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pour les sciences de la vie et de la santé

ITMO Cancer

ACTION REPORT

.2022

Editorial

Building on the success of its Ten-Year Review 2011-2021, the Aviesan ITMO Cancer is repeating the exercise. This document summarises all the actions it has carried out over the course of 2022.

Readers will discover the achievements of the ITMO Cancer in the context of its three cardinal missions:

- Strategic reflection ;
- Thematic programming;
- Coordinating the cancer community.

There were a number of highlights in 2022. For example, the ITMO Cancer organised a multi-agency meeting on the issues and challenges of radiobiology research, culminating in the preparation of a strategic document for the supervisory authorities. The ITMO Cancer has also taken up one of the major objectives of the Ten-Year Cancer Control Strategy, by programming a new call for projects devoted to the microenvironment of cancers with a poor prognosis. In addition, as part of the French Presidency of the European Union, the ITMO Cancer worked alongside the European Cancer Mission to organise a workshop to discuss citizen involvement at national and European level.

At the same time, the ITMO Cancer has maintained its support for multidisciplinary research through its flagship programmes, and continued its long-standing partnerships for research, training and career support.

In 2022, taking all forms of support together, the Aviesan ITMO Cancer singled out 95 projects to which it allocated a total budget of nearly €25M, with the ambition of further strengthening fundamental and translational cancer research.

Yvan de Launoit & Bruno Quesnel
Directors of the Aviesan ITMO Cancer

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Assistant Director of the Aviesan ITMO Cancer

Activity report 2011-2021: Aviesan ITMO Cancer, a major player in national cancer plans

The involvement of Aviesan ITMO Cancer in the design and implementation of successive cancer control plans during the 2011-2021 period was the subject of an assessment published in July 2022. The brochure "Aviesan ITMO Cancer: 2011-2021, A decade of involvement in the Cancer Plans" presents a synthetic view of:

- Its contribution to the definition of the research strategy within the framework of the 2nd and 3rd Cancer Plans and the Ten-Year Strategy 2021-2030;
- Its leading role in the programming of thematic and multidisciplinary basic research on cancer;
- Its historical mission of supporting the French cancer research community.

A Workshop on French Research in Radiobiology

In July 2022, Aviesan ITMO Cancer organised a workshop to reflect on the state of French research in radiobiology. On this occasion, the ITMO and its committee of experts received scientists from various components of the research community in this field (research organisations/institutes, networks, learned societies, etc.): CNRS (GDR MI2B - Modelling and instrumentation for medical imaging – Nuclear tools and methods for cancer control, IN2P3, INSB), Institut Curie, Inserm, CEA, IRSN, RadioTransNet and ResPlaNDIR networks. They came to present the situation of their structure around the following axes:

- Main lines and priorities of research in radiobiology;
- Assessment of the strengths and weaknesses, and the main obstacles;
- Elements of medium and long term prospective.

The findings and avenues of action considered during this workshop will lead to the drafting of a manifesto for the supervisory authorities and ministries. It will list the challenges and major projects for the next 5-10 years, needs and limits that have to be explored.

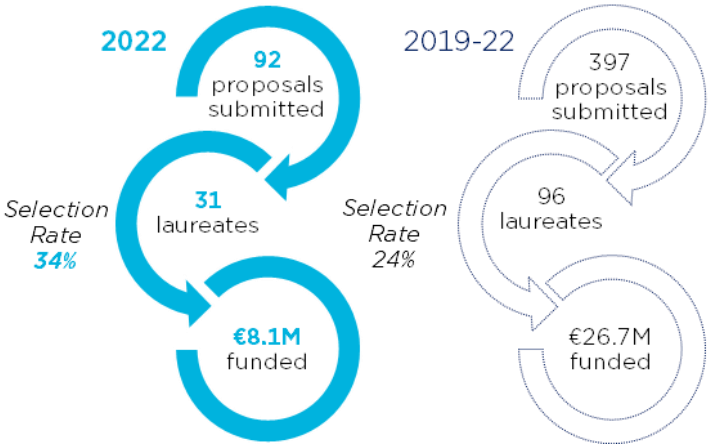
Interdisciplinary approaches to oncogenic processes and therapeutic perspectives: Contributions to oncology of physics, chemistry, and engineering sciences (PCSI)

Objectives of the programme

To support scientific and technological advances in oncology (understanding the mechanisms of carcinogenesis, diagnosis, therapeutic management) using concepts or tools from physics, chemistry or engineering sciences.

