# International Conference PHILOSOPHY AND CANCER (IHPST Paris) April 28,2016


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## Conference PHILOSOPHY AND CANCER

**APRIL 28TH, 2016**
Institute for the History and Philosophy of Science and Technology (IHPST)
13 rue du Four
75006 Paris
Second Floor, conference room
9:30 – 18:00

Organized by Lucie Laplane (CNRS IHPST & UMR 1170) and Thomas Pradeu (CNRS & University of Bordeaux).
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**Program**

9:30 - 9:40 Thomas PRADEU & Lucie LAPLANE
Opening

9:40 - 10:10 Michel MORANGE
The concept of oncogene. What does it mean 40 years after its discovery?

10:10 - 10:50 Eric SOLARY & Lucie LAPLANE
Toward a more integrated understanding of cancer: the case of chronic myelomonocytic leukemia

11:00 - 11:30 Break

11:30 - 12:00 Pierre-Luc GERMAIN
Multi-level somatic selection in cancer

12:00 - 12:30 Sara GREEN
Cancer across scales

12:30 - 14:30 Lunch

14:30 - 15:10 Andreas BIKFALVI & Thomas PRADEU
The concept of the tumor microenvironment

15:10 - 15:40 Marta BERTOLASO
Philosophy of cancer. Overcoming dichotomies in life sciences

15:40 - 16:10 Break

16:10 - 16:40 Jean-Pascal CAPP
Cancer and stochastic gene expression: from a new theoretical model to

epistemological questioning

16:40 - 17:10 Melinda FAGAN
Pathways to the clinic: cancer stem cells and models of development

17:10 - 18:00 General discussion

**ABSTRACTS**

**The concept of oncogene. What does it mean 40 years after its invention?**

Michel Morange
ENS, Centre Cavaillès, Paris

The oncogene model was simple: the mutation of a limited set of genes participating in intercellular communications was involved in the genesis and development of cancer.
Forty years later, the situation is far from being as simple. Emphasis has recently been put on two newly discussed aspects of cancer, the clonal selection of tumor cells and the possibility that epimutations replace mutations that are fully compatible with the oncogene model. Some new observations were included in the model, although they were not expected: the importance of the microenvironment in which the tumor develops as well as the role of the immune reaction against the tumor, the role of stem cells, and the occurrence of catastrophic events in the genome of tumor cells.
Two major issues have emerged, that make the initial model not false, but less significant: the dramatic increase in the number of oncogenes involved in the formation and progression of tumors, and the absence of mutations in some other tumors. In the first case, the distinction between driver and follower mutations does not fully solve the issue: the heuristic value of the oncogene model decreases if too many genes, and too many gene categories are involved in tumor formation. The absence of mutations in some cancers means that the oncogene model is not valid for all forms of tumors.
The most puzzling fact is that no new models have so far emerged from these difficulties. The importance of other levels of organization than the molecular and cellular one in the genesis of tumors is more a philosophical stance than a scientific research program. The present situation of cancer research is very similar to that existing in the 1960s, before the emergence of the oncogene model, when a wealth of potentially competing approaches of cancer coexisted more or less peacefully.

**Toward a more integrated understanding of cancer:**
**The case of chronic myelomonocytic leukemia**

Eric Solary
UMR 1170 (Inserm, Gustave Roussy Cancer Campus, Univeristy Paris-Saclay)

Lucie Laplane
UMR8590-IHPST (CNRS, University Paris I Panthéon-Sorbonne)
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Cancer biology is an increasingly complex field of research. Cancer development depends on factors that are diverse in nature (genetic, epigenetic, phenotypic, and functional) and that act at various levels of organization (genome, individual cells, populations of cells, tumor microenvironment, and more systemic reactions from the organism). Numerous explanatory frameworks are developed to understand the role of each of these factors and levels of organization. Yet they tend to be developed separately and an integrative framework highlighting the interaction between these factors is still lacking. For example, the cancer stem cell (CSC) theory and the clonal evolution (CE) theory provides two independent explanations of two different kinds of intratumor heterogeneity (ITH). The CE theory accounts for genetic ITH: mutations occur in various cancer cells that are then subject to selection. The CSC theory accounts for phenotypic and functional ITH: CSCs can give rise to cells of various cell types and at various level of differentiation. But how does differentiation affect clonal evolution and how does clonal evolution affect differentiation is poorly investigated. In this talk, we aim to build a more integrative understanding of CE and differentiation in the development and progression of a particular leukemia?chronic myelomonocytic leukemia.

**Multi-level somatic selection in cancer**

Pierre-Luc Germain
European Institute of Oncology, Milan

Lean and Plutynski (2016) have recently argued that cooperative interactions? between cancer cells make the tumor an integrated unit? With collective fitness and selection acting on it.
More specifically, they argued that early cancer progression is characterized by an influence of group membership on individual fitness (MLS1 following Damuth and Heisler 1988), while metastasis represents a case of selection acting on groups themselves (MLS2). After a brief review of some of the most relevant evidence, I proceed to evaluate these two claims.
Assuming that co-localization can be meaningfully interpreted as group membership, I show that the release of angiogenesis or growth-promoting factors, as well as the degradation of the extracellular matrix, provide good examples of MLS1, i.e. the effect of group membership on the fitness of individual cells. However, the straightforward reduction of the phenomena to micro-environmental variations, and the difficulty in identifying groups and their boundaries, challenge the utility of a multi-level approach to their study.
The claim to MLS2, in turn, is predicated on an understanding of metastasis as an event of tumor-level reproduction. I therefore first discuss the fundamental conditions rendering such an interpretation sound, and some of the available empirical evidence questioning their fulfillment. I show how Godfrey-Smith's (2009) framework of Darwinian populations can be used to identify and assess the dimensions relevant for tumor-level selection, and argue that tumors hardly meet the requirement for a Darwinian population. Finally, I discuss two dimensions left aside by Godfrey-Smith's framework, but critical to the present issue: the size of the population, and the relevant time-scale. These further question the relevance of higher-level selection for cancer biology.

