aviesan
alliance nationale
pour les sciences de la vie et de la santé

ITMO Cancer

The Epigenetics and Cancer Research Projects Programme

Ex Post Analysis 2013-2015

(March 2022)

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, whose operational management falls to Inserm, are launched in the frame of the research part of the national Cancer Plan, which is coordinated by the National Cancer Institute (INCa).

In accordance with the recommendations of the INCa's international scientific advisory board and the third 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. This 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 Epigenetics and Cancer Programme over the 2013-2015 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 the 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, Chemistry*

Context and Objectives of the Programme

The Epigenetics and Cancer programme was part of the Cancer Plans 2 (2009-2013) and 3 (2014-2019), in particular the following objectives:

- 2nd Cancer Plan, Research theme, 5th objective of measure 1: "Reaffirm the importance of fundamental research by emphasising the originality of research and the importance of interaction between disciplines";
- 3rd Cancer Plan, objective 13: "Provide the means for innovative research", action 13.1: "Guarantee the independence and creativity of research by ensuring that the funding rate for basic cancer research exceeds 50% of the credits for all INCa and Aviesan cancer calls for projects".

Understanding the control of gene expression and genome stability is a major lever for progress in cancer prevention and treatment. This includes the epigenetic mechanisms involved in the processes of locking and unlocking the genome. The main aim of the Epigenetics and Cancer programme was to gain a better understanding of the epigenetic mechanisms associated with cancer, with the projects supported paving the way for innovative concepts to help unravel the processes involved in tumour development, its possible recurrence and ways of preventing it.

The calls for projects emphasised the inherently multidisciplinary and multi-scale nature of epigenetics research, and the need to pool or combine pre-existing knowledge, particularly that derived from high-quality reference maps of the epigenome. However, large-scale mapping of the epigenome without functional analysis remained outside the fields of research eligible for funding under the programme.

Scope of the Epigenetics and Cancer programme (Call 2015)

- Role of the epigenome in the development or progression of cancers;
- Relevant epigenetic mechanisms associated with the onset or progression of cancers;
- Development of experimental models exploring the epigenome and epigenetic mechanisms during cancer transformation or progression;
- Functional and/or transcriptional analysis in experimental models to validate epigenomic results;
- Epigenetic characteristics of cells in the tumour microenvironment likely to promote tumour progression (immune cells, vascular cells, etc.);
- Influence of the environment and individual behaviour on modifications to the epigenome, including normal cells subjected to carcinogenic agents;
- Factors involved in very early events (during gestation or early childhood), which have an impact on individuals' epigenetic profiles and may create an increased susceptibility to the development of cancer: nutrition, exposure to infectious agents, risky behaviour (smoking, alcohol, etc.);
- Epigenetic mechanisms common to different pathologies (e.g. obesity and cancer) or associated with resistance to treatment.

Ex Post Analysis of the Programme

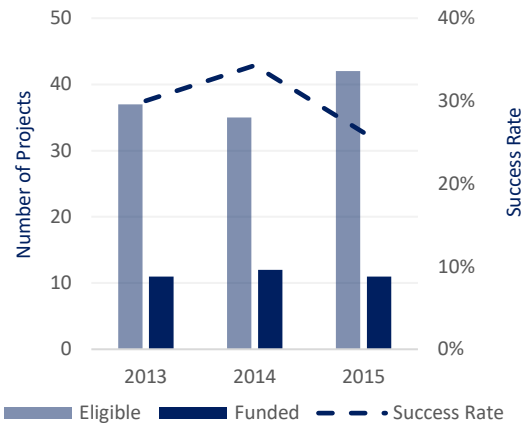
KEY FIGURES

In 3 editions, the Epigenetics and Cancer programme has funded 34 projects, selected out of 114 eligible projects: the average success rate is 30%.

