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Reuniting philosophy and science to advance cancer research

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ABSTRACT

Cancers rely on multiple, heterogeneous processes at different scales, pertaining to many biomedical fields. Therefore, understanding cancer is necessarily an interdisciplinary task that requires placing specialised experimental and clinical research into a broader conceptual, theoretical, and methodological framework. Without such a framework, oncology will collect piecemeal results, with scant dialogue between the different scientific communities studying cancer. We argue that one important way forward in service of a more successful dialogue is through greater integration of applied sciences (experimental and clinical) with conceptual and theoretical approaches, informed by philosophical methods. By way of illustration, we explore six central themes: (*i*) the role of mutations in cancer; (*ii*) the clonal evolution of cancer cells; (*iii*) the relationship between cancer and multicellularity; (*iv*) the tumour microenvironment; (*v*) the immune system; and (*vi*) stem cells. In each case, we examine open questions in the scientific literature through a philosophical methodology and show the benefit of such a synergy for the scientific and medical understanding of cancer.

Key words: driver mutation, clonal evolution, multicellularity, tumorigenesis, tumour microenvironment, oncoimmunology, cancer stem cells, philosophy of cancer.

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I. INTRODUCTION

The biological complexity and heterogeneity of cancer make it very difficult to circumscribe, apprehend, control, and cure. Oncology currently faces countless challenges, not only biological and clinical but conceptual and theoretical too.

The importance of conceptual clarity is indisputable when considering, for example, central notions such as 'cancer stem cells' (Batlle & Clevers, 2017) or 'tumour-associated neoantigens' (Schumacher, Scheper & Kvistborg, 2019). In such cases, the definition one adopts can have a major impact on the experimental and clinical work that follows and on the interpretation of results, as demonstrated by philosophers (Laplane *et al.*, 2018; Pradeu, 2019; Fagan, 2021). For example, the therapeutic strategy of targeting cancer stem cells is based on the definition of stemness as a constitutive property of the cells, but other conceptions of stemness are possible, suggesting alternative therapeutic strategies (Laplane & Solary, 2019). The benefit of defining terms and engaging in theoretical thinking is also clear when considering how other scientific disciplines could shed light on cancer biology – for instance, when evolutionary biologists ask in what sense tumours 'evolve' (e.g. Maley *et al.*, 2017), when ecologists argue that tumours have properties of ecosystems (Pienta *et al.*, 2008), when developmental biologists suggest that tumours can be seen as developing 'organs' (Egeblad, Nakasone & Werb, 2010), or when physicists characterise tumours as material objects where physical forces and properties influence progression and treatment (Nia, Munn & Jain, 2020). One particularly fruitful approach for connecting different disciplines is through the formulation of integrative theoretical frameworks, especially when they are mathematically formalised (Bialek, 2018), as illustrated by many stimulating examples in oncology (e.g. Frank, 2003; Pacheco, Santos & Dingli, 2014). Conceptual clarification and interdisciplinary integration of methods and knowledge can thus enrich our understanding of cancer and suggest new therapeutic avenues.

Continuing a long history of theoretical thinking in oncology since at least the 19th century, many theories of cancer coexist today. Yet most of them face four difficulties. First, they tend to be *narrow* in scope, for example by proposing that one aspect of cancer might be considered as 'the' cause of cancer and/or as the best possible therapeutic target (e.g. somatic mutations, aneuploidy, telomerase activity, cancer stem cells) (Paduch, 2015). Second, they often remain *speculative*, lacking compelling empirical support and/or direct clinical applications. Third, they are generally *disconnected from medical theories of cancer*, which are understood as descriptions of common patterns of neoplastic development in patients (Clark, 1995). Finally, most of them remain *verbal*, i.e. are not expressed in mathematical form, although major contributions to the mathematical modelling of cancer have been made in the last two decades (Komarova, 2005; Frank, 2007; Altrock, Liu & Michor, 2015). Overcoming these difficulties is necessary for building a genuinely fruitful theoretical oncology.

We argue that philosophy can contribute to this aim through its classic tools of conceptual clarification, critical assessment of scientific assumptions, analysis of argumentative consistency, formulation of new concepts, theories or research programs, and connection between different disciplines (Pradeu *et al.*, 2021). Note that (*i*) philosophy here refers to a set of tools or methods, rather than content (the idea is not to apply traditional ideas from philosophers to cancer, but to use philosophical methods); (*ii*) we defend a pragmatic use of philosophy with the clear intent of improving oncology; (*iii*) these methods are also used by scientists, especially conceptually inclined ones. So what we are describing here is ultimately a continuum of scientific contributions. Philosophers, because of their strong background in logic and argumentative reasoning, can operate the above

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tools with higher degrees of thoroughness and freedom. Scientists have better experimental skills and more expert knowledge in their area of specialisation. This spectrum of skills makes the cooperation between these two communities particularly fruitful to build a theoretical oncology (Laplane *et al.*, 2019*b*).

To make progress in this direction, we have gathered philosophers belonging to a tradition of philosophical intervention in science with scientists from various backgrounds – biologists, medical doctors, physicists, and mathematicians – to illustrate, through the examination of six major challenges, how insights coming from conceptual, theoretical, and philosophical perspectives can advance current and future knowledge in cancer biology (Fig. 1).

II. HOW TO UNDERSTAND THE ROLE OF MUTATIONS IN CANCER AND HEALTHY TISSUES

The oncogene and tumour suppressor gene framework, according to which cancer emerges from mutations of particular genes, gained dominance in the 1980s (Morange, 1997). However, progress in sequencing technologies resulted in the discovery of an ever-expanding list of potential oncogenes, complicating the understanding of which mutations play a causal role in cancer, as analysed by a philosopher (Plutynski, 2021*c*). Moreover, it has become increasingly clear that normal tissues also accumulate mutations with age, giving rise to clones which may or may not transform into overt cancers (Wijewardhane, Dressler & Ciccarelli, 2021). Beyond genes, the tumour micro- and macro-environment (see Section V) as well as epigenetic alterations also contribute to cancer development.

Cells accumulate mutations. Yet most of these mutations have no obvious impact on cell function or phenotype. Which mutations, then, are involved in cancer, and how do we know? The concept of 'driver mutations' offers, in theory, a simple way to distinguish the mutations that matter in cancer from those that play no causal role, called 'passenger mutations'. However, what it means to play a causal role in cancer is not always straightforward. First, what do we mean by 'causal'? And can it be quantified? Mathematical theories of causation based on structural models and philosophical accounts of causation could help clarify the causal role of driver mutations in the future (Woodward, 2003; Malaterre, 2011). In particular, the innovative approach of computer scientist and philosopher Judea Pearl, based on the construction of causal diagrams (Pearl & Mackenzie, 2018; Halpern & Pearl, 2020) could be especially useful in cancer research (Greenland, Pearl & Robins, 1999; for a philosophical discussion, see Vineis, Illari & Russo, 2017). Second, some mutations may play no direct role in cancer cells' hallmarks, but may have an indirect causal role, by disrupting the process of mitosis, thus leading to higher rates of mutation. Should such mutations count as drivers? As this example illustrates, the causal role of a mutation is often indirect and uncertain. Thus, the concept of 'driver mutations' is vaguely defined, leading to disagreements on how best to identify them and determine their causal role.

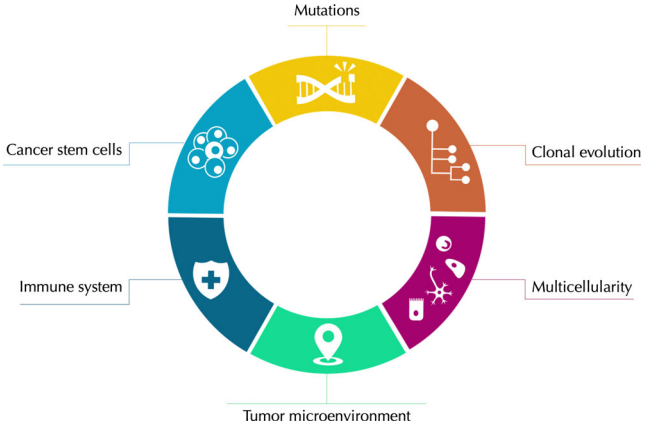

Fig. 1. Six examples of cancer topics for which philosophical, conceptual, and theoretical thinking is useful.

To know whether a mutation is driver or passenger, one would need functional data or experimental assessment of the mutation's impact on the cells. The main way of doing this is by introducing the mutations of interest in mice or in cell lines and studying their impact. These studies face the limits inherent to all experimental models, need to be made for each mutation in each cell type of interest, and lead to an endless process as functional effects of a given mutation frequently depend on other mutations already present in the cell. Different researchers can perform the same experiment and obtain different results due to differences in genomic and cellular context. An alternative is to infer the driver status from sequencing data. Recurrence of mutations (the fact that the same mutation is observed in multiple samples) is taken as evidence of its causal role in cancer development. The underlying assumption here is that mutations are unlikely to be observed to recur so often by mere chance. Yet, assessing which alterations are drivers and which are merely passengers or false positives for a given cancer type or subtype is proving more challenging than anticipated, as emphasised by Plutynski (2021*c*).

The first reason is practical: many confounding factors, like gene size, position effect, chromatin openness, or frailty of particular sequences can change the likelihood for a particular mutation to occur at each genome base. These issues lead to a difficult balance between risks of false positives and false negatives (Lawrence *et al.*, 2013). The Pan-Cancer Analysis of Whole Genomes Consortium failed to identify driver mutations in 5% of samples (The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, 2020). Recent studies have highlighted the existence of passenger hotspots, i.e. inherently more mutable genomic sites leading to false positives (Hess *et al.*, 2019), or possible biases in the mutation rate, with a lower mutation rate in gene bodies (Monroe *et al.*, 2022) (of note, this raises the question of whether the mutation rate is lower in driver mutations). Ambiguities surrounding the

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concept of driver mutation may in part reflect our current state of knowledge and may partly be solved by future technological and computational progress. But even there, there is a place for theoretical work. The direction of such progress depends on where the community thinks progress should be made, i.e. what should be examined. The analysis of underlying assumptions behind competing methods of identifying such genes also appears as a particularly powerful motor to identify unanticipated confounders and accompany progress.

The second reason is conceptual: 'driver' is itself a concept in flux, currently conflating two meanings. Although originally intended to refer to mutations that played some role in the selective advantage, or growth fitness, of cells (drivers drive clonal expansion) (Maley *et al.*, 2004), the concept has expanded to cover any mutation to any gene that plays some functional role in cancer (drivers drive the disease). These two claims only partially overlap and should be disentangled to avoid flawed inferences. Some mutations induce a selective advantage without being malignant (Wijewardhane *et al.*, 2021). Sequencing of non-malignant tissues has shown the accumulation of mutated clones with aging in multiple tissues (Kakiuchi & Ogawa, 2021). While some mutations conferring a fitness advantage are enriched in cancers, others are instead enriched in non-cancer tissues. This is, for example, the case for *TP53* and *NOTCH1*, respectively, in the oesophagus, raising the question of whether the latter mutations might in fact protect against cancer (Martincorena *et al.*, 2018). A mouse model illustrated that non-cancerous mutant clones can efficiently eliminate nascent oesophageal tumours through cell competition (Colom *et al.*, 2021). Likewise, functional studies have shown that partial loss-of-function of *Arid1a* and *Kmt2d*, observed in liver tissues but not cancer, can confer a non-malignant selective advantage in response to liver injury (Zhu *et al.*, 2019). Conversely, some mutations can induce a malignant phenotype while being neutral or even deleterious in terms of fitness, such as *SRSF2* mutations in the haematopoietic system (Bapat *et al.*, 2018). Thus, assessing which mutations are true drivers is difficult because what the operational criterion intends to measure is itself a vague, open-ended, and transient category.

Moreover, there is no clear boundary between driver and passenger mutations, but rather a continuum, as the phenotypic impact of a mutation can vary broadly, from none to drastic. Originally 'hitchhiker' mutations were said to be carried along in a selective sweep driven by a cancer mutation (e.g. p16); currently there are open questions about whether purported passenger mutations play some functional role in cancer. Some have suggested a 'mini-driver' model, given that multiple nearly neutral mutations could have impacts similar to a driver mutation (Castro-Giner, Ratcliffe & Tomlinson, 2015). Conversely, a combination of mathematical modelling, computational analysis, and experimental work suggested that the burden of passenger mutations can be damaging (McFarland *et al.*, 2013, 2017) and could be a barrier to cancer progression (McFarland, Mirny & Korolev, 2014). The same mutation can be driver, neutral, or detrimental depending on the context. The selective environment in which the cell finds itself, the level of expression of the gene in that cell, the associated mutations, and the order in which mutations occur, can all impact how the mutation affects a given cell. *KRAS* (Kirsten rat sarcoma) oncogenic mutations, for example, are the prevalent driver oncogene in pancreatic ductal adenocarcinoma (PDAC), but they lead to transformation in specific contexts only, such as chronically inflamed tissues (Guerra *et al.*, 2007), or in specific cells like acinar cells in which telomerase is activated (Neuhöfer *et al.*, 2021). Furthermore, the same mutation can be driver, neutral, or detrimental depending on the evolutionary trajectory of the cancer cell, which itself depends on intratumoral heterogeneity and drug-selection pressure (Swanton & Govindan, 2016). For example, in *EGFR* (epidermal growth factor receptor)-mutated lung adenocarcinomas, the T790M mutation only becomes a driver under the selective pressure of first-generation EGFR inhibitors. The concepts of driver and passenger mutations should thus be conceived as both quantitative and context dependent.

