year will take place on February 2, 2024, a few days before International Cancer Day,"*** **concludes Dr. Manuel Rodrigues.**

References:

- *Pascale Mariani et al., Circulating tumor DNA as a Prognostic Factor in Patients with Resectable Hepatic Metastases of Uveal Melanoma, Annals of Surgery (2023).*
- Société Française d'Oncologie (SFO), Nathalie Cassoux, Laurence Desjardins, *Oncologie oculaire*, Elsevier Masson, 456 pages (2022).
- Anne-Céline Derrien et al., *Germline MBD4 Mutations and Predisposition to Uveal Melanoma*, Journal of the National Cancer Institute, (2021).
- Jérémy Bigot et al., *Splicing Patterns un SF3B1-Mutated Uvel Melanoma Generate Shared Immunogenic Tumor-Specific Neoepitopes*, Cancer Discov (2021).
- Paul Nathan et al., *Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma*, N Engl J Med (2021).
- Samar Alsafadi et al., *Uveal melanoma, a model disease for spicing alterations and oncogenesis*, Med Sci (Paris), (2018).

[16] Un nouveau facteur de pronostic dans le mélanome de l'uvée métastatique | Institut Curie

Hematological cancers: on the road to new therapeutic strategies for these rare diseases

Hematological cancers are numerous, and each has its own specific features. This diversity is one of the reasons behind the complexity of therapeutic strategies for these blood disorders. Institut Curie brings together a number of teams, each working on a specific type of blood cancer: lymphoma, leukemia, etc.

With 16,000 new cases every year, lymphomas, cancers of the lymphatic system, account for almost half of all hematological cancers. They are nonetheless rare, as **there are around sixty subtypes of lymphoma.** One of Institut Curie's areas of expertise concerns oculocerebral lymphomas (a rare pathology), which has been developed over many years and is coordinated by **Dr. Carole Soussain, a hematologist at Institut Curie.** She has piloted several national multicenter studies that have **standardized certain treatments, such as hematopoietic stem cell autotransplantation, and assessed the toxicity and efficacy of so-called "targeted" drugs in this rare pathology, such as BTK inhibitors or immunomodulators.**

Today, she is leading a national study for patients under 65 (LOC-R01), which aims to improve the complete remission rate by introducing targeted drugs in the first line. Dr. Carole Soussain is also involved in translational research aimed at identifying biological and radiomic prognostic markers and providing a therapeutic response. This work is carried out in collaboration with other teams in France, notably at Institut Curie with Dr. Irène Buvat , who heads the Laboratory of Translational Imaging in Oncology (LITO) , and Prof. Xavier Paoletti, in the Statistical Methods for Precision Medicine team.

Among oculo-cerebral lymphomas, primary lymphomas of the eye, which are very rare, represent another area of expertise for Institut Curie, working alongside Pr. Nathalie Cassoux's ophthalmology team. Dr. Carole Soussain is in charge of hematology for the LOC national expert network for oculocerebral lymphomas, supported by INCA (rare cancer plan). This national reference center for oculocerebral lymphomas develops guidelines for care practices and sets up clinical trials. Dr. Carole Soussain's team is heavily involved in translational research, the aim of which is to combine clinical and basic research at Institut Curie. For example, she will be contributing to an **innovative trial with rare lymphoma patients set up on the cell therapy platform to be built in 2025 as part of the Paris Saclay Cancer Cluster**. This platform, whose medical director is Dr. Marion Alcantara, aims to bring together private and public structures to develop therapies such as CAR-T approaches, a form of immunotherapy based on the genetic modification of a patient's T lymphocytes, which are reinjected to recognize and destroy cancer cells.

The long-term benefits of immunotherapy for mantle cell lymphoma

Institute Curie is also a member of the Lymphoma Study Association ((LYSA) clinical research network, of which Prof. Steven Le Gouill, director of Institut Curie's Hospital Group, Dr. Clémentine Sarkozy, a clinical hematologist at Institut Curie specializing in the care of lymphoma patients, and Carole Soussain, are active members. **At LYSA, Prof. Steven Le Gouill and Dr. Clémentine Sarkozy recently reported the long-term results of a study[17] dedicated to the effect of 3-year maintenance immuno-chemotherapy, after chemotherapy and autograft, on patients with mantle cell lymphoma (LYMA)**. Often aggressive, this lymphoma represents 6% of cancers of the lymphatic system, and affects the B lymphocytes of the immune system. *"6 years ago, we highlighted the benefits of adding immunotherapy,"*[18] says Dr. Clémentine Sarkozy. *This new long-term study shows that the beneficial effect of treatment persists in three quarters of patients, without relapse."* Today, Prof. Steven Le Gouill is conducting the **first national clinical trial (OASIS) for first-line patients, focusing on a chemotherapy-free strategy based on a combination of immunotherapy and targeted therapies.** Results are expected in a few months' time, with a paradigm shift in patient care.

Translational research into follicular lymphoma

Another lymphoma, another search: **follicular lymphoma.** The term "follicular" refers to the arrangement of cells grouped together in lymph nodes. **This is the most common indolent lymphoma. It is characterized by great heterogeneity in its evolution**: some patients remain alive without treatment for decades, while others will have a chemotherapy-refractory form, with survival severely affected. Dr. Clémentine Sarkozy has conducted a single-cell DNA and RNA sequencing study highlighting markers predictive of this aggressive transformation.

