



**Tumor Heterogeneity and Ecosystem program
(THE Program)
2016**

This THE Program is organized by the Cancer ITMO, in collaboration with the CBDE ITMO (Cell biology, development and evolution), the Health Technologies ITMO of the French National Alliance for Life and Health Sciences (AVIESAN) with the Institut National du Cancer (French National Cancer Institute) and Inserm within the context of the French Cancer plan. The operational management is led by Inserm.

On line submission:

https://www.eva2.inserm.fr/EVA/jsp/AppelsOffres/CANCER/index_F.jsp

Letter of intent submission deadline: **April 15th, 2016**

Full project application submission deadline: **July 12th, 2016**

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1. Context and aims of the THE Program

1.a. Context

In the last years, the current field of cancer research warrants to take into account tumor heterogeneity and tumor micro-environment or ecosystem.

Several models of tumor evolution have been proposed and, in each case, it is clear that several clones of tumor cells arise and compete at different time points of the tumor's development (initiation, development, dissemination). This heterogeneity raises a problem when therapy fails and cancer patients face metastases or relapses.

Tumor Heterogeneity: New therapeutic strategies are needed that take into account tumor heterogeneity. Indeed, whole genome sequencing, while being still very expensive for large-scale use, is seen as a central tool to define novel prognostic classification and adapted targeted therapies. Is this strategy appropriate when several tumor cell clones bearing different genotype and phenotype co-exist and may be difficult to detect and monitor? What is the relevance of a given mutation or mutation combination in tumor development? The genotype-phenotype map needs to be defined in a dynamic manner to define the resulting functional modification at the cell/clone level and to anticipate the need/or not to eradicate these cells/clones. Alongside WGS and mutational analysis, epigenetic modifications, altered protein functions may also intervene in modulating altered signalling pathways and as such, need to be integrated into the dynamic genotype-phenotype map of tumor heterogeneity. This functional analysis requires both *in vivo* and *in vitro* approaches, *in silico* as well as mathematical modelling.

Tumor Heterogeneity as an eco-system: Considering tumor heterogeneity as an ecosystem, results in seeing the tumor at each step of its development and unravelling the interactions between the transformed cells and their direct microenvironment during the evolution of this process. The tumor micro-environment is instrumental in contributing to the initiation, development and dissemination capacities of a given clone via bi-directional interactions between tumor-associated cells (fibroblasts, macrophages, lymphocytes, adipocyte...) and the tumor cells at whatever stage of the tumor's development. Unravelling these cross-talks requires in-depth investigations to define which positive and negative factors need to be efficiently targeted. In essence, the sequential acquisition of mutations, the longitudinal evolution and selection of clones in response to environmental cues all need to be integrated into a global view of tumorigenesis in order to define future therapies and monitoring methods. A number of partners in the microenvironment of the tumor have been identified and are the matter of active research. These partners are in part composed of carcinoma-associated fibroblasts (CAF), endothelial cells and/or the complex host immune system. Angiogenesis is known to play a crucial part in cancer cell survival and cancer initiation. Recent findings stress the role of tumor angiogenesis and immune microenvironment. They provide evidence to support a leading role in the assessment of cancer prognosis, and novel therapy avenues.

1.b. Aims of THE Program

Based on these considerations, Cancer ITMO, CBDE (Cell Biology, Development and Evolution) ITMO and Health Technologies ITMO, launched a program, in the context of the 2014-2019 Cancer Plan, to fund research projects in the field of functional **T**umor **H**eterogeneity cell relationships in the tumor's Ecosystem: "**THE Program**".

The aims of THE Program are to promote the implementation of a critical mass in terms of resources and skills to conduct research projects of an interdisciplinary nature ("**the Projects**"), requiring cooperation between teams from different thematic fields such as cell biology, genomics and (epi) genomics, mechanobiology, physics, systems biology, chemistry, pathology, and patient care, in an integrated way using mathematical modelling and *in silico* methods. THE Program will lean on basic knowledge up to and including translational research (excluding clinical research).

The THE Program is organized in 4 work packages (WP1, WP2, WP3, WP4) to fulfil the objectives of THE program.