The success of targeted therapies in cancers with well-defined driver mutations such as BCR-ABL1 (breakpoint cluster region-ABL Proto-Oncogene 1) in chronic myeloid leukaemia offered hope that similar strategies might be used across different malignancies. However, applying this model to other cancer types has proved challenging, in part owing to limitations in identifying actionable driver mutations. Conceptual confusion between 'driver mutation', 'oncogene addiction', and 'actionable addiction' needs to be dispelled. A driver gene can be an oncogene for a given tumour, that is, can be so essential to tumour growth that the inhibition of this driver leads to oncogenic shock and immediate shrinkage of the tumour (Hahn *et al.*, 2021). If a targeted therapy halts this process, then that driver gene is also an actionable mutation. But there are many driver genes that are not necessarily actionable. For example, until very recently the *KRAS* gene was considered 'undruggable' even though it is considered as a driver gene in 25–30% of lung adenocarcinomas. Finally, some actionable mutations are not driver mutations, and likewise, non-oncogene addiction has been described in cancer cells (e.g. Bermúdez-Guzmán, 2021). Philosophers have thus argued that in order to avoid pathologizing incidental mutations and/or essentializing the role of driver mutations in cancer, these three concepts should be extricated (Darrason, 2017).

Overall, this shows that the concept of driver mutation is relative, not absolute, and it is important to disentangle its contribution either to clonal expansion and/or to oncogenic processes (partially overlapping processes). This distinction is important for data interpretation. For example, scientists are surprised that some driver mutations, such as $SRSF2^{P95H}$ in blood cancers, lead to clonal disadvantages in their experimental setting. But the expectation that this so-called driver mutation should provide clonal advantage to the cell reflects the implicit misleading assumption that a mutation is inherently a driver mutation or not, and a confusion between the contribution of a gene to clonal expansion *versus* to a phenotype. Additionally, conceptual clarification may have critical

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consequences in clinical practice. For example, disentangling the complexity of mutational dynamics has implications for the demarcation between normal, premalignant, and malignant cell growth, and pragmatic problems such as *when* and *how* to treat (is the mutation actionable?). Conceptual clarification may help avoid the common conflation of driver mutations and actionable variants, which may affect patients' expectations regarding cancer treatment.

III. CLONAL EVOLUTION IN CANCER

A major challenge for understanding and treating cancer is that tumours are composed of heterogeneous cells and change over time. As such, cancer progression is generally understood as an evolutionary process referred to as 'clonal evolution' (Nowell, 1976). New sequencing technologies and phylogenetic methods have been successfully applied to uncover cancer cell evolution. This proved a fertile approach. However, several conceptual questions remain open, particularly on the exact role of natural selection in cancer, on what promotes and maintains heterogeneity among cancer cells in a patient, as well as what counts as a 'clone'.

(1) To what extent is natural selection explanatory?

The evolutionary framework in oncology is dominated by the idea that cancer cells evolve by natural selection, driving disease progression (Morange, 2012). But to what extent exactly? What can evolve by natural selection and under which circumstances is a question that has received much attention from philosophers and theoretical biologists (Lewontin, 1970; Okasha, 2006). Cancer cells meet the minimal conditions for natural selection: they accumulate variations that can impact their fitness (i.e. the rate of their proliferation within the organism), and are inherited through cell division. There is therefore no doubt that they *can* evolve by natural selection, nor that they often do, sometimes exhibiting a large fitness advantage (Williams *et al.*, 2018). However, recent work, in which mathematical modelling has played a key role, has shown that neutral evolution might be more preeminent than anticipated, at least after cancer initiation, and could occur in 30% of solid cancers (Williams *et al.*, 2018). Key unresolved questions concern whether neutral evolution only occurs when natural selection has driven cancer cells to their local optimum, or whether genetic drift can sometimes be predominant. An interesting question is whether, and how often, pre-existing neutral variations become driver mutations when the ecological circumstances change, such as during therapy.

Measuring the fitness of cancer cells within a patient's tumour poses mathematical as well as conceptual challenges. For example, the size of the clone is often taken as a sign of the cells' fitness: cells with the same fitness should expand at the same rate, while higher clonal expansion indicates higher fitness. This widespread interpretation of clonal expansion relies on the assumption that the effective population size is large. The census population size is indeed high: 1 cm^3 of tumour may contain around a billion cancer cells. The effective population size can however be smaller if only a subset of cancer cells can proliferate indefinitely, as posited by the cancer stem cells (CSCs) model (see Section VII). In this case, only the alterations acquired in the CSCs can meaningfully contribute to clonal evolution, the others being lost through cell exhaustion (Greaves, 2013). The quantity and proportion of cancer cells that are CSCs may vary drastically depending on cancer type and stage. If small, then mathematical modelling shows that clonal expansion could occur by mere chance (Calabrese, Tavaré & Shibata, 2004; Cannataro, McKinley & St Mary, 2017; Cannataro & Townsend, 2018). Clonal outgrowth may thus not always be driven by fitness advantages, as discussed by a mathematician, a philosopher and a biologist (Lyne, Laplane & Perié, 2021). This distinction can have major consequences, for example during surveillance of minimal residual diseases after treatments, or for the development of adaptive therapies against cancer. In all these instances, and many others, sorting out clonal expansion due to fitness advantage from drift is of critical importance to both scientific understanding and making clinical decisions (Lyne *et al.*, 2021).

Natural selection is often perceived as central in explaining the emergence and development of cancer, and response to treatment. However, not all selected traits are explained in the same manner by natural selection. Selection can act as a mere sieve, changing the proportion of cells with different phenotypes and leading to 'simple' adaptations, or it can lead to the emergence of new traits, called 'complex' adaptations. Philosopher Peter Godfrey-Smith identified quantitative characteristics of a population which determine the likelihood that natural selection will generate complex, qualitatively novel adaptations (Godfrey-Smith, 2009). In cancer, there is a widespread view that cancer cells regain the ability for complex adaptations, an ability typically repressed in somatic cells. The 'hallmarks of cancer' (Hanahan & Weinberg, 2011) have for instance been conceived as complex adaptations in that they represent convergences (Fortunato *et al.*, 2017; Somarelli, 2021). However, using Godfrey-Smith's framework, philosopher Pierre-Luc Germain (2012) questioned this view and showed that cancer cells properties depart from paradigmatic Darwinian populations, making complex adaptations highly unlikely. Many of their adaptations, such as the ability to metastasize, likely result from simple selection of properties that were already wired in the architecture of the normal cells. Finally, a further open debate in biology and philosophy of biology is whether evolution by natural selection occurs at a supra-cellular level in cancers, i.e. whether groups of cancer cells, such as metastases, could be the product of a multilevel selection process (Lean & Plutynski, 2016; Germain & Laplane, 2017).

(2) What is a clone?

Cancer cells form a dense phylogenetic tree of cells in which various alterations such as mutations, which may affect their

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phenotype, are inherited. In the clonal evolution model, this evolution is generally represented in a simplified tree of 'clones'. Clones are groups of cells that come from a common ancestral cell and share the same genotype. In this traditional view, clones have different properties and fitness, depending on their mutations, and can evolve under the effect of natural selection (or neutral evolution, as discussed in Section II.1). The notion of clone therefore exemplifies what evolutionist Ernst Mayr (1959) described as 'typological thinking': all cells of a clone are conceived as exemplars of a same type.

The notion of a clone is a useful simplification, but it brings with it conceptual difficulties. As analysed by a group of philosophers and scientists (Jourdain *et al.*, 2021), the cells of a given clone are not genetically identical, but are only identical with respect to a subset of mutations deemed relevant. As such, defining 'clone' precisely requires identifying the relevant mutations. This may be possible in principle by using the distinction between passenger and driver mutations, given that only driver mutations can increase the cells' fitness and thus explain the evolutionary properties of the clone. But the concept of driver mutation itself is not consistently defined (see Section II). A change in the definition of driver genes thus implies change in how we conceptualise a clone, and in turn, track and reconstruct clonal evolution. This has consequences for measures of clonal diversity. Current measures of clonal diversity rely on counting the number of clones (richness) and their relative size (evenness). Changing which traits are used to identify clones will change both the number and size of clones and thus will impact the evaluation of clonal dynamics.

The traditional genetic view of clonal evolution only offers a partial account of the inherited properties that can contribute to the evolution of cancer cells. Increasing attention is given to epimutations, which technical improvements help bring to light (Pan *et al.*, 2015; Gravina, Ganapathi & Vijg, 2015; Ushijima, Clark & Tan, 2021). Heritable epigenetic alterations can occur without identified genetic mutations, and can sometimes even drive relapse (Li *et al.*, 2016). Other traits such as altered tumour microenvironment can also be passed on through generations of cells and can benefit cancer cells' growth (see Section V). The observation of the presence of microbes in cancer cells, and their potential impacts on cancer cells' fitness led a group of biologists, mathematicians and philosophers to advocate for a multispecies view of clonal evolution in which both cancer cells and microbial lineages are tracked and integrated (Sepich-Poore *et al.*, 2022). The respective causal contributions of these traits can vary from one cancer type to another. Chronic myeloid leukemia and ependymomas illustrate two extremes of a spectrum: while the former served as a model of well-characterised genetic clonal evolution, ependymomas are conceived as epigenetically driven tumours, with no recurrent genetic/genomic alterations (Mack *et al.*, 2014; Michealraj *et al.*, 2020).

As emphasised by an interdisciplinary group, some of these difficulties can be met by revising the definition of clones to encompass non-genetic traits (Duchmann, Laplane & Itzykson, 2021). This is increasingly feasible with single-cell multi-omics technologies, including spatial transcriptomics which can help track niche inheritance. Furthermore, tracking intra-clonal heterogeneity could promote new research. For example, the degree of heterogeneity inside a genetic clone could be measured to assess its consequences for clonal evolution and treatment escape.

However, the existence and plausible relevance of non-genetic traits pose the question of whether clonal lineages can accurately capture heterogeneous inheritance. It is, for instance, possible that genetically distinct clones inherit the same micro-environmental stimuli and hence epigenetic traits (e.g. Michealraj *et al.*, 2020). In such a context, the clonal lineage approach would struggle to capture the epigenetic similarity. The possible mix of horizontal and vertical transmission of intracellular microbes (Sepich-Poore *et al.*, 2022), as well as the horizontal transfer of mitochondrial DNA (Hekmatshoar *et al.*, 2018; Burt *et al.*, 2019), and cell fusion (Miroshnychenko *et al.*, 2021), further complicate the picture. The clonal evolution model holds great potential for oncology, yet as we have shown here, conceptual analysis is required to implement and revise the model in directions that can lead to medical innovation.

IV. CANCER AND MULTICELLULARITY

Cancer is often conceptualised as a breakdown of the rules of multicellularity (e.g. Greaves & Maley, 2012; Aktipis *et al.*, 2015; Trigos *et al.*, 2018). This idea, integral to the famous 'hallmarks' of cancer (Hanahan & Weinberg, 2011), is now widespread, even in textbooks (Pezzella, Tavassoli & Kerr, 2019). Trivially, cancer – whose definition involves uncontrolled cell proliferation – can occur only in multicellular organisms. Yet is there a more constitutive connection between cancer and multicellularity? Can the rich scientific (Bonner, 1998; Niklas & Newman, 2016; Herron, Conlin & Ratcliff, 2022) and philosophical (Michod, 2005; Okasha, 2005; Love, 2016) literature on multicellularity shed light on cancer, for example by contributing to explaining how and why it occurs, what its underlying principles are, and by suggesting novel experiments and therapies? The cancer–multicellularity connection illustrates the fecundity of both better defining core scientific concepts and integrating into a unifying and coherent framework lessons from different disciplines (evolutionary biology, developmental biology, philosophy, and mathematics).

A prevalent claim is that cancer must be thought of as a disruption of the cooperative mode of life built in the evolutionary transition from unicellular to multicellular organisms (Nunney, 1999; Gatenby, Gillies & Brown, 2010; Aktipis *et al.*, 2015; Trigos *et al.*, 2018). This idea leads to two questions: (*i*) how do the features of cancer specifically relate to multicellularity; and (*ii*) does cancer constitute an instance of 'cheating'?

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(1) How do the features of cancer specifically relate to multicellularity?

One approach suggests that cancer is a deregulation of the core processes selected in evolution for their capacity to ensure the cohesion of multicellular organisms (Gatenby *et al.*, 2010; Greaves & Maley, 2012; Aktipis *et al.*, 2015). This includes traits such as control over cell proliferation and division of labour. Although that claim seems intuitive as these traits are undeniably disrupted in cancer, it raises at least four difficulties. First, is it saying that cancer *correlates with* a deregulation of multicellular cooperation (which is trivial), or that deregulations of multicellular cooperation *cause* cancer? Only the second claim would really be useful, but more detailed experimental evidence is required to substantiate it. Second, multicellularity appeared at least 25 times through evolution (Niklas & Newman, 2016), so saying that cancer is a disruption of multicellularity requires a precise account of how it emerged several times in different branches of the tree of life, whether these realisations of cancer share the same characteristics, and a detailed analysis in terms of evolutionary homologies or convergences. Third, the idea that cancer results from a loss of multicellularity traits neglects that unicellular organisms possess many of these so-called 'multicellularity traits' (e.g. division of labour, control of cell proliferation) and associated genes (Nedelcu, 2020). Fourth, some cancer features are novel instances of multicellularity rather than manifestations of a loss of multicellularity [typically when tumours are conceptualised as novel quasi-organs (Egeblad *et al.*, 2010; Sprouffske *et al.*, 2013)], including when cancer cells disseminate not as unicellular entities but as multicellular clusters (Cheung & Ewald, 2016). Given these difficulties, a more accurate and promising concept is that cancer is a *partial* breakdown of *certain* core features of multicellularity, but future research must clarify which features, and why. Past work of philosophers examining how the major evolutionary transitions to multicellularity occurred and defining rigorously the core features of the various forms of multicellularity (Okasha, 2005; Arnellos, Moreno & Ruiz-Mirazo, 2013; Love, 2016) will be useful here. An intriguing long-term prospect would be that future therapies may target only these specific features of multicellularity that are deregulated in cancer.