Main Figures of the Epigenetics and Cancer Programme

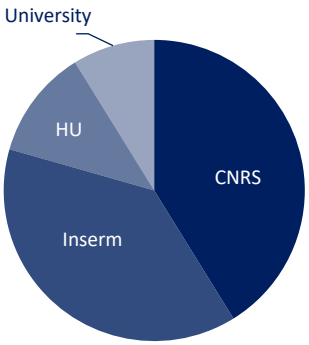
- 114 projects evaluated
- 34 projects funded (success rate: 30%)
- 34 laureates (30% women)
- 83 partners
- €13.65M (average €400k per project)
- Median age of the laureates: 46.5 years old
- 107 new recruitments: 45% post-docs, 27% engineers, 8% engineering assistants, 5% technicians,
  4% masters 2, 11% other
- 1 new research team in epigenetics
- 3 new areas of research in epigenetics, including 1 within a SIRIC
- 1 functional screening platform
- 5 patents (biomarkers and therapeutic approaches)
- Leverage effect for almost half of the projects (14 projects/34, and 16 new funding)
- 20 new international collaborations (Europe and USA)
- 49 publications (37 original articles, 11 literature reviews, 1 editorial) and 3 articles in pre-publication

Eligible and Funded Projects, Success Rate



The duration of projects has increased over time, thanks to a change in the call for projects from an average of 24 months in 2013 to almost 36 months in 2014 and 2015. This has had a slight impact on the average budget of funded projects, which rose from nearly €380k in 2013 to just over €410k in 2014 and 2015 (average budget over the 3 years: €400k).

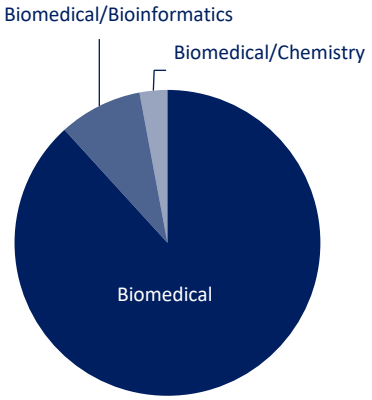
PI Employers



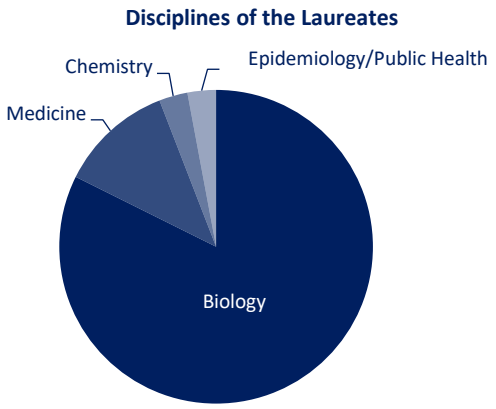
The majority of laureates were employed by the CNRS (41%) or Inserm (38%) and, to a much lesser extent, by the University (9%). The teaching hospital staff (HU) accounted for 12% of laureates.

The average number of partners involved remained constant over the 3 editions of the programme, around 2.4. The vast majority of the consortia created (88%) were made up of biologists and physicians. A few consortia also involved specialists in bioinformatics (9%) or chemistry (3%).

Composition of the Consortia



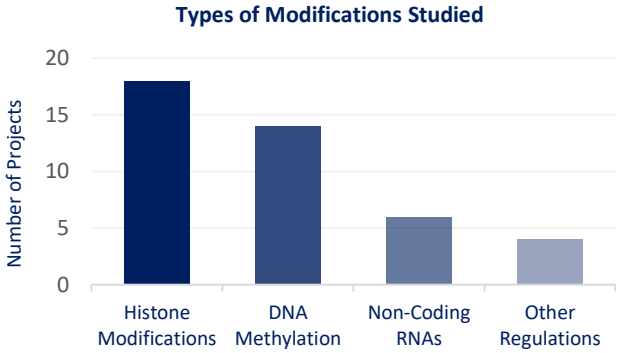
THE MAIN EPIGENETIC MECHANISMS WERE COVERED

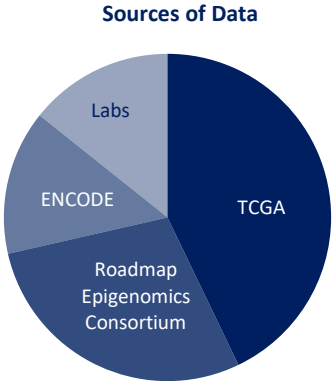


The vast majority of the projects funded were led by biologists (82%), and less frequently by clinicians (12%). One chemist and one molecular epidemiologist were among the project leaders.