WP1: multidisciplinary projects

The present call applies to WP1. Through the selection of « **the Projects** » financed by the Cancer Plan, WP1 aims to answer the following questions:

- ✚ How may two-way interactions of tumor cells with their tumor microenvironment hamper or promote tumour progression?
- ✚ How can we model signaling pathways involved in bi-directional exchange between tumor cells and the microenvironment?
- ✚ Is it feasible to re-program the tumor microenvironment, especially mesenchymal cells, endothelial and immune cells to eradicate cancer?
- ✚ Can models of tumor heterogeneity in the ecosystem be obtained from in-vivo data or 3D models, within the constraint of the microenvironment of the primary tumor and/or metastasis?
- ✚ What is the influence of microbiota on tumor stroma architecture?
- ✚ What methods should be developed to predict the efficacy, resistance to treatment or recurrence of the tumor, according to the degree of interaction with the tumor microenvironment?
- ✚ What are the built-in mechanisms leading to the epithelial-mesenchymal transition (EMT-like) and reverse mesenchyme-epithelia (MET-like) leading to metastasis?
- ✚ What innovative methods or algorithms are required to evaluate treatments (combinations, new strategies, administration schedule) targeting sub-clonal somatic events of the tumor or its microenvironment?

Are considered out of scope:

- ✚ The genetic or epigenetic approaches based only on genome and epigenome maps of tumor cells;
- ✚ Clinical trials.

Subsequently, the following WPs will be developed :

WP2: Knowledge / know-how sharing

WP2 aims to foster internal communications within THE program for exchange of knowledge and skills. In this aim various workgroups or task-forces will be organized following good practice procedures of confidentiality, integrity, intellectual property awareness and protection as defined in the consortium's agreement.

WP3: Resources sharing

WP3 aims to exchange biological resources, digital data and algorithms in accordance to the grant agreement defined by the WP3 leader and the supervisory board and validated by the steering committee.

WP4: Coordination, training, communication/dissemination

WP4 aims to organise the overall coordination and management of THE Program. WP4 will define the rules to provide adequate means of dissemination inside and outside the Consortium of the data and decisions taken between the Steering Committee, the Coordinator and the Supervisory Board and the Networks.

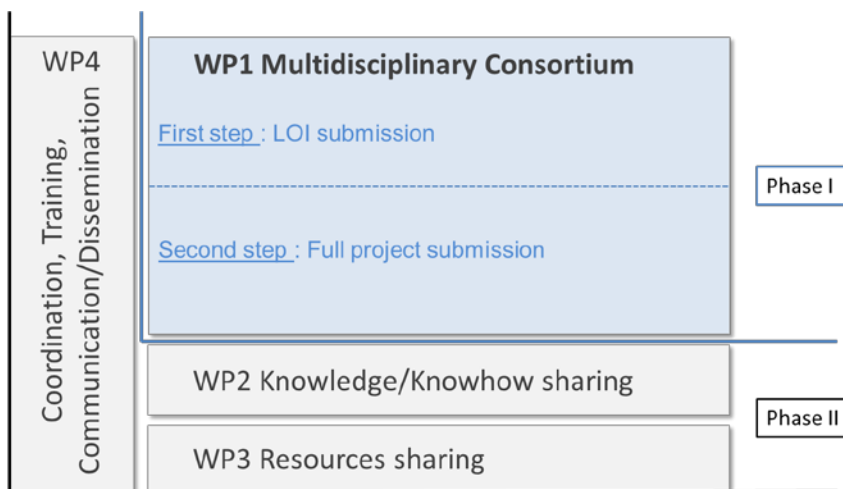
THE program runs in 2 phases:

- Phase I : Call for proposals, WP1 tuning/setting up

The WP1 of the present application proposal is composed of projects which will be carried by multidisciplinary networks, “**the Projects**”. The WP1 tuning will include the submission of letters of intent and thereafter the submission of full scientific projects. The Steering Committee, as part of the Program’s Networking, will invite the applicants of the selected LIs to a co-building project meeting before the full application deadline to improve their network and final project.

- Phase II : Whole THE Program tuning (WP2, WP3, WP4)

The selected networks will work together, in a consortium, through the 3 work packages to fulfill the objectives of THE Program. The consortium will define the WP2 to WP4 tasks (which objectives are defined above) during the kick-off meeting.



2. Actors and bodies involved in THE Program

2.a. Actors of THE Program

Coordination: The coordination is led by THE program’s coordinator. He/she is assisted by a Supervisory Board involving the principal investigators of WP1’s projects and WP2 and 3 leaders.

THE Program’s coordinator: He/she will be chosen during the kick-off meeting by the Supervisory Board among the principal investigators and team leaders and appointed by the Steering Committee. He/she will be assisted in its coordination functions by a project manager. In addition to his/her scientific and technical role, the coordinator is responsible for the networks coordination and the management and monitoring of WP2 to 4 tasks. The coordinator is responsible for the interactions with Inserm, financing body of THE Program within the context of the French Cancer Plan. He/She reports to the Steering Committee at the requested time intervals and submits problems, anticipated risks and resolution policy to the Steering Committee. He/she is responsible for organizing the collaboration between the networks and meetings as well as monitoring progress and communicating results.