Another claim that often accompanies the first claim but is logically independent is that all multicellular organisms can develop cancer (Aktipis *et al.*, 2015; Greaves, 2015). If true, this observation would undeniably strengthen the first claim. The obvious problem is that this necessarily presupposes a broad definition of cancer – one that most medical oncologists and cancer biologists will find unduly inclusive. For example, Aktipis *et al.* (2015) say that cancer or 'cancer-like phenomena' can be found in virtually all multicellular organisms, but their definition of cancer presupposes what is in question by assuming that cancer is a disruption of multicellularity, which allows them to count phenomena such a fasciation in plants as instances of 'cancer'. With narrower definitions of cancer, focusing for instance on histological disorganisation and/or on dissemination and invasion (those that most cancer specialists adopt), many multicellular organisms do *not* get cancer. Plants are a prime example (Doonan & Sablowski, 2010) (although see White & Braun, 1942). It is of course expected that any account of where cancer can be found in the tree of life (i.e. any analysis in terms of comparative oncology) will depend on the definition one adopts of 'cancer'. Yet an exclusively terminological discussion is not helpful. What proponents of the idea that cancer exists in all multicellular organisms must do is to show that this integrative conceptual framework generates novel testable hypotheses and promising therapeutic avenues. This approach has been tried (e.g. Aktipis, 2020, p. 161ff.), especially by citing 'adaptive therapies', which consist of controlling the tumour without destroying it, to avoid the development of treatment resistance (Gatenby *et al.*, 2009; Chmielecki *et al.*, 2011). Yet adaptive therapies could work even if the claim that all multicellular organisms develop cancer is wrong, the two claims being logically independent. So, more work is needed to formulate predictions specific to the idea that cancer exists across all multicellular organisms.

Another obvious challenge to this idea is that some metazoans (paradigmatic instances of cohesive multicellular organisms), e.g. mole rats, almost never develop cancer (Seluanov *et al.*, 2018). One possible explanation would be that certain multicellular organisms do not have cancer at all; another explanation would be that all multicellular organisms can have cancer but some have developed highly efficient anticancer mechanisms (Seluanov *et al.*, 2018). Another possibility would be that non-cancerous multicellular organisms like mole rats have a special kind of multicellularity. All this suggests that it would be more promising to explore how *differences* in the many multicellular modes of life that appeared through evolution lead to different potentialities and realisations of cancer than to make an overall claim about cancer being present everywhere multicellularity is.

(2) Does cancer constitute an instance of 'cheating'?

Recently, the idea that cancer is a form of cheating with regard to the multicellular organism has gained traction (Nunney, 1999; Aktipis *et al.*, 2015; Greaves, 2015; Aktipis, 2020). This hypothesis can have interesting clinical consequences, e.g. the possibility that there are pre-cancers that we miss because they do not form tumours (Aktipis *et al.*, 2015).

In a minimal and metaphoric sense, tumours cheat by hijacking the organism's resources (Suijkerbuijk & van Rheenen, 2017; Plutynski, 2018*a*). Yet 'cheating' has a more specific meaning in theoretical evolutionary biology, related to the social evolution framework, developed by Hamilton (1964*a*,*b*), Maynard-Smith (1964) and others, and explored by theoretical biologists (Frank, 1998) and philosophers (Birch & Okasha, 2015; Birch, 2017): there is cheating if and only if an individual benefits from a cooperative group without contributing, and increases its fitness at the group's expense. Cheating in this sense occurs even in non-cognitive organisms, e.g. social amoebae (Strassmann, Zhu &

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Queller, 2000) and bacteria (Velicer, Kroos & Lenski, 2000). If the social evolution framework also applies to cancer, then important consequences follow, such as the possibility of viewing cancer through the lens of kin selection (Hamilton, 1964*a*,*b*). A parallel can be drawn with microbes, where the application of the social evolution framework has proved to have far-reaching consequences (West *et al.*, 2006). Interestingly, mathematical models integral to the field of evolutionary game theory, already used in oncology for describing various phenomena including cooperation between cancer cells (Archetti & Pienta, 2019), may also shed light on cancer cells defined as cheaters with regard to the organism's normal cells (Csikász-Nagy *et al.*, 2013).

Many evolutionists, however, reject the idea that cancer cells are strictly speaking 'cheaters', at least in the sense applied to paradigmatic 'cheaters' such as selfish genetic elements. In their view, cancer cells are evolutionary dead-ends (they die with the organism) (Gardner, 2015*a*,*b*), so their capacity to proliferate at the organism's expense does not influence the next generation (with respect to the higher level's regeneration time) (Shpak & Lu, 2016) and ultimately cannot be considered an adaptation. Transmissible cancers [in Tasmanian devils (*Sarcophilus harrisii*), dogs, and bivalves] are an exception, as they do constitute a genuine instance of cheating (Shpak & Lu, 2016).

As recently demonstrated by philosopher Samir Okasha (2021), the main way in which (non-transmissible) cancer may be considered a genuine form of cheating is if the so-called 'atavistic' hypothesis holds. Atavism says that cancer represents a reversion to a mode of life found in unicellular ancestors, for whom it was beneficial, and which was suppressed during the evolutionary transition to multicellularity (Davies & Lineweaver, 2011; Lineweaver, Davies & Vincent, 2014; Lineweaver *et al.*, 2021). If atavism is true, then cancer cells are genuine cheaters because they express the selfish tendencies that our cells potentially possess, but which have been suppressed in the transition to multicellularity. It also follows from atavism that cancer therapies should target unicellular-associated processes.

Yet many objections have been raised against atavism. The genes described by atavism's proponents as ancestral genes reactivated in cancer are not actually repressed in normal circumstances and then suddenly activated in cancer: instead, they are highly conserved genes, which play important roles in many normal developmental processes, such as cell proliferation. Moreover, genetic, genomic, cellular, and other dysfunctions found in cancer seem absent in today's unicellular organisms and early metazoans. Cancer cells would be better seen as 'defective' unicellular entities, as they lack traits/genes that play important roles in unicellular organisms (Nedelcu, 2020). Perhaps more compelling arguments in favour of atavism will be developed in the future but, for now, it seems safe to conclude that it has not been demonstrated that cancer is a case of cheating as defined in the social evolution framework.

Overall, connecting the scientific literatures on cancer and multicellularity constitutes a promising and highly interdisciplinary avenue for future research, provided that it builds on the rich work on multicellularity developed both by scientists (Bonner, 1998; Niklas & Newman, 2016, 2020; Herron *et al.*, 2022) and philosophers (Okasha, 2005; Arnellos *et al.*, 2013; Love, 2016; Bich, Pradeu & Moreau, 2019) and that it leads to more precise characterizations of cancer and novel testable hypotheses. Future collaborations between scientists and philosophers are likely to contribute to that programme.

V. DEFINING THE TUMOUR MICROENVIRONMENT

Beyond tumour-intrinsic properties, the role of the tumour microenvironment (TME) in cancer development and dissemination has been increasingly recognised over recent decades. An early approach, in the specific context of cancer dissemination and metastasis, was the suggestion of Paget (1889), that not only the 'seed' (tumour cells) but also the 'soil' (the predisposition of certain tissues and organs to facilitate colonisation by cancer cells) played a role in metastasis (Fidler, 2003). Starting from the 1970s a convergence of insights from developmental biology, vascularization studies, and immunology affirmed the importance of the TME and spurred an entire field devoted to exploring it (Bissell *et al.*, 2002; Maman & Witz, 2018).

The TME is often conceived as the proximal tissue context in which the tumour cell population is embedded, i.e. all the non-malignant elements located in or around the tumour. Determining the exact roles of the TME in cancer development and treatment response remains an essential aim of current cancer research (Anderson & Simon, 2020). Key efforts include characterisation of TME components, their causal roles, either individually or together, and their interactions over time with cancer cells, especially before, during, and after therapy. However, as demonstrated by collaborative work by philosophers and scientists (e.g. Laplane *et al.*, 2018), without a consensus definition of what the TME comprises or its boundaries, the pursuit of these goals can be hindered.

Conceptual analysis is useful to improve the TME definition by clarifying inclusion–exclusion criteria. For instance, must all TME components be non-tumoral, or can they also include tumour or tumour-like features (e.g. populations of cancer cells serving as supportive niches for other cancer cells; field cancerization)? Under which conditions should a non-TME entity or process be reconsidered a TME component? For example, recent research has suggested a role of the intratumoral and gut microbiomes in cancer (reviewed in Sepich-Poore *et al.*, 2021), an observation that raises central conceptual issues, as emphasised by work done at the interface of biology, medicine, and philosophy (Sepich-Poore *et al.*, 2022; Sholl *et al.*, 2022). Should we consider them part of the TME, and why? When microbes invade cancer cells within the tumour (Bullman *et al.*, 2017;

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Nejman *et al.*, 2020; Kalaora *et al.*, 2021), are they part of the TME or of the tumour? Can one element be part of both? Do we consider the causal influence of an element differently depending on whether it is considered part of the tumour *versus* the TME?

Loosely defining the TME as an encompassing list of components with no clear spatial delimitations makes it difficult to understand not only *what* the TME is, but *where* exactly the TME is located. For example, although the immune system, the nervous system, and the microbiome have all been grouped under the TME, their influence can extend from local to distant to systemic effects, which favours a broader macroenvironment, systemic, or organismal environment (McAllister & Weinberg, 2014; Laplane *et al.*, 2018) rather than a neoplasm-circumscribed TME. Better assessing the spatial organisation of the tumour environment from the molecular scale to the organ and even the full body is not just a semantic goal. Spitzer *et al.* (2017) illustrated the practical importance of considering distant elements in a mouse model. They demonstrated that the efficacy of immunotherapies is highly dependent on immune responses at the systemic level. During tumour rejection, immune cell proliferation is not maintained in the TME, and instead occurs at the periphery (including lymph nodes and spleen). The clinical implication is that immunotherapies should favour peripheral immune responses and facilitate the migration of effector immune cells to and from the periphery. This is important across many cancer types, but especially so in PD-L1-negative tumours, where recruitment of effective antitumour immunity from the peripheral compartment turns out to be crucial (Hellmann *et al.*, 2019).

As far as the microbiome is concerned, in certain cancer types, microbes may transit from other body sites to reach tumours but can also exert immunological effects from afar (Mager *et al.*, 2020; Lam *et al.*, 2021). In this case, should we consider both distal and proximal microbes as TME features? Are they always present or does their translocation to the tumour make them dynamic features? Notably, distal, proximal, and intracellular bacteria may influence cancer progression and patients' response to therapies but through different pathways (Sepich-Poore *et al.*, 2021). Facing such under-specifications of the spatial extension of the TME, Laplane *et al.* (2018) offered a conceptual and philosophical framework that proposes criteria to delineate different 'layers' of the microenvironment, from the most local to the most distant. This approach raised several key conceptual challenges: (*i*) 'TME-intrinsic' approaches neglect the role played by distal elements in the organism (Laplane *et al.*, 2019*a*); and (*ii*) the relationship between an element's location and causal role is often nuanced and associated with the various layers of environment (Laplane *et al.*, 2018).

Empirical and conceptual understanding of the spatial role of TMEs in cancer progression and dissemination can be boosted by spatially explicit mathematical models (Anderson & Quaranta, 2008). In a landmark study, Anderson *et al.* (2006) proposed a model predicting that invasion results from cancer cells competing with each other for space and resources in a harsh tissue microenvironment (as opposed to the dominant view that the main factors would be mutations in key genes or a faulty signalling network). Although some medical oncologists question the empirical relevance of such mathematical models, they are very useful, including because they prompt biologists, medical doctors, and philosophers alike to offer explicit and formalizable definitions of central oncological concepts.

Temporal distinctions concerning the TME are equally important. Mina Bissell has played a key role on this topic since the 1970s–1980s (e.g. Bissell, Hall & Parry, 1982) – and, more generally, for putting the TME at the centre of cancer biology's agenda. Conceptually, she proposed to distinguish the *normal microenvironment*, which is not just without cancer but rather actively prevents tumorigenesis – especially by maintaining the normal three-dimensional (3D) structure of the tissue and the extracellular matrix – and the *transformed microenvironment*, which promotes tumorigenesis (Bissell & Hines, 2011). Characterising the factors involved in the switch from one type of microenvironment to the other and enabling precise control of these factors would patently aid cancer treatment (Weaver *et al.*, 1997). 'Dynamical reciprocity' (Bissell *et al.*, 1982; Bissell & Radisky, 2001; Bissell & Hines, 2011) refers to the reciprocal causality between the cell and the extracellular matrix, active in health and disease. This framework is reminiscent of the dialectical approach developed in evolutionary biology and ecology, which explores the co-construction of the organism and the environment (Lewontin, 2000), and has played an important role in the literature on niche construction (Odling-Smee, Laland & Feldman, 2003). Bissell's framework has had a significant impact on cancer science and medicine, illustrating how theoretical reframing of cancer causation can improve our understanding (Bertolaso, 2016; Plutynski, 2018*a*,*b*; Bertolaso & Strauss, 2021). Another important conceptual framework based on temporal considerations has been put forward by Laconi (2007). He distinguishes what we could call the *precancerous TME* from the *tumour-induced TME* (the microenvironment inside the focal lesion that cancer cells contribute to create). Both play a key role in cancer origination, evolution, and progression (Marongiu, Serra & Laconi, 2018).

History and philosophy provide opportunities to revisit old notions, explore how their meaning has been transformed through time, and determine how re-defining them today can be fruitful. For example, a more rigorous conceptualization of Paget's notions of 'seed' and 'soil' may help assess the fecundity of newly proposed terms, e.g. '*self-seeding*' (feedback loops between the primary and secondary sites) (Norton & Massagué, 2006) or '*fertilizer*' (the capacity of some elements, especially immunological ones, to render a given soil more congenial to metastatic cells) (Ng, 2019). Such conceptual reframing inspired novel classifications of causal factors in cancer dissemination in collaborative work by biologists and philosophers (Rondeau *et al.*, 2019). It may also generate new testable hypotheses about organ-specificity of metastasis (i.e. the non-equiprobability of dissemination to different organs for a given tumour, which was Paget's founding

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observation) (Obenauf & Massagué, 2015) and the concept of a premetastatic niche (Kaplan, Rafii & Lyden, 2006), and may also produce new experimental programs and therapeutic opportunities for preventing metastasis. Several mathematical models of metastasis building on the seed and soil hypothesis and the concept of self-seeding have been developed. For example, using a Markov chain/Monte Carlo stochastic mathematical model, Newton *et al.* (2013) propose distinguishing 'sponges' (organs with high absorption probability) and 'spreaders' (low absorption probability) and challenge the classic idea that metastatic spread occurs in a unidirectional way. Applying a similar model to breast cancer longitudinal data, the same group showed that patient survival depended on the location and characteristics of the first metastatic site to which the disease spread (Newton *et al.*, 2015).