Two types of project are funded: short-term projects designed to establish proof of concept (18 months), and large-scale projects based on proof of concept already obtained (36 months).

Key Figures



Target areas/disciplines

- Physics, Medical physics
- Chemistry, Biophysics
- Engineering sciences
- Biochemistry, Cancer biology, Clinics

The projects funded in 2022 had the following objectives:

- Studying mechanisms involved in carcinogenesis:
  - Metabolism of fatty acids and cholesterol in prostate cancer cells;
  - Role of sphingomyelin metabolism in the formation and maintenance of invadopodia, involved in the invasive function of breast cancer cells;
  - Impact of lactate accumulation and acidification on intracellular metabolism of cancer cell;
  - Interactions between acute lymphoblastic leukaemia T-cells and thymic epithelial cells;
  - Mechanisms by which phosphorylation and liquid-liquid phase separation regulate the binding of BRCA2 to its partners;
  - Biogenesis of PML nuclear bodies and association between their dynamics and structure and their antitumour functions;
  - Nature and role in tumour infiltration of proteins involved in the detection of nanotopographic variations by macrophage podosomes;
  - Impact of the mechanical properties of the glioblastoma cells nucleus on their invasiveness and identification of potential therapeutic targets;
  - Contribution of transcription and DNA repair combined with exposure to mutagens to mutational processes in human cancers;

- Developing methods for studying or treating cancer:
  - Study of the mechanical properties of the microenvironment of pancreatic adenocarcinomas on suspended micro-tissue;
  - In vitro and in vivo comparison of two nucleic acid transfer methods that disable DNA repair in cancer cells: lipid-based nanovectors vs sepiolite;
  - Measure of the fluorescence carried by radiosensitising nanoparticles to assess the effectiveness of proton therapy and the dose delivered locally;
  - Calibrated biodosimeter for local assessment of the biological effects of medical irradiation;
  - Study of the chemoradiotherapeutic efficacy of radiosensitising nanoparticles loaded with active principles in murine models of human cancers;
  - Measure of the efficacy of lncRNA antisense oligonucleotides, in combination with MAP kinase inhibitors, to inhibit tumour growth in melanoma and renal cancer CDX and PDX;
  - Method for isolating and amplifying circulating tumour cells for routine use;
  - High-intensity focused ultrasound surgery with thermometric ultrasound guidance for the treatment of breast tumours;
  - Radiofluorinated neurotensin analogues for PET identification of patients eligible for vectored internal radiotherapy;
  - Use of stimulated Raman scattering to obtain instant histological data on intraoperative biopsies without labelling or cryosection;
  - Antibody-loaded vectors to map and analyse the maturation dynamics of invadopodia in primary or metastatic melanoma cells;

- Developing compounds or vectors for therapeutic purposes:
  - Effects of an anti-EG-VEGF antibody in the treatment of choriocarcinoma and characterisation of its interaction with methotrexate;
  - Smart molecular systems releasing calcium channel inhibitors into the tumour microenvironment to eradicate glioblastoma stem cells;
  - Calcium phosphate cement loaded with nanoparticles for local release of active principles in osteosarcomas;
  - Prohibitin inhibitors with antiproliferative activity in osteosarcoma;
  - Hybrid inhibitors of DNMT/EZH2 epigenetic factors to combat chemoresistance in multiple myeloma;
  - Inhibitors of the UBE2N protein to sensitise organoids derived from ovarian cancer to PARP inhibitors;
  - Nanovector releasing into mitochondria an inhibitor of the formation of the AIF/CHCHD4 complex involved in cell survival;
  - Submicronic vectors carrying bispecific anti-tumour and antiCD3 or CD16 antibodies, to mobilise T and NK cells against tumours;
  - Active and selective compounds targeting p53 mutants and their partners in gastric cancer;
  - Compounds inhibiting the UBASH3B protein, a negative regulator of the mitotic spindle assembly checkpoint;
  - Inhibitors of the cholesterol transfer protein STARD3 specifically involved in tumour cell growth.

