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

ITMO Cancer

The Systems Biology Programme

Multidisciplinary Approaches to Progress

in Complex Biologic Processes Modelling

Ex Post Analysis
2012-2017

(July 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, 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 Systems Biology Programme over the 2012-2017 period (5 editions[1]).

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 PIs 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*

[1] In 2016, the Systems Biology programme was replaced by a call for proposals specifically aimed at Tumour Heterogeneity and its Ecosystem. The programme was re-scheduled in 2017.

Context and Objectives of the Programme

The Systems Biology Programme was implemented by ITMO Cancer-Aviesan in the frame of the 2nd (2009-2013) and the 3rd (2014-2019) Cancer Plans:

- 2nd Cancer Plan: action 3.6 "*To fund alongside ANR the development of multidisciplnary approaches for complex biological system modelling (Systems Biology)*";
- 3rd Cancer Plan: objective 13 "*To provide means for an innovative research*", action 13.1: "*To guarantee independence and creativity of research by insuring a funding over 50% of the whole INCA and ITMO Cancer-Aviesan calls for projects funding on fundamental research*", with the objective to "*model key tumour processes in order to improve cancer understanding and patient care*".

Scope of the Systems Biology Programme (Call 2017)

- Modelling of the signalling pathways involved in the tumour progression in a specific cell context;
- Integration and modelling of the tumour microenvironment and its interactions;
- Modelling of interaction networks for new therapeutic targets prediction;
- Modelling of the multiscale molecular systems pharmacology (PK-PD) of cancer drugs and their association in combination therapies, whether targeted or not;
- Modelling of potential new molecular targets for pharmacology research;
- Modelling of treatment or treatment resistance responses;
- Modelling of the role of cancer initiation cells;
- Modelling of the cell adaptive dynamics (tissue malignancy progress and clonal evolution, etc.);
- Modelling of diagnosis, survey and treatment resistance, and population-based analysis for individual assessment;
- Development of models based on patient imaging and biologica data.

Systems biology is an upstream research field which integrates large datasets obtained at various levels (molecule, cell, tissue, organism) in order to understand interactions between biological system components and to model major biological functions, in normal or pathological conditions.

Cancers are in the scope of Systems Biology because they are themselves regarded as complex systems due to tumour and microenvironment interactions, and significant tumour heterogeneity.

The ambition of the Systems Biology Programme was **"**To *support the upstream multidisciplinary research in order to progress towards the complex processes modelling in the area of cancer.***"**

Research fields entering the scope of the Systems Biology Programme were defined by an ad hoc expert committee set by ITMO Cancer-Aviesan. Overall, eligible projects were related to the development of new models integrating data from molecular and cellular to clinical level, and/or related to the various steps of this continuum.

In line with this multiscale approach, the Systems Biology Programme had two objectives:

- To promote the development of new data integration tools and new prediction models:
  - ✓ In a medical application perspective (in terms of diagnosis, prognosis, new therapeutics effectiveness, etc.);
  - ✓ With the goal of acquiring fundamental knowledge related to oncogenic processes (tumour development, cell proliferation, signalling pathways, cell interactions, etc.);
- To gather in the Programme all disciplines involved in the data compilation, data mining and modelling (clinics, anatomopathology, biology, mathematics, chemistry, bioinformatics, etc.).

Ex Post Analysis of the Programme

KEY FIGURES

The analysis focused on the projects funded from 2012 to 2017, apart from outcomes which were only related to the projects funded in 2012 and 2013. These projects were completed at the date of the analysis and were discussed with their PI during a restitution seminar held in February 2018.

Main figures of the Systems Biology Programme*

Projects 2012-2017

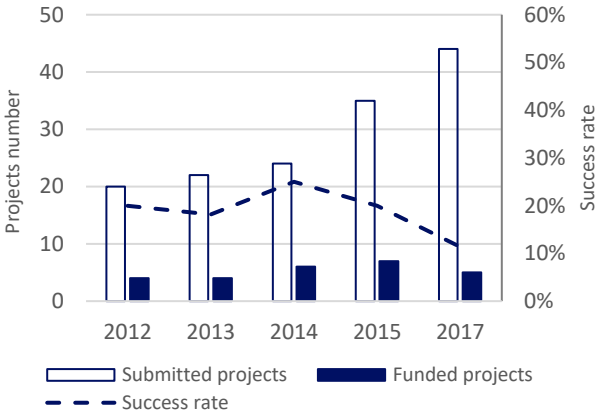
- 26 funded projects
- 25 PI (20% women)
- 80 partners
- €14.28M (median €531k for each project)
- Median age of PI: 43 y.o.

