

The Spontaneous Tumours Programme

*Spontaneous tumour models in animals for translational
research in oncology*

**Ex Post Analysis
2011-2014**

(November 2018)

Introduction

In the frame of the 2nd and 3rd Cancer Plans, the Multi-Organization Thematic Institute (ITMO) Cancer of the Alliance for Life Sciences and Health (Aviesan) is since 2011 responsible for the thematic calls for projects to support emerging research domains. These funding instruments, which operational management falls to Inserm, are launched in the frame of the research part of the national Cancer Plan coordinated by the National Cancer Institute (INCa).

In accordance with the recommendations of the INCa's international scientific advisory board and the 3rd Cancer Plan objectives, a discussion about programme evaluations has started at the national level.

In parallel, ITMO Cancer-Aviesan started assessments of its own programmes for which a sufficient hindsight is possible. A generic analysis grid that can be used for all programmes has been implemented to achieve this. The analysis methodology can be slightly adapted to the specificities of the different calls for projects.

The ex post analyses of ITMO Cancer are fulfilling the following objectives:

- To determine if a funding programme has reached its objectives and to which cancer plan objectives it contributed to;
- To gain insights on the impacts of the funding in terms of tools developed and scientific advances in oncology generated;
- To provide data and information allowing ITMO Cancer to implement evidence-based strategic steering of cancer research.

This document recapitulates the main elements of the ex post analysis of the Spontaneous Tumours Programme over the 2011-2014 period.

Elements Taken into Account in the Analyses

- Key figures of the number of projects submitted, success rate, average budget over time
- Analysis of the projects (*using the submitted information and the selection committee reports*):
 - ✓ PI profile: scientific domain*, experience on cancer, demographic data, affiliation;
 - ✓ Project types: domain (CSO categories), cancer type, duration of funding;
 - ✓ consortiums: partner number, domains*, type (industrial or academic, international);
 - ✓ main reasons of the rejection of non-selected project.
- Impact of the project (*based in the final reports and discussions with PI during the restitution seminars*):
 - ✓ Tools developed: diagnostics, therapeutics, follow up, uses by others;
 - ✓ Advances in knowledge: oncogenesis mechanisms, resistance pathways, potential therapeutic target identifications;
 - ✓ Socio-economical outcomes: manpower hired, patents, collaborations, PI career evolutions, leverage effects;
 - ✓ Communication: publications, oral or poster presentations in congresses, lay public reaching.

**Medicine/Clinical Research, Biology, Physics, Mathematics/Informatics/Engineering, Veterinary Medicine*

Context and Objectives of the Programme

The Spontaneous Tumours Programme was implemented by ITMO Cancer-Aviesan in the frame of the 2nd Cancer Plan (2009-2013) and its mission 1.3 *“To structure and stimulate research in the early-phase trials of new cancer therapies”*. This mission had the ambition to *“develop and support in vitro and animal alternatives to the different phases of clinical trials of cancer therapies on humans”*, a task that was steered by INCa and ITMO Cancer-Aviesan.

The research done on experimentally-induced cancer animal models have shown their limits, and it has been suggested that they should be completed by preclinical models of spontaneous tumours. In fact, some of these spontaneous tumours, notably in dogs, are presenting clinical and biological similarities to human tumours. Furthermore, the sequencing of many animal genomes (including the dog genome, published in 2016) paved the way to the development of a translational research based on these models.

The Spontaneous Tumours Programme had the ambition to promote the integration of the research done on spontaneous tumours models to the global studies of human cancers with the following double objective:

- To foster collaborations between researchers and clinicians in both veterinary medicine and human medicine to stimulate the transfer of results from animal to humans;
- To promote the development of approaches and tools useful for the clinical care of spontaneous cancers in animals, with a perspective to translate them to human cancer treatment.

Priority was on tumour types that were both a concern in veterinary medicine and having a comparable human counterpart.

The fields covered by the Spontaneous Tumours Programme were defined by an ad hoc committee set by ITMO Cancer-Aviesan. New approaches to cure spontaneous cancers in animals which could be transferred to early phase clinical trials in human adults or children were namely eligible, as well as new imaging techniques and new therapeutic tools suitable for animals and characterisation of new biomarkers.

