

## 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<sup>17</sup> 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,"<sup>18</sup> 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<sup>19</sup>."*

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<sup>20</sup>.** *"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?

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<sup>17</sup>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).

<sup>19</sup> Clémentine Sarkozy et al., *Integrated Single Cell Analysis Reveals Co-Evolution of Malignant B Cells and the Tumor Microenvironment in Transformed Follicular Lymphoma*, *Blood* (2022).

<sup>20</sup> [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<sup>21</sup>, 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!"

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<sup>21</sup> [Félicitations à Leïla Périé et Antoine Coulon, médaillés de bronze 2023 du CNRS | Institut Curie](#)