Projects 2012-2013 (outcome analysis)

- 8 projects
- 25 personnel hired (60% post-doctoral fellows, 24% engineers, 8% young researchers, 4% PhD, 4% master students)
- 11 international collaborations
- 1 research unit devoted to the systems biology field
- 5 patents
- 32 original articles

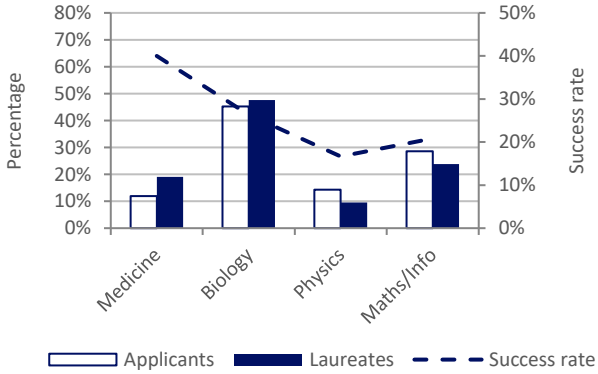
** at the date of the analysis (July 2018)*

Submitted and funded projects, success rate

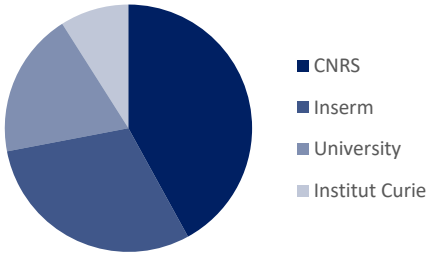


In 5 editions, 26 projects involving 80 partners, including 25 PI, were selected by the selection committees and funded. The success rate remained stable (circa 20%) from 2012 to 2015, then decreased in 2017 (circa 11%) due to an increasing number of submitted projects (44 in 2017, vs 21 in 2012) and the stability of the budget dedicated to the Programme (€2,66M in 2017, vs €2,78M in 2012).

Applicants, laureates and success rate among disciplines



PI Employers



The PI were mainly employed by CNRS (42%) and Inserm (30%), and in a lesser extent by University (19%) and the Institut Curie (9%).

A Multidisciplinary Commitment

Every project involved an average of 3 partners working in different disciplines. Applicants research fields were diversified, in accordance with the scope of the Programme which was to rally all the disciplines needed to get data integration and modelling all along the continuum from biology to clinics: 57% of the applicants had a biomedical profile (medicine or biology) and 43% a profile of physics, mathematics or bioinformatics. Biomedical profile applicants had a success rate slightly higher than the others: they accounted for 67% of the laureates, vs 57% of the applicants only.

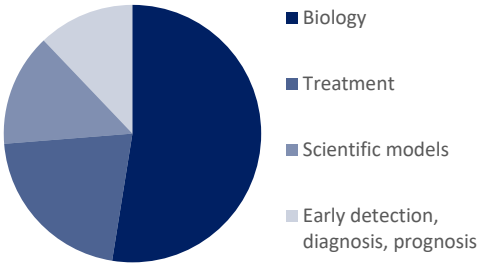
Almost one quarter of the laureates did not have a large experience in oncology. Programming the call encouraged therefore a new population of scientists specialised in biology, biophysics or bioinformatics to strenghten the ranks of the systems biology research field applied to cancer.

The structuring impact of the Programme on the field of systems biology applied to cancer led furthermore to the creation of a research unit dedicated to this research field and the building of 11 international collaborations.

A Preserved Two-Fold Orientation of the Programme (Clinical and Fundamental)

The funded projects were for a narrow majority in the CSO[2] categorie "*Biology*", then in the categories "*Treatment*", "*Scientific models*" and "*Early detection, diagnosis and prognosis*". This distribution reflects the duality of the Systems Biology Programme: to make progress both in the clinical practice and in the fundamental knowledge of oncogenesis.