Scope of the Spontaneous Tumours Programme (Call 2014)

- Development of new research tools in the field of cancer (for example targeted monoclonal antibodies from a bank created in dogs);
- Development of new therapeutic approaches (for example tests of these monoclonal antibodies alone or in association with other molecules in dogs with spontaneous cancers);
- Development of resources and reagents, cell lines, tissue banks and the use of collections of samples in order to validate new classifications of tumors;
- Characterization and pathophysiological studies on animal models and confirmation of their relevance to human diseases;
- Development of new technologies and the use of imaging coupled with antibodies;
- Development of preclinical and clinical studies in the investigation centers of the French national veterinary schools;
- Opportunities for clinical research in humans including a section of preclinical studies in animals.

Ex Post Analysis of the Programme

KEY FIGURES

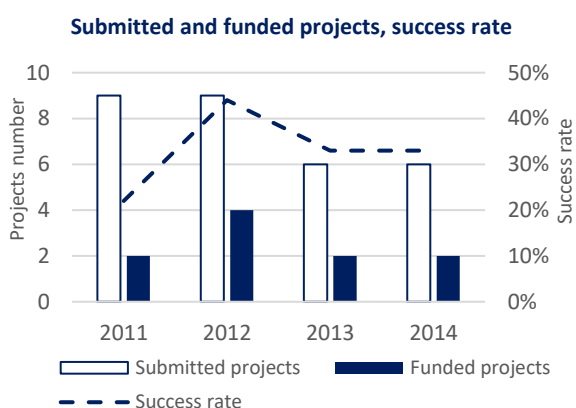
The number of submitted projects has been low and decreased along the years, from 9 submitted projects per year in 2011 and 2012 to 6 in 2013 and 2014, for a total of 30 projects submitted in 4 years.

Main figures of the Spontaneous Tumours Programme (2011-2014)

- 10 funded projects
- 8 PI
- 17 partners
- €3,43M
- median age of PI: 47 y. o.
- 16 personnel hired (62 % engineers or technicians, 15 % PhD students, 15 % post-doctorates, 8 % veterinary clinicians)
- 6 international collaborations (4 in Europe, 2 with the United States)
- 11 original articles

* as mentioned in the final reports

A third of the projects (10/30) was funded. These 10 projects were carried by 17 partner teams, including 8 PI, and received in average €343K.

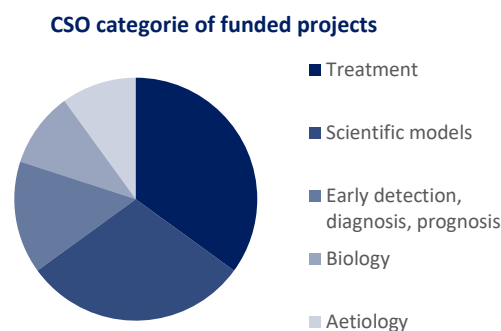


The funded projects were mainly involving canine models (8 projects out of 10), but also swine (1 project) and sheep and goat (1 project).

In contrast to other calls, all projects were on one specific type of cancer, reflecting the specific nature of the spontaneous tumour models.



Funded projects were mainly classified in the CSO¹ category "Treatment" (35%) or "Scientific Models" (30%). The remaining projects were in the categories "Early detection, diagnosis and prognosis" (15%), "Biology" (10%) and "Aetiology" (10%).



The majority of Aviesan founding members were present as PI funded employers in the frame of the Programme: mainly Inserm (37% of PI), Hospitals (25%), but also INRA, CEA and CNRS (12,5% each).

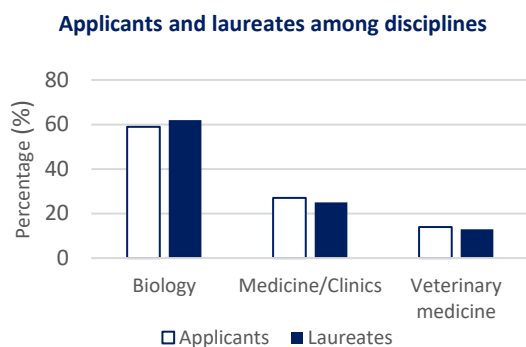
¹ The CSO (Common Scientific Outline) is a universal scientific classification system that covers all domains in cancer research.