Workpackage leader: They will be appointed during the kick-off meeting among the principal investigators and the team’s leaders. In addition to his/her scientific and technical role, the workpackage leader is responsible for the advancement of the WP’s planned actions. He/she is responsible for sending the progress reports to the coordinator. He/She is connected to the other workpackage leaders. The WP leaders are members of the supervisory board.

Consortium: The consortium is made of all the selected networks.

At the project level, the actions are led as follows

Principal investigator: For each project, the principal investigator is chosen by the participating teams among the team's leaders. In the case of an isolated team application, the principal investigator and the team leader are the same person. The principal investigator is in charge of submitting the letter of intent and, after the letter selection, the submission of the full project. In addition to his/her scientific and technical role, the principal investigator is responsible for organizing the collaboration between the teams involved in the network and meetings as well as monitoring progress, the production of deliverables and communicating results. Moreover, he/she is involved in the coordination of THE Program by participating to the Supervisory Board.

Team leader: Each team is under responsibility of a team leader (who can be different of the hierarchical head of the team). In addition to his/her scientific and technical role, the team leader speaks on behalf of the team and is responsible for the advancement of the part of the program which is conducted in his/her team. He/she reports to the Principal Investigator.

2.b. THE Program Evaluation body

Evaluation committee: It is appointed by the steering committee. It is composed of international scientific personalities. This committee will be in charge of the selection of the letters of intent, of making recommendations for bringing together research teams and of the selection of the networks' full projects.

2.c. THE Program Steering Committee

Steering committee: The steering committee is composed of cancer ITMO, Cell biology, development and evolution (CBDE) ITMO and Health Technologies ITMO directors, of ITMO experts and potentially of one or several members of the scientific council. The steering committee will monitor and validate THE Program activities forwarded by the Supervisory Board and the coordinator for its duration. It ensures the interactions with Inserm, financing body of THE Program within the context of the French Cancer Plan.

3. Phase I = Call for proposals, WP1 setting up

The establishment of the multidisciplinary networks will be assisted by an international scientific council which will select the teams and will make recommendations for bringing together these research teams. This phase will run in two steps: first step for the selection of the networks/research teams based on the letters of intent; second step for the selection of the whole networks. For THE Program's success, it is necessary that the networks are composed of multidisciplinary and complementarity teams. To this effect, the selected LI's principal investigators will meet during a co-building project meeting in order to refine or improve the projects for the second step.

3.a. Eligible teams

Teams belong to the following bodies:

- ✚ Public-sector research institutions (EPST, EPIC, etc.),
- ✚ Institutions of higher learning (universities, etc.),
- ✚ Research foundations,
- ✚ Public-sector health care institutions,
- ✚ Other bodies involved in the research field.*

*The participation of industrial partners and/or foreign teams is possible as long as they provide their own funding in THE Program.

The team leader has to:

- ✚ Be a permanent employee of a public-sector research body, a public institution of higher education or a public health care institution;
- ✚ Devote at least 30% of his/her time to the project.

3.b. Step 1: letter of intent

1. Letters of intent submission

An isolated team or a network of several teams can submit a letter of intent. This letter should briefly describe the project and indicate how the expertises/skills of the isolated team or the network of several teams is necessary to overcome the conceptual or technological obstacles identified (§,1 “Context and aims of THE program”).

In the case of an established network, the letter of intent will have to prove the relevance of associating these teams and why this association is important to answer to THE Program aims.

The principal investigator is in charge of submitting the letter of intent (cf §2 “Actors and bodies involved in THE Program”).

2. Selection of the letters of intent by the evaluation committee

The letters of intent will be evaluated according to the following criteria :

- Quality and novelty of the research project
 - Clarity and originality of the objectives and research hypotheses,
 - Novelty of the approaches beyond the current state-of-the-art.
- Expertise/skills
 - Relevance of the expertise and skills of the team or the network according to the objectives of THE Program,
 - Ability to combine expertise and skills in a wide network.
- Team(s)' excellence
 - International notoriety,
 - Team(s)'leader(s) skills in his/her field of research.
- Added value of the network (if relevant)
 - Complementarity of the research teams,
 - Principal investigator's skills in his/her field of research and in coordination of research.
- Quality of the research environment
 - Human resources involved in THE Program,
 - Available infrastructures to conduct THE Program.