Interdisciplinary approaches to oncogenic processes and therapeutic perspectives: Contributions to oncology of mathematics and computer science (MIC)

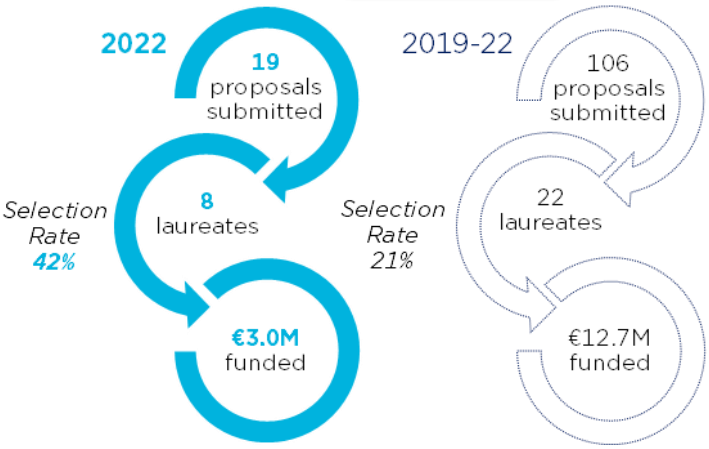
Objectives of the programme

To develop, or validate under experimental conditions, new concepts, models or methods in mathematics and digital sciences that will enable scientific advances in oncology: understanding the biological mechanisms of carcinogenesis, assistance in establishing the diagnosis and predictive analysis of prognosis, optimisation of treatment and therapeutic follow-up, etc.

Target areas/disciplines

- Mathematics
- Theoretical physics
- Statistics
- Computer science

Key Figures



The projects funded in 2022 had the following objectives:

- Analysing and modelling available massive multiomics (genome, transcriptome, miRNome, (phospho)proteome) or histological data obtained on tumour (including single cell) or healthy tissues;
- Improving the understanding of the molecular mechanisms of cancer, to optimise existing treatments, to identify new therapeutic targets or to predict the evolution of the disease.

The projects concerned several types of cancer: glioblastoma, osteosarcoma, adrenocortical carcinoma, ENT cancers, medulloblastoma or myeloproliferative neoplasm.

Webinars to promote the MIC 2023 call for proposals

On the occasion of the launch of the MIC 2023 call for projects, Aviesan ITMO Cancer and the Cancer Unit of Inserm's Department of Program Asessment and Follow-up organised a series of webinars in December 2022 to present the program to the mathematical and computer science communities interested in oncology research.

Context, objectives, eligible disciplinary fields and regulatory issues were detailed, with a particular focus on the nature and quality of the data used to develop new methodologies, as well as the need to validate these innovative methodologies in real-life conditions. A part of these webinars was dedicated to a question-and-answer session with the audience.

Comparative study of PMSI, PCSI and MIC programmes features

In order to give more emphasis to chemistry, mathematics and computer science, the PMSI programme has been split into two programmes - PCSI and MIC - in 2019. At the end of 4 years of programming these new calls for proposals (2019-2022), an analysis was conducted to determine whether the objectives of the PMSI redesign were achieved. The main conclusions are as follows:

- Medicinal chemistry, as well as mathematical and computational approaches applied to oncology, have taken a more important place with the creation of PCSI and MIC;
- Physics-centered approaches remained highly represented in parallel to the funding of these new themes given the increase of the total amount envelop;
- New communities entered the competition: there is only partial overlap between the communities that submitted to PCSI or MIC and those that submitted to PMSI, and the scientists who submitted to PCSI or MIC had little or no experience in cancer research.