**Cancer across scales**

Sara Green
University of Copenhagen, Copenhagen

Conflicting views on whether cancer is a genetic, cell-based or tissue-based disease have intriguing theoretical and practical implications. Current accounts differ with respect to the delineation and nature of the phenomenon to be explained. Among these are conflicting ontologies of biological systems in general and cancer in particular, e.g. whether cancer cells with significant molecular properties exist and whether mutations can be said to be the cause or result of cancer. Among the practical implications are issues pertaining to the design of relevant experiments and models, and about what researchers take to be the most promising strategies for cancer treatment. In this paper I explore whether the viewpoints are methodologically compatible in the same sense as models relying on conflicting idealizing assumptions can be integrated in multi-scale models in biology and physics. Moreover, I highlight important ramifications of multi-scale modeling of cancer including the role of boundary conditions to clarify the controversial notion of “downward causation”

**The Concept of the tumor microenvironment**

Andreas Bikfalvi
Angiogenesis and Tumor Microenvironment Laboratory (INSERM U1029), University Bordeaux
Thomas Pradeu
Immuno ConcEpT Laboratory (CNRS U 54), University Bordeaux

Beyond uniquely genetic characterizations of cancer, it is now well-known that the Tumor Micro-environment (TME) is an important driver of tumor development. Interactions between vascular cells, immune cells, fibroblasts have been identified that control growth invasion and metastasis of many tumors. Molecular drivers of the TME have been identified and are currently the subject of intense research. Yet the current general concept of the TME is still fragmentary, as it lacks fully descriptive and explanatory power, and has a number of drawbacks. The philosophy of biology is an emerging area in philosophical studies with, in some cases at least, a potentially important impact on the biological and medical fields themselves. In recent years, several philosophers of biology have started to work on the definition and the understanding of cancer, but the scientific and medical communities have hitherto largely ignored those reflections. Some light has been shed into this area by reexamining the notions of multistage progression or mechanisms in cancer biology. However, a comprehensive attempt in conceptualizing the TME in a way that would articulate lessons taken from philosophy, biology, and medicine, has yet to be undertaken. In this presentation, we will review some of the current knowledge related to the TME and discuss relevant historical and conceptual issues.

**Philosophy of cancer: Overcoming dichotomies in life sciences**

Marta Bertolaso
Università Campus Bio-Medico di Roma, Italy

Continuing high cancer incidence and mortality raise concern about the prevailing overall approach to the control of this disease. Following scientific literature I will first analyze some fundamental dichotomies between traditional and revisionist viewpoints and spell out some biological and methodological issues. The tensions in cancer research ask for a new synthesis that will account for inter-level biological dynamics by overcoming the reductionist and anti-reductionist debate and a “mereological” framework (i.e., a problem setting that takes parts-whole organization as a core assumption). In particular I will argue that current issues in cancer research imply a dynamic and relational view of living entities. What follows is also a new epistemological view of scientific practice that, while opening new possibilities of action, accounts for the successes and limits of the available explanatory models (Bertolaso 2016).

Bertolaso M (2016) Philosophy of Cancer. A Dynamic and Relational View. Springer Series HPTLS, in press

**Cancer and stochastic gene expression:**
**From a new theoretical model to epistemological questioning**

Jean-Pascal Capp
INSA/Université Fédérale Toulouse Midi-Pyrénées, LISBP (UMR CNRS 5504 ; UMR INRA 792)

Researches performed on cancer along the XXth century led to the paradigm of its genetic origin. The most popular research themes in recent years (whole cancer genome sequencing, epigenetics, cancer stem cells, tumor microenvironment) provide results that are generally interpreted and integrated in the dominant framework without any questioning. Nevertheless the reductionist approach of the disease based on oncogenes and tumor suppressor genes now shows its limits. Many results, by the contradictions they highlight in the genetic model, show the need for an alternative cancer model able to coherently integrate them and to go beyond genetic reductionism. After mentioning some of these contradictions, a new theoretical model of cancer will be proposed. It might solve them by admitting a role for genetic alterations in the disease progression, while considering its origin at the tissue level and stochastic gene expression as a driving force. Finally, this presentation will raise several epistemological questions about development biology and the confrontation between reductionism and holism in biology.

References:
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**Pathways to the clinic: cancer stem cells and models of development**

Melinda Fagan
University of Utah, USA

Cancer stem cells (CSC) are thought to be a small subpopulation of self-renewing stem cells within a tumor or blood-borne cancer, which are responsible for maintaining and growing the malignancy. The concept has profound clinical implications. However, after more than a decade of research, the evidence for CSC is equivocal and clinical translation of such results as there are has been lacking. I examine conceptual and evidential challenges blocking clinical translation of CSC, and propose a way forward. Briefly, my solution is to distinguish two CSC concepts (or models) with different substantive content, suited to their respective purposes and criteria for success: basic and clinic-oriented. Contrasting the two models charts a path for clinical translation of CSC. I also assess some basic assumptions about development implicit in CSC models.