The main research theme was epigenetics for 53% of the laureates and cancer for 32%. However, almost 90% of the projects were led by researchers who had at least one previous experience of cancer research. Although the project leaders were mainly from the 'epigenetics' community, a very large majority of them therefore had experience of cancer.

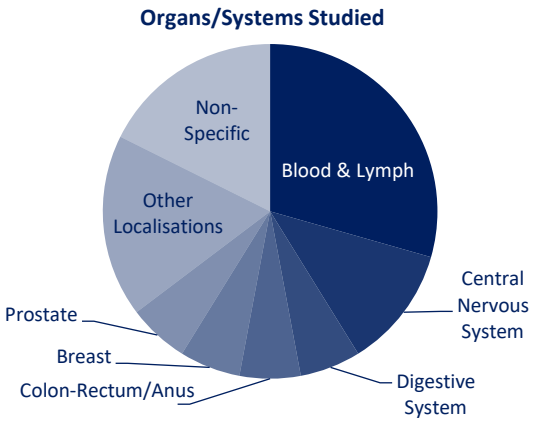
The projects funded concerned most of the factors known to be involved in epigenetic mechanisms: histone modifications (acetylation and methylation, 53% of projects), DNA modifications (methylation and hydroxymethylation, 41% of projects) and non-coding RNAs (in particular long non-coding RNAs (lncRNAs), 18% of projects). Other regulatory mechanisms, such as chromatin remodelling, were addressed by 12% of projects.





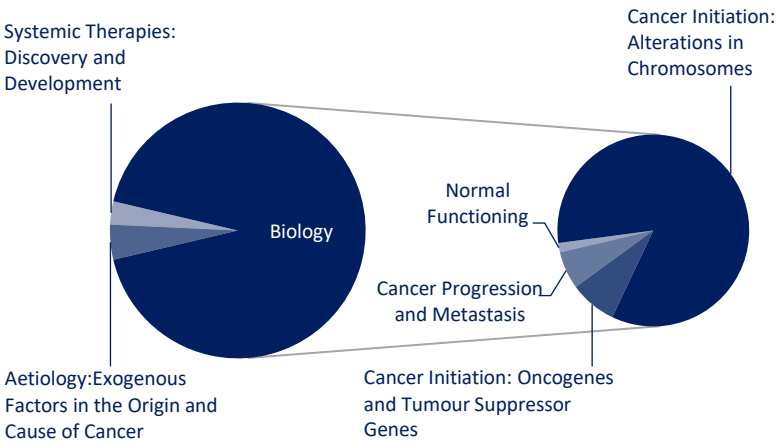
Just over 20% of the projects used public data produced in advance, as recommended in the calls for projects. These data mainly came from the Cancer Genome Atlas Program (TCGA, 43%) and the Roadmap Epigenomics Consortium (29%), more rarely from the Encyclopedia of DNA Elements project (ENCODE, 14%).

Haematological cancers were the most studied (29% of projects), followed by cancers of the central nervous system (12%). The digestive system, colon-rectum/anus, breast and prostate were also addressed by several projects (6% each). Nearly 20% of the projects did not focus on a particular type of cancer.



Almost all of the projects funded (93%) were in the "Biology" CSO category, with 85% in the "Cancer Initiation" sub-category ("Alterations in Chromosomes" or "Oncogenes and Tumour Suppressor Genes"). The remaining projects fell into the "Aetiology" (4%) and "Systemic Treatments" (3%) categories.

CSO Categories of the Projects



CONCRETE PROGRESS IN TERMS OF TOOLS AND SCIENTIFIC ADVANCES

The projects supported by the programme have led to the development of a number of tools and models. Progress has also been made, some of which goes beyond the field of oncology: identification of previously uncharacterised non-coding RNAs (lncRNA, dsRNA and miRNA), identification of interaction partners of epigenetic modulators.