Ex Post Analysis of the Programme "Epigenetics and cancer research projects"

Carried out in March 2022, this analysis covered the entire programme period, from 2013 to 2015. A feedback seminar, organised in October 2021 with former laureates of the programme and members of the selection committees, enriched this analysis.

The Ex Post analysis shows that the projects funded addressed most of the factors known at the time to be involved in epigenetic mechanisms, as well as other mechanisms for regulating gene expression. The projects led to the development of several tools and models, as well as scientific advances that went beyond the field of oncology in some cases.

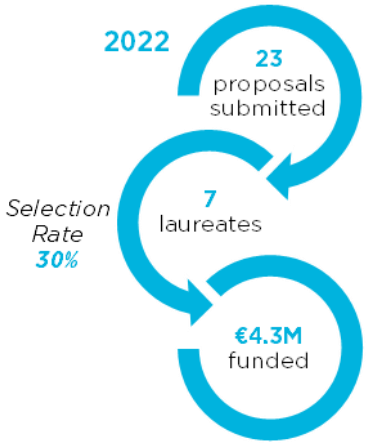
Interdisciplinary approaches to oncogenic processes : Functional exploration of the microenvironment of cancers with a poor prognosis (MCMP)

Objectives of the programme

To gain a better understanding of the role of the tumour microenvironment in the development of cancers for which therapeutic options are not very effective, and which are characterised by a standardised net survival rate 5 years after diagnosis of less than 33%. Four lines of research were proposed:

- High definition spatiotemporal characterisation of the microenvironment leading to a functional study;
- High definition decoding of cellular networks and local signalling;
- Reprogramming of the tumour microenvironment;
- Development of in vitro or ex vivo models reproducing the spatiotemporal evolution of the tumour-microenvironment pair.

Key Figures



Target areas/disciplines

- Biochemistry, Mechanobiology, Cell biology
- Infectiology, Immunology, Vascular and lymphatic biology, Cancer biology
- Image Analysis, Spatial profiling, Bioengineering
- Surgery, Anatomopathology, Haematology, Clinical medicine
- Physics, Biophysics, Chemistry, Mathematics

The projects funded in 2022 had the following objectives:

- Unravelling the mechanisms underlying the protumoural effects of the tumour microenvironment:
  - Impact of microenvironmental cells (tumour associated macrophages (TAMs), fibroblasts, dendritic cells DC2 CD207+) or matrix cells on T lymphocytes mobilisation and activity (non-small cell lung carcinoma, malignant pleural mesothelioma, digestive carcinomas);
  - Impact of myeloid immunosuppressive cells on tumorigenic, metastatic and resistance properties of circulating cancer stem cells (gastric cancer);
- Analysing the impact of chemotherapies on the immune tumour microenvironment and its modulation by the inhibition of histone-deacetylases in gastric cancer;
- Characterising the cellular networks and microbial or metabolic signals in the microenvironment of hepatocellular carcinoma.

Projects were all based on patients' samples, as well as animal models (including xenografts) or cocultures (including spheroids). They included single cell (and single nucleus) RNA sequencing, high resolution imaging, multiomics (spatial transcriptomics, matrisome and microbiome), mathematical modeling and bioinformatics.

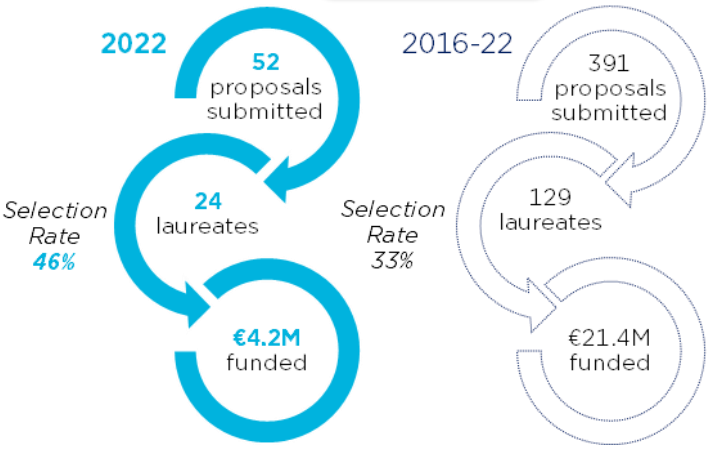
Equipment for cancer research

Objectives of the programme

Funding the acquisition of heavy or semi-heavy devices to:

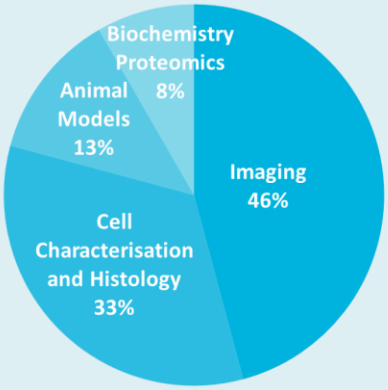
- Foster the development of ambitious research in the field of oncology;
- Encourage interactions between research teams;
- Increase the attractiveness and the position of French teams on the international arena.

Key Figures



The projects funded in 2022:

- Belonged to the categories Imaging, Cell characterisation and histology, Animal models, Biochemistry and proteomics;



- Were devices such as:
  - High-resolution and high-throughput microscopes, live cell imagers, multiplex spatial imaging systems, spectrometers;
  - Cell sorters, cytometers, single-cell proteome analyser, biological nanoparticle analyser, energy metabolism analyser;
  - Preclinical irradiator, aquatic system for zebrafish, high-resolution ultrasound scanner;
  - Pyrosequencer;
- Were dedicated in particular to:
  - Monitoring cellular behaviour in real time;
  - Characterising extracellular vesicles;
  - Exploring tumour heterogeneity and the microenvironment (RNome, proteome, metabolome) on a single-cell scale;
  - Visualising the spatial organisation of tumour cells, immune cells and the microenvironment;
  - Studying the telomeres and chromatin structure;
  - Searching for epigenetic markers;
  - Non-invasive longitudinal monitoring of murine cancer models.

60 % of the equipment was open access, and in 1/3 of the cases (20% of the equipment) was installed on an IBiSA-accredited platform.

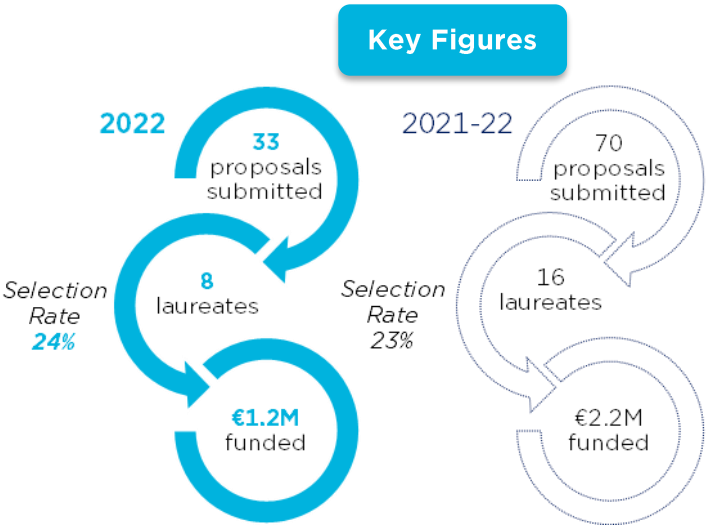
Basic and translational research training to obtain PhD (FRFT-Doc)

Objectives of the programme

Promote training of students or young medical, pharmacy and veterinary science graduates in translational research by funding doctoral theses on cancer.

Launched in 2007, led by Avisean ITMO Cancer since 2011, the FRFT programme was analysed in 2019.

The analysis pointed out that only few laureates of a M2 degree were continuing with research activities. In 2021, the scope of the programme FRFT was therefore reassessed to focus on PhD thesis grants (FRFT-Doc).