Finally, in addition to circumscribing *what* the TME is, it is also important to characterise *how* we can study it, because experimental tools and therapeutic strategies are intimately tied to and inform theoretical framework development. Techniques such as organoids and spheroids that model per-patient therapeutic efficacy are very promising, while also raising numerous challenges because they exclude known or probable TME components (Alessandri *et al.*, 2013; Shamir & Ewald, 2014; Huch *et al.*, 2017; Simian & Bissell, 2017; Tuveson & Clevers, 2019). Another interesting question deserving more conceptual attention concerns the myriad of innovative approaches developed to explore the TME. A multiscale investigation of the TME, both spatially and temporally, is required, though for this approach to work a complex hybridization strategy between these approaches will be needed. Physicists and engineers can help explore the TME in three dimensions (Wirtz, Konstantopoulos & Searson, 2011; Bhat *et al.*, 2016; Nia *et al.*, 2020). They can examine mechanical cues coming from the TME (extracellular matrix, ECM). Nanotechnologies used in neuroscience can be applied to the study of the TME (Soria *et al.*, 2020). Physicists can also contribute to better understand, model, and experimentally test *in vivo*, with both controlled hyperproliferation and magnetic forces, the role of physical forces in tumorigenesis, most prominently pressure (Fernández-Sánchez *et al.*, 2015; for a philosophical discussion, see Green, 2021). These approaches raise important questions about trade-offs in cancer modelling, such as the benefits and challenges of switching from traditional two-dimensional (2D) to more complex 3D models. Collectively, the combination of such perspectives from diverse fields not traditionally involved in cancer research or treatment, including philosophy and the physical sciences, may contribute key advances in cancer biology, diagnostics, prognostics, and therapeutics.

VI. UNDERSTANDING THE PARADOXICAL ROLES OF THE IMMUNE SYSTEM IN CANCER

There is now a consensus that the immune system influences cancer progression, both in animal models and in humans (Chen & Mellman, 2017). Depending on the context, the immune system can inhibit or, more paradoxically, promote cancer growth and dissemination (de Visser, Eichten & Coussens, 2006), simultaneously or sequentially. The original concept of immunosurveillance (i.e. the idea that the immune system can detect and eliminate cancerous tumours), suggested by Thomas and Burnet in the 1950s and later expanded by them (Burnet, 1970; Thomas, 1982), made the explicit evolutionary hypothesis that cancer was central in the emergence of adaptive immunity some 500 million years ago. It also connects immunology with multicellularity (see Section IV) by stating that the immune system has been a key policing mechanism in the evolutionary transition to multicellularity (Pradeu, 2013).

Since the 2000s, the 'immunoediting' concept has superseded 'immunosurveillance' (Dunn *et al.*, 2002). According to the former, there are three phases in the interactions between the immune system and a cancerous tumour: elimination, equilibrium, and escape (by which some resistant tumour cells evade the immune system, and can disseminate into the body) (Schreiber, Old & Smyth, 2011). Immunoediting offers an evolutionary approach to the within-organism crosstalk between the immune system and cancer: one way by which the immune system may promote cancer progression is by selecting immuno-resistant variants in a population of cancer cells.

In addition to the role of adaptive immune cells (responses mediated by lymphocytes and associated with immunological memory) in cancer, the importance of innate immune cells [especially macrophages, neutrophils, and natural killer (NK) cells] in either controlling or promoting cancer is increasingly recognised (Mantovani & Sica, 2010; Woo, Corrales & Gajewski, 2015). Innate components play a central role in inflammation, which depending on the context may favour or disfavour cancer (Mantovani *et al.*, 2008). Emerging approaches combining immunology, evolutionary biology, and ecology have been suggested recently, and may open up novel research areas, with therapeutic potential (Kareva *et al.*, 2021).

Years of basic research have led to the development of various immunotherapies, which involve inducing and/or restoring anti-cancer immune responses. Immunotherapies have raised much enthusiasm (Kelly, 2018), especially after the award of the 2018 Nobel Prize to James Allison and Tasuku Honjo for their discoveries related to the lymphocyte inhibitory receptors CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein 1). Today, 'checkpoint inhibitors' and CAR (chimeric antigen receptors)-T cells are the most extensively studied immunotherapies (June & Sadelain, 2018; Sharma & Allison, 2020), while innate immunity-based immunotherapies are increasingly seen as promising and complementary (Mantovani & Longo, 2018; Demaria *et al.*, 2019). Yet there is much to learn – for example why only a minority of patients respond to immunotherapies, or how one can clinically manipulate the dual roles of the immune system ('anti' and 'pro' cancer) in service of therapy. An important

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development of the field is the increasing appreciation that most successful therapies are likely to combine immunotherapies with other types of therapies, including radiotherapy and chemotherapy.

Immune cells and molecules constitute an essential component of the tumour microenvironment and macroenvironment (Joyce & Fearon, 2015; Binnewies *et al.*, 2018; Laplane *et al.*, 2019*a*). The role of tumour-infiltrating immune cells in cancer control has been documented by many groups. The 'immune contexture' denotes the density, immune functional orientation, and spatial organisation of the immune infiltrate in relation to patient survival (Fridman *et al.*, 2017; Bruni, Angell & Galon, 2020). This led to the concept of 'immunoscore' (Galon *et al.*, 2012), a quantification of immune cell infiltration shown to be a prognostic factor superior to traditional classifications in colorectal cancer and potentially in other cancer types (Pagès *et al.*, 2018; Angell *et al.*, 2020). The same group has shown the influence of the immune system as a selection pressure on the metastatic process through space and time (Angelova *et al.*, 2018). Overall, the role of immune components is extremely complex, not only because they can be cancer-inhibiting or cancer-promoting, but also because how they influence cancer development and progression depends on their interactions with the tumour, the stroma, and the rest of the organism, and because all these interactions change through time (Binnewies *et al.*, 2018). A clear manifestation of the fact that immune responses must be understood not just at a local level (e.g. tumour, lymph nodes) but also at the organismal level is that the efficacy of immunotherapies is dependent on system-level immunity (Spitzer *et al.*, 2017). Related to this, an increasing number of experimental and clinical studies are exploring the influence of the microbiota, diet, or psychological stress on immune responses to cancer (Sepich-Poore *et al.*, 2021). Thus, it is crucial to understand the dialogue between the immune system and cancer both locally and systemically.

As examined by philosophers (Pradeu, 2019; Zach & Greslehner, 2023), the role of the immune system in cancer progression is at odds with most traditional views in immunology, especially those based on self–non-self and defence (Pardoll, 2003). Most tumours originate from the self, and yet are detectable by the immune system. This raises a conundrum of how exactly the immune system is able to detect and respond to tumours. It has been suggested that the immune system recognises tumour 'neo-antigens' (i.e. abnormal epitopes expressed by cancer cells following an accumulation of mutations) (Schumacher *et al.*, 2019), the underlying idea being that the more tumour surface patterns differ from 'self' patterns, the more likely they are to be detected and eliminated by the immune system. This approach ultimately connects immunogenicity with the tumour mutational burden (Klempner *et al.*, 2020). Yet it remains a challenge to define rigorously the notion of neo-antigen (Lu & Robbins, 2016) and situate it on the spectrum going from non-self to self through altered self (Houghton, 1994). Moreover, as philosophical analysis has shown, the very concept of an 'altered self' is tautologically defined, when an antigen is said to belong to the 'altered self' because it is immunogenic, creating a logical circularity (Pradeu, 2012). A rigorous assessment of the neo-antigen notion may help determine how it can be used in clinical practice (Klempner *et al.*, 2020; Capietto *et al.*, 2020), including in cases where the connection between the tumour mutational load and the response to immunotherapies is questioned (Yarchoan *et al.*, 2017; Chowell *et al.*, 2022). Clarifying the nature of this connection through rigorous conceptual and empirical analyses is crucial, as the use of tumour mutational burden has been recently approved by the U.S. Food and Drug Administration (Subbiah *et al.*, 2020).

Philosophical and conceptual analysis can help clarify cancer immunogenicity by proposing theoretical frameworks departing from the application to cancer of the traditional self–non-self dichotomy. An important example is the 'danger theory', developed in the 1990s by Polly Matzinger (Matzinger, 1994) as an explicit critique of the empirical inadequacy of the self–non-self theory. This theory explains immune responses as responses to tissue damage. In the context of cancer, this led to the quest for damage-associated molecular patterns (DAMPs) (Krysko *et al.*, 2013), based on the underlying idea that tumours would be immunogenic only in contexts of tissue damage or distress (Fuchs & Matzinger, 1996). In the 'discontinuity theory' formulated by a philosopher in collaboration with several scientists (Pradeu & Carosella, 2006; Pradeu, 2012), the immune system responds to the speed of antigenic change, i.e. the time derivative of antigenic difference. This theory leads to a new prediction, that tumours changing slowly are unlikely to be eliminated by the immune system. This theory opens new therapeutic possibilities: if true, the immune responses to cancer could be boosted by increasing antigenic change (Pradeu, Jaeger & Vivier, 2013). Such ideas have been tested (Liu *et al.*, 2021) and modelled (Sontag, 2017; George & Levine, 2020) in different cancer settings, with potentially significant therapeutic consequences, including promises of innate immunity-based immunotherapies, such as transformed-induced NK cells that can have both a cytotoxic activity and promote the response of adaptive immune cells (Demaria *et al.*, 2019). As predicted by the discontinuity theory, NK cells in cancer respond to rapid modifications in their environment and when these alterations are long lasting, NK cells adapt to them by ceasing to be responsive (Boudreau & Hsu, 2018). In the future, other types of data could help decide whether this theory is valid. For instance, spontaneous or transplanted tumours with different growth rates in mice could be compared in the laboratory for their degree of immunogenicity.

Even more crucially, philosophical work can contribute to re-defining the immune system functionally. For example, conceptualising the immune system as a system of not only defence but also tissue regulation and repair helps understand how the immune system can favour cancer growth and dissemination *via* repair mechanisms (Pradeu, 2019), especially considering the connection between cancer and unsuccessful tissue repair (Dvorak, 1986, 2015). Finally, philosophy in so far as it considers the big picture, could help put research on immune–cancer interactions into a wider

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integrative context (Plutynski, 2013, 2021*a*; Plutynski & Bertolaso, 2018). For example, several conceptually oriented biologists propose that immune responses to cancer can be understood only in the context of tissue-level regulation (de Visser *et al.*, 2006), including *via* modulation of the extracellular matrix (Pickup, Mouw & Weaver, 2014).

VII. DO STEM CELLS PLAY A CENTRAL ROLE IN CANCER?

Human healthy tissues are maintained by a pool of stem cells that ensure the production of new cells necessary for tissue homeostasis and repair. They are also involved in cancers, but their role remains a topic of much debate in oncology.

(1) Stem cell division and the risk of cancer

The relationship between stem cell numbers and cancer has long been the focus of theoretical attention. Cairns (1975) hypothesised that stem cell tissue architecture may have been selected for the protection it confers against cancer: if only tissue stem cells can self-renew over long time periods, while all other cells have a limited proliferative capacity, differentiate, and die, then any cancerous mutation occurring in non-stem cells will be naturally expelled. For cancer to develop, multiple hits need to occur in the stem cell population. More recently, there has been an avid debate in the scientific literature about the significance of the total number of stem cell divisions in a tissue or organ for explaining the variation in the lifetime risk of developing cancer in various tissues. The debate started with a controversial publication from Tomasetti & Vogelstein (2015) arguing that there was a direct causal relationship between the number of stem cell divisions and relative cancer risk. They further argued that one can use this correlation to estimate the relative significance of endogenous causes of cancer risk in a particular cancer type or subtype and exogenous factors. Dozens of papers have criticised their argument, questioning their methods, reasoning, and conclusions. However, the debate has been obstructed by hidden premises, conceptual fuzziness, and argumentative inconsistencies. Philosopher Anya Plutynski (2021*b*) offered an analysis of the main issues at stake. For instance, she highlighted that many criticisms were due to a lack of clarity on the part of Tomasetti & Vogelstein (2015), particularly in the use of the concept of 'luck'. Apparently opposing claims were made based on different understandings of luck. She also highlighted several flawed presuppositions in Tomasetti & Vogelstein's argument, such as taking stem cell turnover to be the exclusive cause of intrinsic relative cancer risk across tissue type. While differences in the total number of stem cell divisions in different tissues do provide a plausible partial explanation of the differences in lifetime risk of cancer in these tissues, this is only one of several endogenous factors at work in carcinogenesis. Moreover, their attempt at quantifying the causal implications of accumulation of mutations in stem cells *versus* inherited or environmental factors treated such factors as independent. This was a flawed assumption, as well as their assumption that the proportional risk adds to 100. Population attributable fraction – the incidence of all cases of a particular disease in a population that is attributable to a specific exposure – can add to more than 1 (Krieger, 2017). Some individuals with more than one risk factor can have disease prevented in more than one way, i.e. removing one cause does not necessarily lower the risk proportionally. This analysis has serious implications for cancer prevention. It undermines Tomasetti & Vogelstein's (2015) argument that their quantification could serve as a basis to decide when to invest more effort on primary or secondary prevention.

