

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.

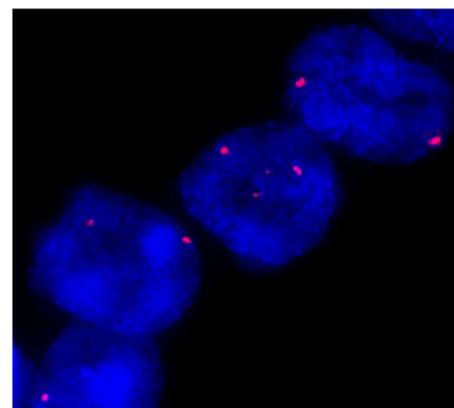
Ocular tumors are not harmless. If detected too late, they can become so large that they require removal of the eye. Institut Curie therefore advocates early diagnosis, to access treatments that preserve vision as far as possible and reduce the risk of relapse. *"To facilitate patient care for patients with uveal melanoma, we have set up the M elachonat 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 M elachonat 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 M elachonat 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 the¹¹ MBD4 gene¹², 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 melanomas¹³.** 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 splicing alterations and oncogenesis*, Med Sci (Paris), 2018, 34 :255-160.

¹³ J er my Bigot et al., *Splicing Patterns un SF3B1-Mutated Uveal Melanoma Generate Shared Immunogenic Tumor-Specific Neoepitopes*, Cancer Discov (2021).

research is currently being pursued as part of an ambitious project¹⁴, 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 blood¹⁶ 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:

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- Samar Alsafadi et al., *Uveal melanoma, a model disease for splicing alterations and oncogenesis*, *Med Sci (Paris)*, (2018).

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