The projects funded in 2022 had the following objectives:

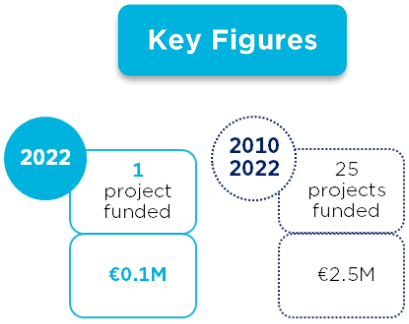
- Unravelling mechanisms involved in oncogenesis:
  - Oncogenic network involved in the early stages of TLX3-related T oncogenesis in acute lymphoblastic leukaemia;
  - Single-cell dynamics of transcriptomic (coding and non-coding RNA) and epigenomic changes in anti-PARP-treated cancers;
  - Role of tumour cells and the microenvironment in inflammation during Waldenström disease;
  - Study of the tumour residue and its microenvironment to characterise metastatic recurrence in triple-negative breast cancer;
  - Interactions between acute myeloid leukaemia cells and their microenvironment in a humanised mouse model;
- Developing models for studying or monitoring cancers and their treatment:
  - Biomarkers predictive of response or resistance to immunotherapy for non-small cell lung cancer;
  - Organoid models of high-grade gliomas to understand the development of resistance and test new therapeutic combinations;
- Developing inhibitors of the interaction between casein kinase 2 subunits and evaluate their anticancer activity in 2D and 3D models of renal cancers.

Support to Training and Career programmes

Doctoral school FIRE

The Frontiers of Innovation in Research and Education (FIRE) doctoral school (Paris-Cité and Paris Sciences et Lettres universities) is an international, interdisciplinary doctoral programme. Aviesan ITMO Cancer has been supporting the FIRE programme since 2010 to promote multidisciplinary training to adapt and meet the needs of cancer research.

◗ The project funded in 2022 aimed at dissecting the response of the tumor microenvironment to nanoparticles-mediated hyperthermia combined with anti-cancer drugs in tumor on chip devices.

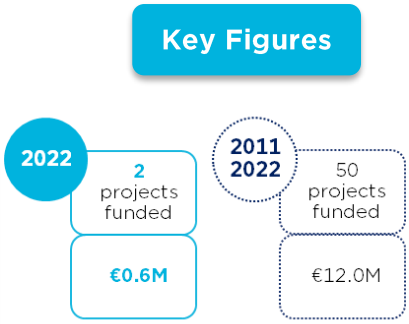


ATIP-Avenir Programme

The ATIP-Avenir programme enables young scientists to create and lead their own research team within an established Inserm or CNRS laboratory in France. Avisean ITMO Cancer contributes to the funding of the awardees pursuing a cancer research project.

◗ The projects funded in 2022 had the following objectives:

- Characterising the chromatin network that stabilizes and repairs replication fork damages, in order to identify new chromatin targets to overcome chemoresistance;
- Deciphering how glioblastoma (GBM) heterogeneity affects the metabolic determinants of GBM patient-derived stem cells adaptation to stress.

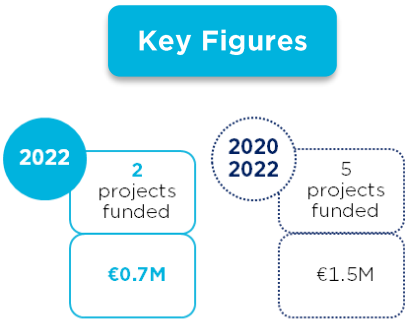


JCJC Programme

The JCJC (Jeunes chercheurs ou jeunes chercheuses) programme of the French National Research Agency (ANR). enables young scientists to access funding in addition to their recurring grants. Since 2020, Aviesan ITMO Cancer has been funding JCJC projects focusing on cancer.