(2) Cancer stem cells

Accumulating data have led to the idea that like normal tissues, tumour development and maintenance also relies on a pool of cancer stem cells (CSCs). The CSC model led to the hypothesis, in the early 2000s, that eliminating CSCs would be necessary and sufficient to cure cancer (Reya *et al.*, 2001), opening new avenues for improving cancer treatment. But the identification of CSCs has proved challenging, and many data depart from the initial model, leading to confusion about what CSCs exactly are, whether they really exist, and debates about whether the CSC model holds. To know whether the CSC model holds, one needs to have a clear view of what stem cells are. Stem cells are defined by the ability to self-renew and differentiate but this definition faces several issues (Laplane, 2021). Philosopher Melinda Fagan framed a useful model that clarifies both what stem cells are and what we mean by self-renewal and differentiation. Her model depicts stem cells as cells belonging to a lineage in which they have the highest abilities to self-renew and differentiate, where these abilities are relative to a set of properties that are characteristic of stem cells and differentiated cells of that lineage (Fagan, 2013, 2021). This unifying model allows clearer thinking across tissues and species. Heterogeneity between stem cells across tissues creates much confusion. We thus also need a clear view of how different stem cells depart from each other. Philosophy has a tradition of characterising properties. There are different kinds of properties: constitutive, extrinsic, dispositional, relational, etc. Applying this tradition to CSCs, Laplane clarified the nature of 'stemness' – the property of being a stem cell (Laplane, 2016). Current evidence does not converge toward a unified view of stemness, but rather suggests that stemness is a different property in different types of stem cells (Table 1). In some tissues like the haematopoietic system, stemness is a constitutive property of stem cells, whose expression is regulated by the niche – a 'dispositional property' in philosophy. In others, like the colon epithelium, cells are more plastic, and non-stem cells can acquire stemness under the influence of the microenvironment, making stemness a 'relational property' (a property that is not constitutive and relies on a relationship between different entities). For example, physical cues, such as pressure induced by growth,

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were recently found to be able to induce stemness acquisition in mice colon cancer, a process blocked by Ret-kinase pharmacological inhibition (Nguyen Ho-Bouldoires *et al.*, 2022). Some *in vitro* experiments performed on breast cancer cell lines, accompanied by mathematical modelling, also suggested that regeneration of lost stem cells can occur in the absence of a particular microenvironment, with a return of the whole cell population to its initial equilibrium in cell composition (Gupta *et al.*, 2011), a case where stemness appears as a systemic property (stem cells are substitutable and which cell is a stem cell is regulated at the cell population/system level). In cancers, some alterations might change the nature of the stemness property. For example, alterations in some myeloproliferative neoplasms disrupt the signalling relationship between the leukaemic stem cells (LSCs) and the bone marrow microenvironment. This loss of regulation of the LSCs by their niche might make stemness become a 'categorical property' (still constitutive but no longer regulated by the microenvironment). Different types of alteration might impact stemness in different ways (Laplane & Solary, 2019), a question that needs further experimental exploration.

Such a conceptual analysis allows a clearer view of the diverse ways in which stem cells behave, and come to be, across different tissues, in both normal and pathological situations. It also has practical implications for fundamental research, regenerative medicine, and therapeutic strategies against cancers. First, for research, depending on what type of property stemness is in a given tissue, different experimental procedures will be required to understand the potential role of its stem cells. Second, regeneration of tissues relies on different requirements depending on what stem cells are. For example, tissues in which stemness is a categorical or dispositional property cannot regenerate if their stem cells are lost; successful regeneration of a tissue in which stemness is a relational property will need the presence of a functional stem cell niche; and so on. Third, the efficiency of anti-cancer therapies targeting CSCs or their niche will depend on the nature of stemness (Table 1). Targeting CSCs can actually be 'necessary and sufficient' to cure cancer when stemness is a categorical or dispositional property. Niche-targeting is an interesting alternative when stemness is a dispositional or relational property. Stemness as a systemic property

Table 1. Philosophical characterisation of stemness and consequences for therapeutic strategies against cancer. CSC, cancer stem cell.

Stemness property	Philosophical definition	Biological examples	Therapeutic strategies
Dispositional	A constitutive property regulated by extrinsic stimuli	The haematopoietic system	CSC targeting Niche targeting
Relational	A property that can be acquired, and that emerges from a particular relationship	Some epithelial tissues such as the colon; germline in *Drosophila*	Niche targeting
Systemic	A property that can be acquired, and that is regulated at the system level. Entities are substitutable	Breast cancer cell lines	Surgery + novel strategies to be developed
Categorical	A constitutive property that relies only on intrinsic properties of the entity	The traditional view of stem cells; some leukaemia in case of loss of regulation by the niche	CSC targeting

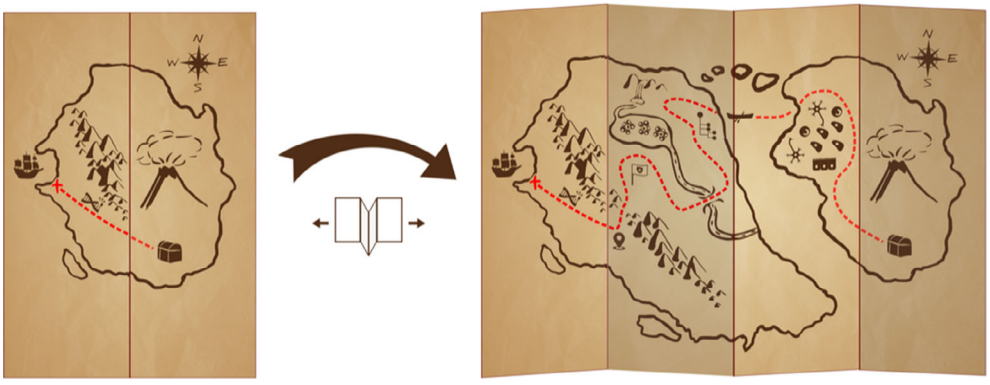

Fig. 2. A map showing that reaching a treasure sometimes requires a detour. The shortest and most obvious route (left) can be misleading. Conceptual, theoretical, and philosophical thinking is often a detour, but this detour can be productive or even necessary (right) for making scientific progress. The map illustrates that going through different philosophical steps can help us reach the final point (represented as a treasure), including by its capacity to connect (represented as bridges) different scientific issues, approaches, and communities (represented as different regions on the map).

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appears as a blind spot, in need of innovative strategies, if we want to do better than the traditional approaches aiming at (but often failing in) eradicating all the malignant cells. More research will be required to understand better what triggers stemness acquisition, and what could block such acquisition. Overall, this analysis shows that whether the CSC model applies might not be the best way to frame research. A better way would be to ask how it may apply, which allows us to distinguish four situations and adapt therapeutic strategies to these situations.

VIII. CONCLUSIONS

(1) Philosophical, theoretical, and interdisciplinary approaches to oncology have great potential to enhance progress in our scientific and medical understanding of cancer (Fig. 2).
(2) More precise definitions and conceptualizations of cancer biology, and more rigorous reasoning are instrumental to disentangling causal and non-causal roles in cancer development, a pillar of modern biology. This issue is pervasive throughout this article: which mutations are causal and under which conditions (Section II), whether the deregulation of multicellular cooperation is causal in cell transformation (Section IV), what elements outside of the tumour cells play a causal role in oncogenesis and cancer progression (Section V), and what causal role stem cells play in the risk of transformation (Section VII).
(3) They can also help avoiding flawed inferences, as for example those made from clone size (Section III) or from characterising a mutation as a 'driver' (Section II); and help to identify under which conditions a claim is true (Sections IV and VII).
(4) Analysis of hidden assumptions and argumentative consistency can create new testable hypotheses, as in the case of the relationship between multicellularity and cancer (Section IV), new avenues for research, such as new or more complete evaluations of evolutionary dynamics in cancer (Section III), new therapeutic strategies, such as in the case of cancer stem cells (Section VII), or for preventing metastases (Section V).
(5) More generally, our review illustrates how more work on the theoretical foundations of cancer can have consequences for medical issues such as the demarcation between normal, premalignant and malignant stages, depending on the notion of driver mutation (Section II), when to treat, depending on the interpretation of clonal expansions (Section III), what to target, depending on the conceptualization of the TME (Section V) or of the CSC (Section VII), and how to intervene, for example depending on the theorization of the immune system (Section VI).
(6) An alliance between biologists, medical doctors, mathematicians, physicists, and philosophers is essential for advancing theoretical oncology in ways that will prove experimentally and therapeutically fruitful.

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X. AUTHOR CONTRIBUTIONS

T. P. and L. L. coordinated the collective work and wrote the initial manuscript. P.-L. G. co-wrote Section II, A. P. co-wrote Section VII. B. D.-F., F. G., S. O., J. F., E. S. and A. E., contributed to all sections. M. D., E. G., S. G., B. C.-Y., I. C.-Y. and D. S. contributed to Section II. A. P., J. S. B., C. M. and S. B. contributed to Section III. A. S., F. J. and C. M. contributed to Section IV. M. Be., E. R., S. Y., M. Bi., L. C., E. F., R. K., E. L., N. L., P. N. and G. D. S.-P. contributed to Section V. N. L., A. M., E. R., V. S. and J. G. contributed to Section VI. C. M. S. and H. C. contributed to Section VII. All authors contributed to revisions and approved the final version. Figures were drawn by Wiebke Lautré.

XI. REFERENCES

Aktipis, A. (2020). *The Cheating Cell: How Evolution Helps us Understand and Treat Cancer*. Princeton University Press, Princeton.
Aktipis, C. A., Boddy, A. M., Jansen, G., Hibner, U., Hochberg, M. E., Maley, C. C. & Wilkinson, G. S. (2015). Cancer across the tree of life: cooperation and cheating in multicellularity. *Philosophical Transactions of the Royal Society London B* **370**, 20140219.
Alessandri, K., Sarangi, B. R., Gurchenkov, V. V., Sinha, B., Kiessling, T. R., Fetler, L., Rico, F., Scheuring, S., Lamaze, C., Simon, A., Geraldo, S., Vignjević, D., Doméjean, H., Rolland, L., Funfak, A., *et al.* (2013). Cellular capsules as a tool for multicellular spheroid production and for investigating the mechanics of tumor progression in vitro. *Proceedings of the National Academy of Sciences* **110**, 14843–14848.
Altrock, P. M., Liu, L. L. & Michor, F. (2015). The mathematics of cancer: integrating quantitative models. *Nature Reviews. Cancer* **15**, 730–745.
Anderson, A. R. A. & Quaranta, V. (2008). Integrative mathematical oncology. *Nature Reviews Cancer* **8**, 227–234.
Anderson, A. R. A., Weaver, A. M., Cummings, P. T. & Quaranta, V. (2006). Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. *Cell* **127**, 905–915.
Anderson, N. M. & Simon, M. C. (2020). The tumor microenvironment. *Current Biology* **30**, R921–R925.
Angell, H. K., Bruni, D., Barrett, J. C., Herbst, R. & Galon, J. (2020). The immunoscore: colon cancer and beyond. *Clinical Cancer Research* **26**, 332–339.
Angelova, M., Mlecnik, B., Vasaturo, A., Bindea, G., Fredriksen, T., Lafontaine, L., Buttard, B., Morgand, E., Bruni, D., Jouret-Mourin, A., Hubert, C., Kartheuser, A., Humblet, Y., Ceccarelli, M., Syed, N., *et al.* (2018). Evolution of metastases in space and time under immune selection. *Cell* **175**, 751–765.e16.
Archetti, M. & Pienta, K. J. (2019). Cooperation among cancer cells: applying game theory to cancer. *Nature Reviews Cancer* **19**, 110–117.
Arnellos, A., Moreno, A. & Ruiz-Mirazo, K. (2013). Organizational requirements for multicellular autonomy: insights from a comparative case study. *Biology & Philosophy* **29**, 851–884.

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Bapat, A., Keita, N., Martelly, W., Kang, P., Seet, C., Jacobsen, J. R., Stoilov, P., Hu, C., Crooks, G. M. & Sharma, S. (2018). Myeloid disease mutations of splicing factor SRSF2 cause G2-M arrest and skewed differentiation of human hematopoietic stem and progenitor cells. *Stem Cells* **36**, 1663–1675.

Batlle, E. & Clevers, H. (2017). Cancer stem cells revisited. *Nature Medicine* **23**, 1124–1134.

Bermúdez-Guzmán, L. (2021). Pan-cancer analysis of non-oncogene addiction to DNA repair. *Scientific Reports* **11**, 23264.

Bertolaso, M. (2016). *Philosophy of Cancer: A Dynamic and Relational View*. Springer, The Netherlands.

Bertolaso, M. & Strauss, B. (2021). The search for progress and a new theory framework in cancer research. In *Rethinking Cancer: A New Paradigm for the Postgenomics Era* (eds B. Strauss, M. Bertolaso, I. Ernberg and M. J. Bissell), pp. 13–40. MIT Press, Cambridge.

Bhat, R., Belardi, B., Mori, H., Kuo, P., Tam, A., Hines, W. C., Le, Q.-T., Bertozzi, C. R. & Bissell, M. J. (2016). Nuclear repartitioning of galectin-1 by an extracellular glycan switch regulates mammary morphogenesis. *Proceedings of the National Academy of Sciences* **113**, E4820–E4827.

Bialek, W. (2018). Perspectives on theory at the interface of physics and biology. *Reports on Progress in Physics* **81**, 012601.

Bich, L., Pradeu, T. & Moreau, J.-F. (2019). Understanding multicellularity: the functional organization of the intercellular space. *Frontiers in Physiology* **10**, 1170.

Binnewies, M., Roberts, E. W., Kersten, K., Chan, V., Fearon, D. F., Merad, M., Coussens, L. M., Gabrilovich, D. I., Ostrand-Rosenberg, S., Hedrick, C. C., Vonderheide, R. H., Pittet, M. J., Jain, R. K., Zou, W., Howcroft, T. K., *et al.* (2018). Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nature Medicine* **24**, 541–550.

Birch, J. (2017). *The Philosophy of Social Evolution*, First Edition. Oxford University Press, Oxford.

Birch, J. & Okasha, S. (2015). Kin selection and its critics. *BioScience* **65**, 22–32.

Bissell, M. J., Hall, H. G. & Parry, G. (1982). How does the extracellular matrix direct gene expression? *Journal of Theoretical Biology* **99**, 31–68.