3.c. Step 2 : Full projects

1. Co-Building project meeting

The selected principal investigators and team leaders will be invited to a meeting in order to build several optimised networks. The newly formed networks will then submit a full project to answer to THE Program's aims.

Date of the meeting: June 13th and 14th, 2016

2. Full proposal submission

Following the meeting, the established networks will have to:

- Submit a project allowing to answer to THE Program's aims,
- Describe the involvement of each team,
- Explain the complementary of the teams,
- Identify the milestones and results planned,
- Establish a 4 year financial plan,
- Identify the principal investigator of the project.

3. Full projects selection by the evaluation committee

The evaluation committee will meet again to select among the submitted projects. The selected networks will receive a grant to carry out their projects.

Networks and Projects will be evaluated according to the following criteria:

- ✚ Relevance of the project to the objectives of the program
 - Focus of the project on microenvironment and tumor heterogeneity
 - Translational potential of the project
- ✚ Innovation and development:
 - Innovative nature (strategy, concept, technology, etc.),
 - Perspectives in terms of later developments.
- ✚ Scientific qualities:
 - Project relevance and originality,
 - Positioning of the project in the national and international context,
 - Clarity of the objectives.
- ✚ Principal investigator and participating teams:
 - Skills of the Principal investigator in his/her discipline
 - Complementarity and multidisciplinary of the various associated teams and their integration into the project,
 - Organisation of collaboration between candidate groups, planning review document production, holding follow up meetings and formatting results.
- ✚ Methodology and feasibility:
 - Methodological relevance,
 - Justification of the biological resources availability
 - Project environment (human resources, host structure),
 - Credibility of the Project's calendar and of the financing requested.

3.d. Time line

Date of publication of the call for proposals:		February 2016
Step 1 : Letters of intent	Opening of submission site	February 15 th 2016
	Submission deadline	April 15 th 2016
	Tentative meeting date for the evaluation committee	End of May 2016
Step 2 : Full Projects from the selected LIs	Date of co-Building projects meeting	June 13 th and 14 th 2016
	Submission deadline	July 12 th 2016
	Tentative meeting date for the evaluation committee	Middle of September 2016

3.e. Application's file submission

1. Submission procedure

For each step (letter of intent submission and full project submission), the application submission is made of two parts:

1- Registration on the EVA website and online application submission

Website: https://www.eva2.inserm.fr/EVA/jsp/AppelsOffres/CANCER/index_F.jsp

2- Paper format transmission

The application file, including all the documents submitted online, has to be sent to the following address :

Inserm – DESP
Plan Cancer
Programme HTE 2016
101, rue de Tolbiac
75013 Paris

2. Application's file

a) Letter of intent

The applicant's file is composed by:

- **The letter of intent (template to upload to the EVA website)**

Electronic submission deadline: **April 15th, 2016**, before 4 pm.

Paper format transmission deadline: **April 15th, 2016** (submission date based on the postmark).

Applicants are strongly advised not to wait until the closure deadline to submit their application.

b) Full project

The applicant's file is composed by:

- **The project (template to upload to the EVA website)**
- **The financial file (excel template to upload to the EVA website)**

Electronique submission deadline : **July 12th 2016**, before 4 pm.

Paper format transmission deadline: **July 12th 2016** (submission date based on the postmark).

Applicants are strongly advised not to wait until the closure deadline to submit their application.

3.f. Publications of the results

The results will be published on the EVA website of Inserm.

4. Phase II: THE Program global tuning (WP2, WP3, WP4)

The steering committee will organize a kick-off meeting of THE program with the selected networks. This meeting will aim to define the consortium goals, the management and the responsibilities of all the participating teams. The consortium will appoint THE Program coordinator. THE Program's coordinator and the Supervisory Board will define the goals, deliverables and milestones of WP2 and WP3 and will appoint the WP2 and WP3 leaders. The coordination modalities will be also determined during this meeting (WP4). The coordination will have to be straightforward with high reactivity. Its tasks will include the scientific and budget monitoring of the WP2 to 4. The WP4 leader will be in charge of results dissemination and valuation. A consortium agreement will have to be established and sent to the steering committee within 3 months from the date of the kick-off meeting.

5. THE Program monitoring

Once a year, the steering committee will meet to follow the projects advancement and make some recommendations of redirections if necessary. This analysis will be done with the help of an advancement report by THE Program coordinator in collaboration with the WP leaders and the principal investigators and/or by an oral presentation to the Steering Committee.

6. Contacts

For further information, please contact:

- ✚ For scientific and technical aspects: plancancer-HTE@inserm.fr
- ✚ For problems relative to the electronic submission: eva@inserm.fr