Tools and Scientific Advances in the Epigenetics and Cancer programme

Tools developed

- Mouse or cell models: conditional KO mice for genes of interest, genetic models of cancer;
- Bioinformatics analysis pipelines: RNA sequencing data, methylomes;
- Other tools: in vivo chromatin mapping method, antibodies against methylated forms of histones, inhibitors of epigenetic modulators.

Scientific advances

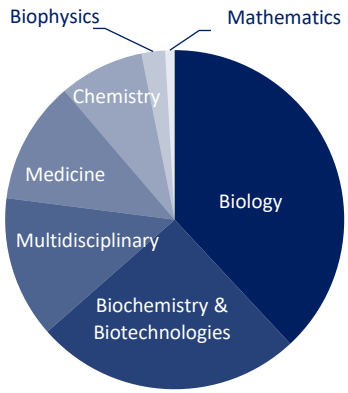
- Identification of new epigenetic modifications associated with cancer and, in more than a third of cases, description of their functional involvement in the disease; identification of new epigenetic modulators associated with cancer;
- Functional characterisation of epigenetic modulators or identification of their role in cancer, particularly in the regulation of oncogenes or tumour suppressor genes;
- Demonstration of links between epigenetic modifications and cancer phenotype/prognosis;
- Identification of potential therapeutic targets;
- Obtention of proofs of concept of the cancer activity of several compounds, including inhibitors of epigenetic modulators.

The follow-up to the projects supported by the programme concerned the functional impact of the epigenetic modifications observed, the study of the mechanisms of action of identified epigenetic modulators (e.g. non-coding RNAs, histone modulators or ubiquitination regulators) and the development of new inhibitors or the characterisation of identified inhibitors. Several laureates have also decided to pursue descriptive or screening studies to identify new epigenetic marks, new non-coding RNAs or potential therapeutic targets.

At the date of submission of the final reports, the projects had resulted in 49 publications, including 37 original articles, 11 literature reviews and one editorial. In addition, 3 articles were available for pre-publication.

Nearly 3/4 of the publications (72%) were open access, in line with action 13.5 of the Cancer Plan: "Sharing information and data nationally and internationally between professionals [and with the general public]".

Original Articles: Publication Domains of the Journals



The majority of original articles were published in biology journals (38%) or biochemistry/biotechnology journals (25%). Multidisciplinary, medical and chemical journals accounted for 14%, 12% and 8% of articles respectively.

KEY ISSUES FOR PROGRESS

For the programme's feedback seminar in October 2021, the project leaders had identified 3 key issues for the Epigenetics and Cancer theme, which were discussed at round tables. The conclusions drawn call on the concerned community to continue its reflection in several directions.

Issues Identified During the Feedback Seminar of the Epigenetics and Cancer Programme

Single cell approaches

- Scaling down to a truly single-cell level;
- Combining multimodal single cell technologies;
- Developing specific epigenetic technologies;
- Increasing the power of bioinformatics methods.

Chemical inhibitors of epigenetic modulators

- Improving the specificity and efficacy of molecules;
- Developing compounds compatible with clinical use, alone or in combination.

Functional consequences of epigenetic modifications

- Targeting epigenetic processes and characterising their actual causal effects;
- Developing specific methods with short impact windows.

Conclusion

The Epigenetics and Cancer programme has supported research into various types of epigenetic modification or regulation in relation to carcinogenesis. Several projects have used pre-existing data, in line with one of the programme's recommendations. Although some projects involved specialists in bioinformatics or chemistry, the community supported by this programme was essentially made up of biologists, with expertise mainly in epigenetics or oncology. With the creation of a new team and new research areas around this theme, the programme had a certain structuring effect in a context where the subject of epigenetics in oncology was still emerging. According to the laureates of the programme at the feedback seminar, the development of single-cell approaches, the development of chemical inhibitors of specific epigenetic modulators that are effective and have few side-effects, and the determination of the functional impact of epigenetic marks are the main current challenges in the field.