Bissell, M. J. & Hines, W. C. (2011). Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. *Nature Medicine* **17**, 320–329.

Bissell, M. J. & Radisky, D. (2001). Putting tumours in context. *Nature Reviews Cancer* **1**, 46–54.

Bissell, M. J., Radisky, D. C., Rizki, A., Weaver, V. M. & Petersen, O. W. (2002). The organizing principle: microenvironmental influences in the normal and malignant breast. *Differentiation* **70**, 537–546.

Bonner, J. T. (1998). The origins of multicellularity. *Integrative Biology: Issues, News, and Reviews* **1**, 27–36.

Boudreau, J. E. & Hsu, K. C. (2018). Natural killer cell education and the response to infection and cancer therapy: stay tuned. *Trends in Immunology* **39**, 222–239.

Bruni, D., Angell, H. K. & Galon, J. (2020). The immune contexture and immunoscore in cancer prognosis and therapeutic efficacy. *Nature Reviews Cancer* **20**, 662–680.

Bullman, S., Pedamallu, C. S., Sicinska, E., Clancy, T. E., Zhang, X., Cai, D., Neuberg, D., Huang, K., Guevara, F., Nelson, T., Chipashvili, O., Hagan, T., Walker, M., Ramachandran, A., Diosdado, B., *et al.* (2017). Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. *Science* **358**, 1443–1448.

Burnet, F. M. (1970). *Immunological Surveillance*. Pergamon, Oxford.

Burt, R., Dey, A., Aref, S., Aguiar, M., Akarca, A., Bailey, K., Day, W., Hooper, S., Kirkwood, A., Kirschner, K., Lee, S.-W., Lo Celso, C., Manji, J., Mansour, M. R., Marafioti, T., *et al.* (2019). Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. *Blood* **134**, 1415–1429.

Cairns, J. (1975). Mutation selection and the natural history of cancer. *Nature* **255**, 197–200.

Calabrese, P., Tavaré, S. & Shibata, D. (2004). Pretumor progression: clonal evolution of human stem cell populations. *The American Journal of Pathology* **164**, 1337–1346.

Cannataro, V. L., McKinley, S. A. & St Mary, C. M. (2017). The evolutionary trade-off between stem cell niche size, aging, and tumorigenesis. *Evolutionary Applications* **10**, 590–602.

Cannataro, V. L. & Townsend, J. P. (2018). Neutral theory and the somatic evolution of cancer. *Molecular Biology and Evolution* **35**, 1308–1315.

Capietto, A.-H., Jhunjhunwala, S., Pollock, S. B., Lupardus, P., Wong, J., Hänsch, L., Cevallos, J., Chestnut, Y., Fernandez, A., Lounsbury, N., Nozawa, T., Singh, M., Fan, Z., de la Cruz, C. C., Phung, Q. T., *et al.* (2020). Mutation position is an important determinant for predicting cancer neoantigens. *Journal of Experimental Medicine* **217**(4), e20190179.

Castro-Giner, F., Ratcliffe, P. & Tomlinson, I. (2015). The mini-driver model of polygenic cancer evolution. *Nature Reviews Cancer* **15**, 680–685.

Chen, D. S. & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature* **541**, 321–330.

Cheung, K. J. & Ewald, A. J. (2016). A collective route to metastasis: seeding by tumor cell clusters. *Science* **352**, 167–169.

Chmielecki, J., Foo, J., Oxnard, G. R., Hutchinson, K., Ohashi, K., Somwar, R., Wang, L., Amato, K. R., Arcila, M., Sos, M. L., Socci, N. D., Viale, A., de Stanchina, E., Ginsberg, M. S., Thomas, R. K., *et al.* (2011). Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. *Science Translational Medicine* **3**, 90ra59.

Chowell, D., Yoo, S.-K., Valero, C., Pastore, A., Krishna, C., Lee, M., Hoen, D., Shi, H., Kelly, D. W., Patel, N., Makarov, V., Ma, X., Vuong, L., Sabio, E. Y., Weiss, K., *et al.* (2022). Improved prediction of immune checkpoint blockade efficacy across multiple cancer types. *Nature Biotechnology* **40**, 499–506.

Clark, W. H. (1995). The nature of cancer: morphogenesis and progressive (self)-disorganization in neoplastic development and progression. *Acta Oncologica* **34**, 3–21.

Colom, B., Herms, A., Hall, M. W. J., Dentro, S. C., King, C., Sood, R. K., Alcolea, M. P., Piedrafita, G., Fernandez-Antoran, D., Ong, S. H., Fowler, J. C., Mahbubani, K. T., Saeb-Parsy, K., Gerstung, M., Hall, B. A., *et al.* (2021). Mutant clones in normal epithelium outcompete and eliminate emerging tumours. *Nature* **598**, 510–514.

Csikász-Nagy, A., Escudero, L. M., Guillaud, M., Sedwards, S., Baum, B. & Cavaliere, M. (2013). Cooperation and competition in the dynamics of tissue architecture during homeostasis and tumorigenesis. *Seminars in Cancer Biology* **23**, 293–298.

Darrason, M. (2017). Médecine de précision et médecine des systèmes : La médecine personnalisée se trompe-t-elle de cible? *Lato Sensu: Revue de la Société de philosophie des sciences* **4**(2), 66–82.

Davies, P. C. W. & Lineweaver, C. H. (2011). Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors. *Physical Biology* **8**, 015001.

de Visser, K. E., Eichten, A. & Coussens, L. M. (2006). Paradoxical roles of the immune system during cancer development. *Nature Reviews. Cancer* **6**, 24–37.

Demaria, O., Cornen, S., Daëron, M., Morel, Y., Medzhitov, R. & Vivier, E. (2019). Harnessing innate immunity in cancer therapy. *Nature* **574**, 45–56.

Doonan, J. H. & Sablowski, R. (2010). Walls around tumours—why plants do not develop cancer. *Nature Reviews Cancer* **10**, 794–802.

Duchmann, M., Laplane, L. & Itzykson, R. (2021). Clonal architecture and evolutionary dynamics in acute myeloid leukemias. *Cancers* **13**, 4887.

Dunn, G. P., Bruce, A. T., Ikeda, H., Old, L. J. & Schreiber, R. D. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. *Nature Immunology* **3**, 991–998.

Dvorak, H. F. (1986). Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *The New England Journal of Medicine* **315**, 1650–1659.

Dvorak, H. F. (2015). Tumors: wounds that do not heal–redux. *Cancer Immunology Research* **3**, 1–11.

Egeblad, M., Nakasone, E. S. & Werb, Z. (2010). Tumors as organs: complex tissues that interface with the entire organism. *Developmental Cell* **18**, 884–901.

Fagan, M. B. (2013). *Philosophy of Stem Cell Biology. Knowledge in Flesh and Blood*. Palgrave-Macmillan, London.

Fagan, M. B. (2021). *Stem Cells*, First Edition. Cambridge University Press, Cambridge.

Fernández-Sánchez, M. E., Barbier, S., Whitehead, J., Béalle, G., Michel, A., Latorre-Ossa, H., Rey, C., Fouassier, L., Claperon, A., Brullé, L., Girard, E., Servant, N., Rio-Frio, T., Marie, H., Lesieur, S., *et al.* (2015). Mechanical induction of the tumorigenic β-catenin pathway by tumour growth pressure. *Nature* **523**, 92–95.

Fidler, I. J. (2003). The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nature Reviews Cancer* **3**, 453–458.

Fortunato, A., Boddy, A., Mallo, D., Aktipis, A., Maley, C. C. & Pepper, J. W. (2017). Natural selection in cancer biology: from molecular snowflakes to trait hallmarks. *Cold Spring Harbor Perspectives in Medicine* **7**, a029652.

Frank, S. A. (1998). *Foundations of Social Evolution*. Princeton University Press, Project MUSE, Princeton, Baltimore.

Frank, S. A. (2003). Somatic mosaicism and cancer: inference based on a conditional Luria-Delbrück distribution. *Journal of Theoretical Biology* **223**, 405–412.

Frank, S. A. (2007). *Dynamics of Cancer: Incidence, Inheritance, and Evolution*. Princeton University Press, Princeton.

Fridman, W. H., Zitvogel, L., Sautès-Fridman, C. & Kroemer, G. (2017). The immune contexture in cancer prognosis and treatment. *Nature Reviews Clinical Oncology* **14**, 717–734.

Fuchs, E. J. & Matzinger, P. (1996). Is cancer dangerous to the immune system? *Seminars in Immunology* **8**, 271–280.

Galon, J., Pagès, F., Marincola, F. M., Angell, H. K., Thurin, M., Lugli, A., Zlobec, I., Berger, A., Bifulco, C., Botti, G., Tatangelo, F., Britten, C. M., Kreiter, S., Chouchane, L., Delrio, P., *et al.* (2012). Cancer classification using the Immunoscore: a worldwide task force. *Journal of Translational Medicine* **10**, 205.