CSO categorie of funded projects



The proportion of projects in the categories "*Biology*" and "*Treatment*" is higher in the Systems Biology Programme than within all cancer projects during the same period on the IRCP database[3], in accordance with the research fields defined. Projects in the field of biology were mainly in the subcategories "*Resources*" (including mathematical models) and "*Chromosomal aberrations*" or "*Oncogenes*" (in relation with cancer initiation), in accordance to the scope of the Programme.

Tools and models developped in the Systems Biology Programme (8 projects 2012-2013)

- 2 complementary pipelines of RNASeq analysis aiming at identify splice variants*;
- Exon functional annotation database*;
- 2 murine models*;
- Integration models of quantitative proteomics data and protein interaction network to identify dysregulated cell functions*;
- Model of gene, protein and physiological regulation aiming at predicting intervention impact*;
- 2 mathematical models of tumour growth (1 cellular automaton and 1 metastasis growth model)*;
- Algorithm for transcriptomics and interactomics data integration over time;
- Software for automatical analysis of fission yeast mitotic events in microscopy*;
- Mathematical model of mitotic spindles dynamics
- Logic model of tumour invasion*;
- Extensive map of molecular interactions throughout the epithelial-mesenchymal transition*, which was included in the Institut Curie Atlas of Cancer Signalling Network (ACSN).

** results published at the date of the analysis (July 2018)*

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

[3] Data from the IRCP (*International Cancer Research Partnership*) database.

TOOLS ALREADY VALUATED, KNOWLEDGE STILL TO BE CONFIRMED

The 8 funded projects in 2012 and 2013 allowed the development of around 15 tools, models or data sets (at the ex post analysis date). Some of them were made available in open access to the scientific community (RNASeq analysis processes, mitotic events analysis software, proteomic data sets). These tools were mainly published at the date of the analysis. Furthermore, the 8 funded projects led to 5 patent requests by 2 PI.

Scientific knowledge generated in the Systems Biology Programme (8 projects 2012-2013)

- Identification of a splice variant potentially involved in treatment resistance in breast and lung cancers;
- Identification of a driver gene in kidney cancer;
- Identification of 2 metabolic pathways involved in pancreatic cancer progression;
- Identification of a potential therapeutic target in pancreatic cancer;
- Identification of potential markers of hormone resistance in prostatic cancer;
- Characterisation of physical forces involved in mitotic spindles and of the fission yeast kinesin 8 role in the chromosome congression*;
- Validation of the low frequency of genetic alterations in ductal carcinomas in situ; identification of potential driver genes.

** results published at the date of the analysis (July 2018)*

The new fundamental knowledge (including markers, treatment targets or signalling pathways) was less disseminated (e.g., published) than new tools. This highlights how time to validate biological findings is incompressible.

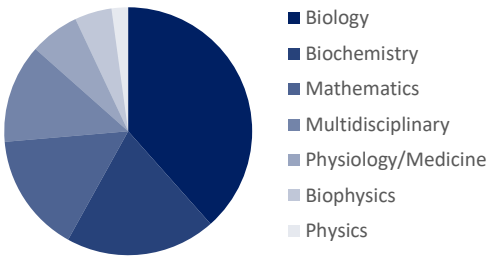
At the date of the analysis, the 8 projects funded in 2012-2013 led to 42 publications in peer-reviewed journals: 32 original articles, 8 reviews and 2 editorials.

About three-quarters (74%) of these publications were in open access, in accordance to the Cancer plan objective of *"sharing knowledge and data nationally and internationally between professionals [and the lay public]."*

Original articles were mainly published in reviews of good reputation in their field (ranked in the 1st quartile). This reflects the good quality of the research studies funded through the Systems Biology Programme.

Domains of the most represented journals were biology, biochemistry and mathematics. Multidisciplinary journals were also well represented. This distribution is in accordance with the multidisciplinary objective of the Programme.

Original articles: Publication domains of the journals



Conclusion

The success of the ITMO Cancer-Aviesan Systems Biology Programme indicates that France has a good reservoir of research teams in this field applied to cancer. The projects from these research teams were regarded by the evaluation committees as beeing of very good quality and presenting a great diversity, in accordance to the multidisciplinary approach of the systems biology.

When gathered in a restitution seminar, laureates have underlined that large-scale data integration and inclusion of the dynamic component of biological systems were both still crucial issues.

Ultimately, principles established through the systems biology could be transposed to systems medicine and systems pharmacology, two emerging research fields aiming at improving personalised treatments.