According to her,***"This study, combined with bioinformatics analyses, demonstrated the relationship between cancer cell evolution and the microenvironment when follicular lymphoma takes on an aggressive form."*** *"Modifications to this microenvironment, which can be the subject of therapeutic targets, therefore become a marker of disease worsening*[19]*."*

Against this backdrop, LYSA has set up a consortium of ten research teams specializing in translational and basic research on follicular lymphoma, as part of the **joint BidiFly program, coordinated by Dr. Clémentine Sarkozy. This research project is based on artificial intelligence analyses, carried out at LITO by Irène Buvat's team, to integrate large clinical, imaging and sequencing datasets collected over the last 20 years within the LYSA group. The goal? To use artificial intelligence to establish specific disease profiles with markers of response to treatment**[20]. *"This program puts Institut Curie at the cutting edge of AI in lymphoma research! And that's not all, as Institut Curie has expertise in radiomics (image analysis), immunomonitoring (development of biomarkers of response to immunotherapy, with Dr. Cécile Alanio in the Clinical Immunology Laboratory), molecular biology with Dr. Céline Callens in the Molecular Biology Laboratory... And it's by combining these areas of expertise that we can make more effective progress against diseases."*

Why do cells become leukemic?

[17] Clémentine Sarkozy et al., ***Long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study,*** *Journal of Clinical Oncology (18/12/2023).*

[19] Clémentine Sarkozy et al., *Integrated Single Celle Analysis Reveals Co-Evolution of Malignant B Cells and the Tumor Microenvironment in Transformed Follicular Lymphoma,* Blood (2022).

[20] bidifly-communique-de-presse-2023-fr.pdf (lymphoma-research-experts.org)

Institut Curie is also involved in leukemia, another blood cancer caused by the uncontrolled multiplication of immature blood cells in the bone marrow. They can be acute or chronic.

Age is known to be a risk factor in their development, but why remains a mystery. **The Quantitative Approaches in Immuno-hematology team led by Dr. Leïla Perié at Institut Curie has recently shown that the number of active stem cells increases with age.** Previously, it was thought that age led to a reduction in the number of stem cells. What's the link with leukemia risk? *"The risk of mutation increases if there are more stem cells, and with them, the risk of developing cancer,"* states Dr. Leila Perié.

When it comes to leukemia, the institute has **another speciality: studying the occurrence of leukemia years after another cancer has been treated with chemotherapy.** ***"We call these secondary acute myeloid leukemias.*** *To understand what triggers these very aggressive myeloid leukemias, Adil Midoun, a PhD student in our team, and Dr. Jacques Vargaftig, a hematologist at Institut Curie and an expert in the management of acute myeloid leukemias, are trying to* ***understand the effect of chemotherapy on healthy stem cells.***" With this in mind, the team is looking at both the pre-leukemic myeloproliferative state of the cells, and cell maturation defects (without proliferation), which can also lead to leukemia. "*If we understand how this works, we'll be able to develop new therapies,*" says Dr. Alessandro Donada, a researcher at Institut Curie specializing in blood stem cells. ***We use Single Cell analysis techniques to study each progenitor cell individually. We have shown that stem cells are heterogeneous, which may play a role in the fact that there are so many different types of cancer.*** As a result, **Dr. Leila Perié's team has developed novel cell line tracing methods[21], to follow the descendants of individual cells, with the idea of building up the genealogy from stem cells to mature cells**. ***"We are working closely with clinicians and bioinformaticians in our team to understand this highly complex data,"*** says Dr. Perié. *The use of Machine Learning algorithms helps us to analyze aspects of cell biology, such as the links between messenger RNA and the division cycle. Our ambition? To develop ways of preventing leukemia. This is the future!*"

References:

- Clémentine Sarkozy et al., ***Long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study,*** *Journal of Clinical Oncology (2023).*
- Alessandro Donada et al., *Phenotype via Flow Cytometry for Hematopoietic Stem and Progenitor Cells*, Journal of Visualized Experiments (2023).
- Jos Urbanus, Jason Cosgrove et al., *DRAG in situ barcoding reveals an increased number of HSPCs contributing to myelopoeisis with age*, nature communications (2023).
- Clémentine Sarkozy et al., *Integrated Single Celle Analysis Reveals Co-Evolution of Malignant B Cells and the Tumor Microenvironment in Transformed Follicular Lymphoma*, Blood (2022).
- Caroline Houillier et al., *Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients Age 60 Years and Younger: Long-Term Results of the Randomized Phase II PRECIS Study*, JCO (2022).
- Caroline Houillier, Carole Soussain et al., *Management and outcome of primary CNS lymphoma in the modern era: An LOC network study*, Neurology (2020).
- Carole Soussain et al., *Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network*, Eur J Cancer (2019).
- Hervé Ghesquieres et al., *Lenalidomide in Combination with Intravenous Rituximab (REVRI) in Relapsed/Refractory Primary CNS Lymphoma or Primary Intraocular Lymphoma: a Multicenter Prospective "Proof of Concept" Phase II Study of the French Oculo-Cerebral Lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)*, Ann Oncol. (2019).
- Caroline Houillier et al., *Whole Brain Radiotherapy (WBRT) Versus Intensive Chemotherapy with Haematopoietic Stem Cell Rescue (IC + HCR) for Primary Central Nervous System Lymphoma (PCNSL) in Young Patients: An Intergroup Anocef-Goelams Randomized Phase II Trial (PRECIS)*, J Clin Oncol. (2019).
- Carole Soussain C et al., *Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network*, Eur J Cancer. (2019).

[21] Félicitations à Leïla Périé et Antoine Coulon, médaillés de bronze 2023 du CNRS | Institut Curie