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Gardner, A. (2015*a*). More on the genetical theory of multilevel selection. *Journal of Evolutionary Biology* **28**, 1747–1751.
Gardner, A. (2015*b*). The genetical theory of multilevel selection. *Journal of Evolutionary Biology* **28**, 305–319.
Gatenby, R. A., Gillies, R. J. & Brown, J. S. (2010). The evolutionary dynamics of cancer prevention. *Nature Reviews Cancer* **10**, 526–527.
Gatenby, R. A., Silva, A. S., Gillies, R. J. & Frieden, B. R. (2009). Adaptive therapy. *Cancer Research* **69**, 4894–4903.
George, J. T. & Levine, H. (2020). Sustained coevolution in a stochastic model of cancer–immune interaction. *Cancer Research* **80**, 811–819.
Germain, P.-L. (2012). Cancer cells and adaptive explanations. *Biology & Philosophy* **27**, 785–810.
Germain, P. L. & Laplane, L. (2017). Metastasis as supra-cellular selection? A reply to Lean and Plutynski. *Biology and Philosophy* **32**, 281–287.
Godfrey-Smith, P. (2009). *Darwinian Populations and Natural Selection*. Oxford University Press, Oxford.
Gravina, S., Ganapathi, S. & Vijg, J. (2015). Single-cell, locus-specific bisulfite sequencing (SLBS) for direct detection of epimutations in DNA methylation patterns. *Nucleic Acids Research* **43**, e93.
Greaves, M. (2013). Cancer stem cells as 'units of selection'. *Evolutionary Applications* **6**, 102–108.
Greaves, M. (2015). Evolutionary determinants of cancer. *Cancer Discovery* **5**, 806–820.
Greaves, M. & Maley, C. C. (2012). Clonal evolution in cancer. *Nature* **481**, 306–313.
Green, S. (2021). Cancer beyond genetics: on the practical implications of downward causation. In *Biological Levels: Composition, Scale and Evolution in Complex Systems* (eds D. S. Brooks, J. DiFrisco and W. C. Wimsatt), pp. 195–213. MIT Press, Cambridge, Massachusetts & London, England.
Greenland, S., Pearl, J. & Robins, J. M. (1999). Causal diagrams for epidemiologic research. *Epidemiology* **10**, 37–48.
Guerra, C., Schuhmacher, A. J., Cañamero, M., Grippo, P. J., Verdaguer, L., Pérez-Gallego, L., Dubus, P., Sandgren, E. P. & Barbacid, M. (2007). Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. *Cancer Cell* **11**, 291–302.
Gupta, P. B., Fillmore, C. M., Jiang, G., Shapira, S. D., Tao, K., Kuperwasser, C. & Lander, E. S. (2011). Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. *Cell* **146**, 633–644.
Hahn, W. C., Bader, J. S., Braun, T. P., Califano, A., Clemons, P. A., Druker, B. J., Ewald, A. J., Fu, H., Jagu, S., Kemp, C. J., Kim, W., Kuo, C. J., McManus, M. T., Mills, G. B., Mo, X., *et al.* (2021). An expanded universe of cancer targets. *Cell* **184**, 1142–1155.
Halpern, J. Y. & Pearl, J. (2020). Causes and explanations: a structural-model approach. Part I: causes. *The British Journal for the Philosophy of Science* **56**, 843-887.
Hamilton, W. D. (1964*a*). The genetical evolution of social behaviour I. *Journal of Theoretical Biology* **7**, 1–16.
Hamilton, W. D. (1964*b*). The genetical evolution of social behaviour II. *Journal of Theoretical Biology* **7**, 17–52.
Hanahan, D. & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *Cell* **144**, 646–674.
Hekmatshoar, Y., Nakhle, J., Galloni, M. & Vignais, M.-L. (2018). The role of metabolism and tunneling nanotube-mediated intercellular mitochondria exchange in cancer drug resistance. *Biochemical Journal* **475**, 2305–2328.
Hellmann, M. D., Paz-Ares, L., Bernabe Caro, R., Zurawski, B., Kim, S.-W., Carcereny Costa, E., Park, K., Alexandru, A., Lupinacci, L., de la Mora Jimenez, E., Sakai, H., Albert, I., Vergnenegre, A., Peters, S., Syrigos, K., *et al.* (2019). Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *New England Journal of Medicine* **381**, 2020–2031.
Herron, M. D., Conlin, P. L. & Ratcliff, W. C. (eds) (2022). *The Evolution of Multicellularity*. CRC Press, Boca Raton.
Hess, J. M., Bernards, A., Kim, J., Miller, M., Taylor-Weiner, A., Haradhvala, N. J., Lawrence, M. S. & Getz, G. (2019). Passenger hotspot mutations in cancer. *Cancer Cell* **36**, 288–301.e14.
Houghton, A. N. (1994). Cancer antigens: immune recognition of self and altered self. *The Journal of Experimental Medicine* **180**, 1–4.
Huch, M., Knoblich, J. A., Lutolf, M. P. & Martinez-Arias, A. (2017). The hope and the hype of organoid research. *Development (Cambridge, England)* **144**, 938–941.
Jourdain, A., Duchmann, M., Willekens, C., Solary, É., Perié, L. & Laplane, L. (2021). Evolution clonale: qu'est-ce qu'un clone? In *La biologie au défi de l'histoire. Mélanges offerts à Michel Morange* (eds L. Loison and T. Pradeu), p. 222. Éditions Matériologiques, Paris.
Joyce, J. A. & Fearon, D. T. (2015). T-cell exclusion, immune privilege, and the tumor microenvironment. *Science* **348**, 74–80.
June, C. H. & Sadelain, M. (2018). Chimeric antigen receptor therapy. *The New England Journal of Medicine* **379**, 64–73.
Kakiuchi, N. & Ogawa, S. (2021). Clonal expansion in non-cancer tissues. *Nature Reviews Cancer* **21**, 239–256.
Kalaora, S., Nagler, A., Nejman, D., Alon, M., Barbolin, C., Barnea, E., Ketelaars, S. L. C., Cheng, K., Vervier, K., Shental, N., Bussi, Y., Rotkopf, R., Levy, R., Benedek, G., Trabish, S., *et al.* (2021). Identification of bacteria-derived HLA-bound peptides in melanoma. *Nature* **592**, 138–143.
Kaplan, R. N., Rafii, S. & Lyden, D. (2006). Preparing the 'soil': the premetastatic niche. *Cancer Research* **66**, 11089–11093.
Kareva, I., Luddy, K. A., O'Farrelly, C., Gatenby, R. A. & Brown, J. S. (2021). Predator-prey in tumor-immune interactions: a wrong model or just an incomplete one? *Frontiers in Immunology* **12**, 3391.
Kelly, P. N. (2018). The cancer immunotherapy revolution. *Science* **359**, 1344–1345.
Klempner, S. J., Fabrizio, D., Bane, S., Reinhart, M., Peoples, T., Ali, S. M., Sokol, E. S., Frampton, G., Schrock, A. B., Anhorn, R. & Reddy, P. (2020). Tumor mutational burden as a predictive biomarker for response to immune checkpoint inhibitors: a review of current evidence. *The Oncologist* **25**, e147–e159.
Komarova, N. L. (2005). Mathematical modeling of tumorigenesis: mission possible. *Current Opinion in Oncology* **17**, 39–43.
Krieger, N. (2017). Health equity and the fallacy of treating causes of population health as if they sum to 100%. *American Journal of Public Health* **107**, 541–549.
Krysko, O., Løve Aaes, T., Bachert, C., Vandenabeele, P. & Krysko, D. V. (2013). Many faces of DAMPs in cancer therapy. *Cell Death & Disease* **4**, e631.
Laconi, E. (2007). The evolving concept of tumor microenvironments. *Bioessays* **29**, 738–744.
Lam, K. C., Araya, R. E., Huang, A., Chen, Q., Modica, M. D., Rodrigues, R. R., Lopès, A., Johnson, S. B., Schwarz, B., Bohrnsen, E., Cogdill, A. P., Bosio, C. M., Wargo, J. A., Lee, M. P. & Goldszmid, R. S. (2021). Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment. *Cell* **184**, 5338–5356.
Laplane, L. (2016). *Cancer Stem Cells: Philosophy and Therapies*. Harvard Univerity Press, Cambridge.
Laplane, L. (2021). Stem cell conceptual clarifications. In *Stem Cell Biology and Regenerative Medicine*, Second Edition (eds C. Durand and P. Charbord), pp. 685–704. River Publishers, Gistrup.
Laplane, L., Duluc, D., Bikfalvi, A., Larmonier, N. & Pradeu, T. (2019*a*). Beyond the tumour microenvironment. *International Journal of Cancer* **145**, 2611–2618.
Laplane, L., Duluc, D., Larmonier, N., Pradeu, T. & Bikfalvi, A. (2018). The multiple layers of the tumor environment. *Trends Cancer* **4**, 802–809.
Laplane, L., Mantovani, P., Adolphs, R., Chang, H., Mantovani, A., McFall-Ngai, M., Rovelli, C., Sober, E. & Pradeu, T. (2019*b*). Why science needs philosophy. *Proceedings of the National Academy of Sciences* **116**, 3948–3952.
Laplane, L. & Solary, E. (2019). Towards a classification of stem cells. *eLife* **8**, e46563.
Lawrence, M. S., Stojanov, P., Polak, P., Kryukov, G. V., Cibulskis, K., Sivachenko, A., Carter, S. L., Stewart, C., Mermel, C. H., Roberts, S. A., Kiezun, A., Hammerman, P. S., McKenna, A., Drier, Y., Zou, L., *et al.* (2013). Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* **499**, 214–218.
Lean, C. & Plutynski, A. (2016). The evolution of failure: explaining cancer as an evolutionary process. *Biology and Philosophy* **31**, 39–57.
Lewontin, R. C. (1970). The units of selection. *Annual Review of Ecology and Systematics* **1**, 1–18.
Lewontin, R. C. (2000). *The Triple Helix: Gene, Organism, and Environment*. Harvard University Press, Cambridge, Mass.
Li, S., Garrett-Bakelman, F. E., Chung, S. S., Sanders, M. A., Hricik, T., Rapaport, F., Patel, J., Dillon, R., Vijay, P., Brown, A. L., Perl, A. E., Cannon, J., Bullinger, L., Luger, S., Becker, M., *et al.* (2016). Distinct evolution and dynamics of epigenetic and genetic heterogeneity in acute myeloid leukemia. *Nature Medicine* **22**, 792–799.
Lineweaver, C. H., Bussey, K. J., Blackburn, A. C. & Davies, P. C. W. (2021). Cancer progression as a sequence of atavistic reversions. *BioEssays* **43**, 2000305.
Lineweaver, C. H., Davies, P. C. W. & Vincent, M. D. (2014). Targeting cancer's weaknesses (not its strengths): therapeutic strategies suggested by the atavistic model. *BioEssays* **36**, 827–835.
Liu, C., Qi, T., Milner, J. J., Lu, Y. & Cao, Y. (2021). Speed and location both matter: antigen stimulus dynamics controls CAR-T cell response. *Frontiers in Immunology* **12**, 4225.
Love, A. C. (2016). Explaining the origins of multicellularity: between evolutionary dynamics and developmental mechanisms. In *Multicellularity: Origins and Evolution* (eds K. J. Niklas and S. A. Newman), pp. 279–295. MIT Press, Cambridge.
Lu, Y.-C. & Robbins, P. F. (2016). Cancer immunotherapy targeting neoantigens. *Seminars in Immunology* **28**, 22–27.
Lyne, A.-M., Laplane, L. & Perié, L. (2021). To portray clonal evolution in blood cancer, count your stem cells. *Blood* **137**, 1862–1870.
Mack, S. C., Witt, H., Piro, R. M., Gu, L., Zuyderduyn, S., Stütz, A. M., Wang, X., Gallo, M., Garzia, L., Zayne, K., Zhang, X., Ramaswamy, V.,

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Jäger, N., Jones, D. T. W., Sill, M., *et al.* (2014). Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. *Nature* **506**, 445–450.
Mager, L. F., Burkhard, R., Pett, N., Cooke, N. C. A., Brown, K., Ramay, H., Paik, S., Stagg, J., Groves, R. A., Gallo, M., Lewis, I. A., Geuking, M. B. & McCoy, K. D. (2020). Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* **369**, 1481–1489.
Malaterre, C. (2011). Making sense of downward causation in manipulationism: illustrations from cancer research. *History and Philosophy of the Life Sciences* **33**, 537–561.
Maley, C. C., Aktipis, A., Graham, T. A., Sottoriva, A., Boddy, A. M., Janiszewska, M., Silva, A. S., Gerlinger, M., Yuan, Y., Pienta, K. J., Anderson, K. S., Gatenby, R., Swanton, C., Posada, D., Wu, C.-I., *et al.* (2017). Classifying the evolutionary and ecological features of neoplasms. *Nature Reviews Cancer* **17**, 605–619.
Maley, C. C., Galipeau, P. C., Li, X., Sanchez, C. A., Paulson, T. G. & Reid, B. J. (2004). Selectively advantageous mutations and hitchhikers in neoplasms: p16 lesions are selected in Barrett's esophagus. *Cancer Research* **64**, 3414–3427.
Maman, S. & Witz, I. P. (2018). A history of exploring cancer in context. *Nature Reviews Cancer* **18**, 359–376.
Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. (2008). Cancer-related inflammation. *Nature* **454**, 436–444.
Mantovani, A. & Longo, D. L. (2018). Macrophage checkpoint blockade in cancer—back to the future. *New England Journal of Medicine* **379**, 1777–1779.
Mantovani, A. & Sica, A. (2010). Macrophages, innate immunity and cancer: balance, tolerance, and diversity. *Current Opinion in Immunology* **22**, 231–237.
Marongiu, F., Serra, M. & Laconi, E. (2018). Development versus evolution in cancer biology. *Trends in Cancer* **4**, 342–348.
Martincorena, I., Fowler, J. C., Wabik, A., Lawson, A. R. J., Abascal, F., Hall, M. W. J., Cagan, A., Murai, K., Mahbubani, K., Stratton, M. R., Fitzgerald, R. C., Handford, P. A., Campbell, P. J., Saeb-Parsy, K. & Jones, P. H. (2018). Somatic mutant clones colonize the human esophagus with age. *Science* **362**, 911–917.
Matzinger, P. (1994). Tolerance, danger, and the extended family. *Annual Review of Immunology* **12**, 991–1045.
Maynard Smith, J. (1964). Group selection and kin selection. *Nature* **201**, 1145–1147.
Mayr, E. (1959). Darwin and the evolutionary theory in biology. In *Evolution and Anthropology: A Centennial Appraisal*. J. Harvard University Press, Cambridge.
McAllister, S. S. & Weinberg, R. A. (2014). The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. *Nature Cell Biology* **16**, 717–727.
McFarland, C. D., Korolev, K. S., Kryukov, G. V., Sunyaev, S. R. & Mirny, L. A. (2013). Impact of deleterious passenger mutations on cancer progression. *Proceedings of the National Academy of Sciences* **110**, 2910–2915.
McFarland, C. D., Mirny, L. A. & Korolev, K. S. (2014). Tug-of-war between driver and passenger mutations in cancer and other adaptive processes. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 15138–15143.
McFarland, C. D., Yaglom, J. A., Wojtkowiak, J. W., Scott, J. G., Morse, D. L., Sherman, M. Y. & Mirny, L. A. (2017). The damaging effect of passenger mutations on cancer progression. *Cancer Research* **77**, 4763–4772.
Michealraj, K. A., Kumar, S. A., Kim, L. J. Y., Cavalli, F. M. G., Przelicki, D., Wojcik, J. B., Delaidelli, A., Bajic, A., Saulnier, O., MacLeod, G., Vellanki, R. N., Vladoiu, M. C., Guilhamon, P., Ong, W., Lee, J. J. Y., *et al.* (2020). Metabolic regulation of the epigenome drives lethal infantile ependymoma. *Cell* **181**, 1329–1345.e24.
Michod, R. E. (2005). On the transfer of fitness from the cell to the multicellularorganism. *Biology and Philosophy* **20**, 967–987.
Miroshnychenko, D., Baratchart, E., Ferrall-Fairbanks, M. C., Velde, R. V., Laurie, M. A., Bui, M. M., Tan, A. C., Altrock, P. M., Basanta, D. & Marusyk, A. (2021). Spontaneous cell fusions as a mechanism of parasexual recombination in tumour cell populations. *Nature Ecology & Evolution* **5**, 379–391.
Monroe, J. G., Srikant, T., Carbonell-Bejerano, P., Becker, C., Lensink, M., Exposito-Alonso, M., Klein, M., Hildebrandt, J., Neumann, M., Kliebenstein, D., Weng, M.-L., Imbert, E., Ågren, J., Rutter, M. T., Fenster, C. B., *et al.* (2022). Mutation bias reflects natural selection in *Arabidopsis thaliana*. *Nature* **602**, 101–105.
Morange, M. (1997). From the regulatory vision of cancer to the oncogene paradigm, 1975–1985. *Journal of the History of Biology* **30**, 1–29.
Morange, M. (2012). What history tells us XXVIII. What is really new in the current evolutionary theory of cancer? *Journal of Biosciences* **37**, 609–612.
Nedelcu, A. M. (2020). The evolution of multicellularity and cancer: views and paradigms. *Biochemical Society Transactions* **48**, 1505–1518.
Nejman, D., Livyatan, I., Fuks, G., Gavert, N., Zwang, Y., Geller, L. T., Rotter-Maskowitz, A., Weiser, R., Mallel, G., Gigi, E., Meltser, A., Douglas, G. M., Kamer, I., Gopalakrishnan, V., Dadosh, T., *et al.* (2020). The human tumor microbiome is composed of tumor type–specific intracellular bacteria. *Science* **368**, 973–980.
Neuhöfer, P., Roake, C. M., Kim, S. J., Lu, R. J., West, R. B., Charville, G. W. & Artandi, S. E. (2021). Acinar cell clonal expansion in pancreas homeostasis and carcinogenesis. *Nature* **597**, 715–719.
Newton, P. K., Mason, J., Bethel, K., Bazhenova, L., Nieva, J., Norton, L. & Kuhn, P. (2013). Spreaders and sponges define metastasis in lung cancer: a Markov Chain Monte Carlo mathematical model. *Cancer Research* **73**, 2760–2769.
Newton, P. K., Mason, J., Venkatappa, N., Jochelson, M. S., Hurt, B., Nieva, J., Comen, E., Norton, L. & Kuhn, P. (2015). Spatiotemporal progression of metastatic breast cancer: a Markov chain model highlighting the role of early metastatic sites. *NPJ Breast Cancer* **1**, 1–9.
Ng, L. G. (2019). Neutrophil: a mobile fertilizer. *Journal of Experimental Medicine* **216**, 4–6.
Nguyen Ho-Bouldoires, T. H., Sollier, K., Zamfirov, L., Broders-Bondon, F., Mitrossilis, D., Bermeo, S., Guerin, C. L., Chipont, A., Champenois, G., Leclère, R., André, N., Ranno, L., Michel, A., Ménager, C., Meseure, D., *et al.* (2022). Ret kinase-mediated mechanical induction of colon stem cells by tumor growth pressure stimulates cancer progression in vivo. *Communications Biology* **5**, 1–18.
Nia, H. T., Munn, L. L. & Jain, R. K. (2020). Physical traits of cancer. *Science* **370**, eaaz0868.
Niklas, K. J. & Newman, S. A. (2016). *Multicellularity: Origins and Evolution*. MIT Press, Cambridge.
Niklas, K. J. & Newman, S. A. (2020). The many roads to and from multicellularity. *Journal of Experimental Botany* **71**, 3247–3253.
Norton, L. & Massagué, J. (2006). Is cancer a disease of self-seeding? *Nature Medicine* **12**, 875–878.
Nowell, P. (1976). The clonal evolution of tumor cell populations. *Science* **194**, 23–28.
Nunney, L. (1999). Lineage selection and the evolution of multistage carcinogenesis. *Proceedings Biological Sciences* **266**, 493–498.
Obenauf, A. C. & Massagué, J. (2015). Surviving at a distance: organ-specific metastasis. *Trends in Cancer* **1**, 76–91.
Odling-Smee, F. J., Laland, K. N. & Feldman, M. W. (2003). *Niche Construction: The Neglected Process in Evolution*. Princeton University Press, Princeton.
Okasha, S. (2005). Multilevel selection and the major transitions in evolution. *Philosophy of Science* **72**, 1013–1025.
Okasha, S. (2006). *Evolution and the Levels of Selection*. Clarendon Press; Oxford University Press, Oxford.
Okasha, S. (2021). Cancer and the levels of selection. *The British Journal for the Philosophy of Science*. in press.
Pacheco, J. M., Santos, F. C. & Dingli, D. (2014). The ecology of cancer from an evolutionary game theory perspective. *Interface Focus* **4**, 20140019.
Paduch, R. (2015). Theories of cancer origin. *European Journal of Cancer Prevention (ECP)* **24**, 57–67.
Pagès, F., Mlecnik, B., Marliot, F., Bindea, G., Ou, F.-S., Bifulco, C., Lugli, A., Zlobec, I., Rau, T. T., Berger, M. D., Nagtegaal, I. D., Vink-Börger, E., Hartmann, A., Geppert, C., Kolwelter, J., *et al.* (2018). International validation of the consensus immunoscore for the classification of colon cancer: a prognostic and accuracy study. *The Lancet* **391**, 2128–2139.
Paget, S. (1889). The distribution of secondary growths in cancer of the breast. *The Lancet* **133**, 571–573.
Pan, H., Jiang, Y., Boi, M., Tabbò, F., Redmond, D., Nie, K., Ladetto, M., Chiappella, A., Cerchietti, L., Shaknovich, R., Melnick, A. M., Inghirami, G. G., Tam, W. & Elemento, O. (2015). Epigenomic evolution in diffuse large B-cell lymphomas. *Nature Communications* **6**, 6921.
Pardoll, D. (2003). Does the immune system see tumors as foreign or self? *Annual Review of Immunology* **21**, 807–839.
Pearl, J. & Mackenzie, D. (2018). *The Book of Why: The New Science of Cause and Effect*, First Edition. Basic Books, New York.
Pezzella, F., Tavassoli, M. & Kerr, D. J. (eds) (2019). *Oxford Textbook of Cancer Biology*. Oxford University Press, Oxford.
Pickup, M. W., Mouw, J. K. & Weaver, V. M. (2014). The extracellular matrix modulates the hallmarks of cancer. *EMBO Reports* **15**, 1243–1253.
Pienta, K. J., McGregor, N., Axelrod, R. & Axelrod, D. E. (2008). Ecological therapy for cancer: defining tumors using an ecosystem paradigm suggests new opportunities for novel cancer treatments. *Translational Oncology* **1**, 158–164.
Plutynski, A. (2013). Cancer and the goals of integration. *Studies in History and Philosophy of Biological and Biomedical Sciences* **44**, 466–476.
Plutynski, A. (2018*a*). *Explaining Cancer: Finding Order in Disorder*. Oxford University Press, Oxford.
Plutynski, A. (2018*b*). The origins of 'dynamic reciprocity': Mina Bissell's expansive picture of cancer causation. In *Dreamers, Visionaries, and Revolutionaries in the Life Sciences* (eds O. Harman and M. Dietrich), pp. 96–110. University of Chicago Press, Chicago.