◗ The projects funded in 2022 had the following objectives:

- Exploring the granulopoiesis alteration linked with the chronic inflammation contexture in lung cancer;
- Studying the involvement of the arginine methyltransferase PRMT5 in glucocorticoid-induced resistance to chemotherapy in triple negative breast.



Support to research programmes on the thematic "Cancer & Environment"

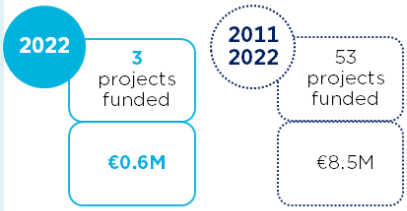
National Environmental and Occupational Health Research Programme (PNR-EST)

This multi-agency programme of the French National Agency for Food, Environmental and Occupational Health and Safety (Anses) addresses various public health issues related to the environment and workplace. Aviesan ITMO Cancer has been funding cancer-related projects within this programme since 2011.

◗ The projects funded in 2022 had the following objectives:

- Understanding the link between external and internal exposome in lung carcinogenesis in non-smoking women;
- Estimating the risk of ionizing radiation (IR)-induced central nervous system cancer death in relation to occupational dose of IR received (case-control study);
- Evaluating the impact of road traffic induced atmospheric pollution on the the risk of cancer in childhood.

Key Figures

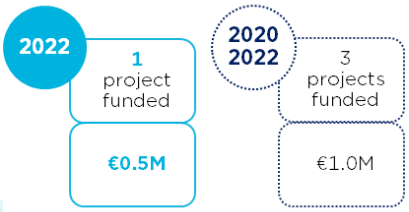


Écophyto 2+ Programme

The French national Écophyto 2+ plan aims to reduce phytopharmaceutical compound use, dependence, risks and impacts by supporting changes in practices. In this context, the French Office for Biodiversity and the Ministries overseeing the Écophyto 2+ plan launched a call for proposals aimed at exploring the human health and ecosystem effects of exposure to these compounds. Aviesan ITMO Cancer supports this initiative by funding cancer-related projects.

◗ The project funded in 2022 aimed at characterising the impact of pesticide exposome on lymphomagenesis, chemoresistance and survival outcomes.

Key Figures



SIRIC : A strong support for the structuring of integrated cancer research

Since 2012, the Aviesan ITMO Cancer has been providing substantial financial support to the network of Integrated Cancer Research Sites (SIRIC), alongside INCa and the Healthcare Supply General Directorate. These structures are responsible for implementing multidisciplinary research programmes to accelerate the production of new knowledge and promote its dissemination in patient care. In 2022, the ITMO Cancer was involved in the discussions leading up to the drafting of the call for projects and assisted in the selection process for the 8 laureate projects. It financed each of them to the tune of €200,000 in 2022, for a total of **€1.6M** (€12.3 M since 2012).

A Leading Role in the European initiative UNCAN.eu

The initiative to UNderstand CANcer is one of the 13 specific objectives of the Mission on Cancer and one of the ten flagships of the Europe's Cancer Beating Plan. The Coordination and Support Action (CSA) "4.UNCAN.eu" is planned to generate a blueprint for UNCAN.eu by 2023. Aviesan ITMO Cancer was involved in the very first steps of UNCAN.eu by participating in:

- The setting-up of the French task force who applied to the coordination of the 4.UNCAN.eu CSA and was selected in 2022;
- The launching of the UNCAN.eu initiative at the meeting "Joining European forces to understand cancer" organised in Paris during the French Presidency of the European Union (June 23rd 2022).

Support to the Cancer Europe Mission Workshop on Citizen Engagement

As part of the French Presidency of the European Union, the Ministry of Higher Education and Research organised in March 2022 a high-level conference on citizen involvement in the European missions of the Horizon Europe programme.

On this occasion, the Cancer Europe Mission held a workshop with the aim of defining the framework needed to facilitate the involvement of European citizens in the future actions of the Cancer Europe Mission at European and national level.

In close collaboration with the Mission's vice-president, Aviesan ITMO Cancer helped to organise the workshop by proposing themes and speakers.