A SMALL RESEARCH COMMUNITY IN FRANCE

The Programme has attracted a small number of research teams, with only 30 projects submitted in 4 years by 57 partners, including 22 PI. This low mobilisation indicates that the research community working on spontaneous tumour models in France remains restricted to a handful of actors only.

AN INTERDISCIPLINARITY EFFORT

An objective of the Programme was to put together researchers from different disciplines on the projects: veterinary oncologists, clinical oncologists, pathologists, surgeons, geneticists, molecular and cellular biologists, statisticians, etc.



Researchers who submitted were mainly biologists (59%), and the remainder were clinicians (27%) or veterinary clinicians (14%). The funded PI were mainly biologists (62%), clinicians (25%) or veterinary clinicians (13%).

However, the objective to foster collaborations between various disciplines has been partially reached as 60% of the consortia were involving at least one veterinary clinician.

ADVANCES IN KNOWLEDGE, BUT FEW TOOLS DEVELOPED

In accordance to the objectives of the call, the funded projects were aiming at developing experimental alternatives to preclinical trials.

The Programme has allowed the development of a few tools, exclusively on the canine model. Knowledge advances have been larger. Mostly, the Programme has allowed characterisations and comparisons of canine, sheep or goat tumours to their human counterparts, thereby confirming their pertinence as models. New signalling pathways involved in carcinogenesis or associated with prognosis have also been identified. A clinical trial on dogs was touted as a way to continue the development of an antibody for therapeutic purposes, and the further development of an oncolytic virus was also considered.

Tools and scientific advances in the Spontaneous Tumours Programme* (2011-2014)

Tools (exclusively on canine models):

- 3 antibodies for therapeutic or diagnosis purpose;
- 2 sample collections of lymphomas and melanomas.

Main scientific knowledge advances:

- comparative data indicating the pertinence of B cell lymphomas and melanoma canine models as well as sheep models for JSRV-linked pulmonary adenocarcinomas;
- infectivity characteristics of oncolytic vaccinia virus;
- characterisation of the immune response in a spontaneously regressing melanoma porcine model;
- identification of a protein involved in cell transformation after an oncogenic virus infection;
- identification of an autocrine loop in invasive mucinous adenocarcinomas;
- link between calpaïne 1 secretion and bad prognosis.

* as mentioned in the final reports

FEW OUTCOMES

There has been so far no economical valorisation of the research done in the Programme at the time of analysis (November 2018), and no PI reported having received further funding to continue the project, indicating a lack of lever effect.

However, positive impacts on PI have been reported: 4 new collaboration with European partners, including one for clinical trials on animals, and 2 with partners in the United States; development of expertise in veterinary nuclear medicine by one research team; participation of one partner to an international consortium on animal genome annotation.

Furthermore, the Programme led to 11 publications as mentioned in the final reports, in vast majority in journals with a good reputation in their domains (ranked in the 1st quartile). More than half of these publications were available in open access, in accordance with the Cancer Plan objective of *“sharing knowledge and data nationally and internationally between professionals [and the lay public].”*

Conclusion

The main lesson of the ex post analysis of the ITMO Cancer-Aviesan Spontaneous Tumours Programme is the small size of the research community involved in this field, explaining the small number of projects submitted.

This was also a conclusion made during a seminar on canine comparative oncology organized by INCa in January 2014. The French community at that time came mainly from two veterinary schools specialized in oncology and their associated research teams, two private clinics associated with the SIRIC in Lille, and a research unit working on canine genetics. It is in this context that ITMO Cancer-Aviesan decided not to continue the Programme after 2014. The French community on spontaneous tumours has yet to gain expertise in conducting clinical trials to see their research translated and ultimately tested in human clinical trials.

This however does not brush away the relevance of spontaneous tumour models in cancer research, as the knowledge gathered in the projects indicates. This is why research on this topic is one of the fields covered by new call for projects entitled *“Development and integration of new experimental models for research on cancer: optimizing the 3R rule”* launched in 2019 by ITMO Cancer-Aviesan. The scope of this new call goes beyond spontaneous tumour models and includes other types of models in oncology, animal or not, induced or spontaneous and should gather a broader scientific community.