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Plutynski, A. (2021*a*). How is cancer complex? *European Journal for Philosophy of Science* **11**, 55.
Plutynski, A. (2021*b*). Is cancer a matter of luck? *Biology & Philosophy* **36**, 3.
Plutynski, A. (2021*c*). The cancer genome atlas project: data-driven, hypothesis-driven or something In-between? In *Perspectives on the Human Genome Project and Genomics* (eds C. Donohue and A. C. Love). Minnesota Studies in the Philosophy of Science, Minneapolis.
Plutynski, A. & Bertolaso, M. (2018). What and how do cancer systems biologists explain? *Philosophy of Science* **85**, 942–954.
Pradeu, T. (2012). *The Limits of the Self: Immunology and Biological Identity*. Oxford University Press, Paperback 2018, New York.
Pradeu, T. (2013). Immunity and the emergence of individuality. In *From Groups to Individuals: Evolution and Emerging Individuality* (eds F. Bouchard and P. Huneman), pp. 77–96. MIT Press, Cambridge.
Pradeu, T. (2019). *Philosophy of Immunology*. Cambridge University Press, Cambridge.
Pradeu, T. & Carosella, E. D. (2006). On the definition of a criterion of immunogenicity. *Proceedings of the National Academy of Sciences* **103**, 17858–17861.
Pradeu, T., Jaeger, S. & Vivier, E. (2013). The speed of change: towards a discontinuity theory of immunity? *Nature Reviews Immunology* **13**, 764–769.
Pradeu, T., Lemoine, M., Khelfaoui, M. & Gingras, Y. (2021). Philosophy in science: can philosophers of science permeate through science and produce scientific knowledge? *The British Journal for the Philosophy of Science*. in press.
Reya, T., Morrison, S. J., Clarke, M. F. & Weissman, I. L. (2001). Stem cells, cancer, and cancer stem cells. *Nature* **414**, 105–111.
Rondeau, E., Larmonier, N., Pradeu, T. & Bikfalvi, A. (2019). Philosophy of biology: characterizing causality in cancer. *eLife* **8**, e53755.
Schreiber, R. D., Old, L. J. & Smyth, M. J. (2011). Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* **331**, 1565–1570.
Schumacher, T. N., Scheper, W. & Kvistborg, P. (2019). Cancer neoantigens. *Annual Review of Immunology* **37**, 173–200.
Seluanov, A., Gladyshev, V. N., Vijg, J. & Gorbunova, V. (2018). Mechanisms of cancer resistance in long-lived mammals. *Nature Reviews Cancer* **18**, 433–441.
Sepich-Poore, G. D., Guccione, C., Laplane, L., Pradeu, T., Curtius, K. & Knight, R. (2022). Cancer's second genome: microbial cancer diagnostics and redefining clonal evolution as a multispecies process. *BioEssays* **44**, 2100252.
Sepich-Poore, G. D., Zitvogel, L., Straussman, R., Hasty, J., Wargo, J. A. & Knight, R. (2021). The microbiome and human cancer. *Science* **371**, eabc4552.
Shamir, E. R. & Ewald, A. J. (2014). Three-dimensional organotypic culture: experimental models of mammalian biology and disease. *Nature Reviews Molecular Cell Biology* **15**, 647–664.
Sharma, P. & Allison, J. P. (2020). Dissecting the mechanisms of immune checkpoint therapy. *Nature Reviews Immunology* **20**, 75–76.
Sholl, J., Sepich-Poore, G. D., Knight, R. & Pradeu, T. (2022). Redrawing therapeutic boundaries: microbiota and cancer. *Trends in Cancer* **8**, 87–97.
Shpak, M. & Lu, J. (2016). An evolutionary genetic perspective on cancer biology. *Annual Review of Ecology, Evolution, and Systematics* **47**, 25–49.
Simian, M. & Bissell, M. J. (2017). Organoids: a historical perspective of thinking in three dimensions. *The Journal of Cell Biology* **216**, 31–40.
Somarelli, J. A. (2021). The hallmarks of cancer as ecologically driven phenotypes. *Frontiers in Ecology and Evolution* **9**, 226.
Sontag, E. D. (2017). A dynamic model of immune responses to antigen presentation predicts different regions of tumor or pathogen elimination. *Cell Systems* **4**, 231–241.e11.
Soria, F. N., Paviolo, C., Doudnikoff, E., Arotcarena, M.-L., Lee, A., Danné, N., Mandal, A. K., Gosset, P., Dehay, B., Groc, L., Cognet, L. & Bezard, E. (2020). Synucleinopathy alters nanoscale organization and diffusion in the brain extracellular space through hyaluronan remodeling. *Nature Communications* **11**, 3440.
Spitzer, M. H., Carmi, Y., Reticker-Flynn, N. E., Kwek, S. S., Madhireddy, D., Martins, M. M., Gherardini, P. F., Prestwood, T. R., Chabon, J., Bendall, S. C., Fong, L., Nolan, G. P. & Engleman, E. G. (2017). Systemic immunity is required for effective cancer immunotherapy. *Cell* **168**, 487–502.e15.
Sprouffske, K., Athena Aktipis, C., Radich, J. P., Carroll, M., Nedelcu, A. M. & Maley, C. C. (2013). An evolutionary explanation for the presence of cancer nonstem cells in neoplasms. *Evolutionary Applications* **6**, 92–101.
Strassmann, J. E., Zhu, Y. & Queller, D. C. (2000). Altruism and social cheating in the social amoeba *Dictyostelium discoideum*. *Nature* **408**, 965–967.
Subbiah, V., Solit, D. B., Chan, T. A. & Kurzrock, R. (2020). The FDA approval of pembrolizumab for adult and pediatric patients with tumor mutational burden (TMB) ≥10: a decision centered on empowering patients and their physicians. *Annals of Oncology* **31**, 1115–1118.
Suijkerbuijk, S. J. E. & van Rheenen, J. (2017). From good to bad: Intravital imaging of the hijack of physiological processes by cancer cells. *Developmental Biology* **428**, 328–337.
Swanton, C. & Govindan, R. (2016). Clinical implications of genomic discoveries in lung cancer. *New England Journal of Medicine* **374**, 1864–1873.
The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium (2020). Pan-cancer analysis of whole genomes. *Nature* **578**, 82–93.
Thomas, L. (1982). On immunosurveillance in human cancer. *The Yale Journal of Biology and Medicine* **55**, 329–333.
Tomasetti, C. & Vogelstein, B. (2015). Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* **347**, 78–81.
Trigos, A. S., Pearson, R. B., Papenfuss, A. T. & Goode, D. L. (2018). How the evolution of multicellularity set the stage for cancer. *British Journal of Cancer* **118**, 145–152.
Tuveson, D. & Clevers, H. (2019). Cancer modeling meets human organoid technology. *Science* **364**, 952–955.
Ushijima, T., Clark, S. J. & Tan, P. (2021). Mapping genomic and epigenomic evolution in cancer ecosystems. *Science* **373**, 1474–1479.
Velicer, G. J., Kroos, L. & Lenski, R. E. (2000). Developmental cheating in the social bacterium *Myxococcus xanthus*. *Nature* **404**, 598–601.
Vineis, P., Illari, P. & Russo, F. (2017). Causality in cancer research: a journey through models in molecular epidemiology and their philosophical interpretation. *Emerging Themes in Epidemiology* **14**, 7.
Weaver, V. M., Petersen, O. W., Wang, F., Larabell, C. A., Briand, P., Damsky, C. & Bissell, M. J. (1997). Reversion of the malignant phenotype of human breast cells in three-dimensional culture and in vivo by integrin blocking antibodies. *The Journal of Cell Biology* **137**, 231–245.
West, S. A., Griffin, A. S., Gardner, A. & Diggle, S. P. (2006). Social evolution theory for microorganisms. *Nature Reviews Microbiology* **4**, 597–607.
White, P. R. & Braun, A. C. (1942). A cancerous neoplasm of plants. Autonomous bacteria-free crown-gall tissue. *Cancer Research* **2**, 597–617.
Wijewardhane, N., Dressler, L. & Ciccarelli, F. D. (2021). Normal somatic mutations in cancer transformation. *Cancer Cell* **39**, 125–129.
Williams, M. J., Werner, B., Heide, T., Curtis, C., Barnes, C. P., Sottoriva, A. & Graham, T. A. (2018). Quantification of subclonal selection in cancer from bulk sequencing data. *Nature Genetics* **50**, 895–903.
Wirtz, D., Konstantopoulos, K. & Searson, P. C. (2011). The physics of cancer: the role of physical interactions and mechanical forces in metastasis. *Nature Reviews Cancer* **11**, 512–522.
Woo, S.-R., Corrales, L. & Gajewski, T. F. (2015). Innate immune recognition of cancer. *Annual Review of Immunology* **33**, 445–474.
Woodward, J. F. (2003). *Making Things Happen: A Theory of Causal Explanation*. Oxford University Press, New York.
Yarchoan, M., Johnson, B. A., Lutz, E. R., Laheru, D. A. & Jaffee, E. M. (2017). Targeting neoantigens to augment antitumour immunity. *Nature Reviews Cancer* **17**, 209–222.
Zach, M. & Greslehner, G. P. (2023). Understanding immunity: an alternative framework beyond defense and strength. *Biology and Philosophy* **38**, 7.
Zhu, M., Lu, T., Jia, Y., Luo, X., Gopal, P., Li, L., Odewole, M., Renteria, V., Singal, A. G., Jang, Y., Ge, K., Wang, S. C., Sorouri, M., Parekh, J. R., MacConmara, M. P., *et al.* (2019). Somatic mutations increase hepatic clonal fitness and regeneration in chronic liver disease. *Cell* **177**, 608–621.e12.

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